**Washington State Pharmacy and Therapeutics Committee**
**Drug Utilization Review Board**
**Meeting Transcription**
**April 21, 2021**

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| Leta Evaskus: | Okay, well it's 9:02. So why don't we get started? I'll keep working with my IT to see if we can get the camera function working. This is Leta Evaskus. Go To Webinar is not allowing us to share our cameras right now. So I'm sorry about that. But Ginni, do you want to kick us off? |
| Ginni Buccola: | Sure. Good morning, everyone. This is Ginni Buccola the chair of the P&T committee meeting. And we're going to go ahead then and convene. And we're studying this morning with the P&T committee meeting. We don't have cameras. If I'm missing anybody as we go through introductions or as we move on, if I'm missing any of my committee members, anyone needs attention, please use that chat box. I feel like we're driving blind a little bit without at least being able to see each other. Okay. But I am going to read off the names of the participating attendees today. And after I call your name, if you could please say "here", that would be great. So I'll start with our P&T committee members, with Alex Park. |
| Alex Park: | Good morning. Alex Park is present. |
| Ginni Buccola: | Thank you. Good morning. Diane Schwilke? We'll come back to you, Diane. Jordan Storhaug? |
| Jordan Storhaug: | Present. |
| Ginni Buccola: | And Nancy Lee? |
| Nancy Lee: | Here. |
| Ginni Buccola: | And Leah Marcotte? |
| Leah Marcotte: | Here. |
| Ginni Buccola: | Susan Flatebo? |
| Susan Flatebo: | Here. |

Ginni Buccola: And Catherine Brown?

Catherine Brown: Here.

Ginni Buccola: Thanks. And then the HCA members. We've heard from Leta Evaskus. Donna Sullivan will not be here the first half of the meeting but will be attending this afternoon. Going next to Ryan Pistoresi.

Ryan Pistoresi: Good morning.

Ginna Buccola: Morning. Luke Dearden?

Ryan Pistoresi: Luke will be joining us a little later this morning.

Ginni Buccola: Great. Ryan Taketomo? We'll move to Marissa Tabile.

Marissa Tabile: Good morning. I'm here.

Ginni Buccola: Amy Irwin? And we'll go next to Jose Zarate. And then to Chris Chen. And then back to our P&T committee members. I can see that Diane Schwilke's in the chat box that she's here. We just couldn't hear her.

[unrelated discussion]

Ginni Buccola: This is Ginni again. Our Magellan Medicaid administration member is Umang Patel.

Umang Patel: Good morning.

Ginni Buccola: And our DERP presenters are Leila Kahwati.

Leila Kahwati: Present.

Ginni Buccola: And Shauna Durbin.

Shauna Durbin: Good morning.

Ginni Buccola: And Candi Wines.

Candi Wines: Hello, I'm here.

Ginni Buccola: Great. Our managed care organization representatives are Greg Simas with Molina. I'll move to Heidi Goodrich with Molina. And I'll go to Petra Eichelsdoerfer with United.

Petra Eichelsdoerfer: Good morning.

Ginni Buccola: Morning. And Catherine Vu with Community Health Plan of Washington. Okay, that's the end of our attendee list. I don't know, Leta, do you feel ready for us to go to our first class of asthma biologics or should we hold on a little bit?

Leta Evaskus: No, we're going to be able to share screens. First, I'm going to go over some meeting logistics though. The committee presenters and MCO representatives are all added as organizers. You can mute and unmute yourselves. But please mute yourself when not speaking to limit the background noise. I'm hopefully going to get the webcams working sometime during this meeting so that the presenters and the committee can share their cameras. I'm sorry that GoTo Webinar is having some kind of problem and is not giving us that option right now. For stakeholder participation, the chair will read the list of stakeholder names who have pre-registered to speak and I will unmute you. After, the chair will ask if there's any other stakeholders. So if you did not pre-register, you can use the raise hand icon and I will call on you and unmute you. You'll have three minutes to speak. You can also use the question function, the question box, to ask questions and I will address your questions during the stakeholder time. The meeting is being recorded so please state your name every time you speak. And our first presenter is going to be Leila Kahwati from DERP and she is going to present. So Leila, I'm going to make you the presenter right now.

Leila Kahwati: Okay, I'm ready to share my screen when that becomes available. Okay. Great. Well, good morning, everybody. As was mentioned, I'm Leila Kahwati, presenting on biologic drugs to treat asthma and chronic spontaneous urticaria. This is a review that was originally presented at the DERP conference, a DERP meeting in February. And just by way of introductions, I'm the Associate Director of the RTI UNC evidence based practice center. This is an overview of the presentation this morning. First, we'll go through a little bit of background, talk about the structure of the review, and then spend most of the time on the findings. By way of background, as you probably all know, asthma is a chronic airway disease defined by history of respiratory symptoms including wheeze, shortness of breath, chest tightness, and cough. And then chronic spontaneous urticaria is the appearance of hives, angioedema, or both for more than six weeks because of unknown causes. The first biologic was approved for asthma in 2003. And the first biologic was approved for CSU in 2014. This next slide provides a snapshot of the different

biologics that were included in the review, which was an update of a previous review, I should mention. Overall, there were five agents that were covered that include three different mechanisms of action, which are noted here across the top in the green boxes. Omalizumab over here in the blue box is approved for use for both asthma and CSU. The other agents, Dupilumab, Benralizumab, Mepolizumab, and Resilzumab are only approved for asthma. This slide demonstrates the study selection criteria that we use for this update. The populations included adults or children with persistent or chronic asthma or CSU, as I've already mentioned, the biologics that were included. The competitors for this review included head to head comparisons, so one biologic compared to another or biologics compared to placebo, or usual care. And then this second to last bullet lists the types of outcomes that we're looking at. We focused on domains of symptom control, exacerbations for asthma, steroid use - again, that's only for asthma - anti-urticarial medication use, which was only for CSU, quality of life, overall adverse events, and then serious adverse events. And then lastly, the review was limited to randomized trials. This slide just provides the five key questions that guided the review. Key questions one and two were about effectiveness and harms of biologics for asthma. Key questions three and four were about the effectiveness and harms of biologics for CSU. And then the fifth question was about characteristics of ongoing studies not yet published for either of these conditions. In terms of our methods, the search for this updated review covered August 2017, which was when the last review left off, through last July. And we continued active surveillance of the literature through about November of last year. As I mentioned, this presentation was originally presented to the DERP conference meeting in February. We conducted risk of bias assessments on individual studies and used this data to conduct some random effects meta analyses when we had at least two similar studies. We use grade for rating the overall quality of the evidence. And lastly, ongoing studies were primarily based on clinicaltrials.gov and an international trials registry search. As a reminder, DERP assessment of risk of bias uses standardized assessments resulting in ratings of low, moderate, or high risk of bias and the definitions of each of those ratings are on this slide. And, as a reminder, the great approach evaluates the body of evidence for each comparison in this review and we graded several kinds of outcomes that I kind of already mentioned on an earlier slide. For example, for

symptom control, we graded measures like the asthma control questionnaire or the urticaria activity score over seven days for CSU. We'll talk a little bit in more detail about the specific measures that we looked at. As a reminder for grade, we assessed the evidence with respect to consistency, precision, study limitations, which is essentially captured as risk of bias, and directness. Bodies of evidence for a comparison and an outcome are then rated as either high, moderate, low, or very low quality. And as a reminder, bodies of a randomized control trial evidence, generally start at a high rating and then we downgrade them one or more levels for concerns in any of those previous areas that I just mentioned: consistency, precision, et cetera. This particular slide just suggests how each grade rating can be interpreted with respect to confidence in the findings. Now we'll move into reviewing the results. This first slide gives you an overview of the 53 included studies that were in the update review. 21 of them were new to this update, so since 2017 or so. And then 32 had been included in a previous review on this topic. We rated 43 of them as moderate risk of bias and 10 we rated as high risk of bias. 43 of the 53 were focused on asthma and then the other 10 were on participants with CSU. 50 of the 53 studies were placebo controlled and three studies were usual care controlled. So first takeaway from the presentation, there are no head to head studies published. So this graphic, or what we call heat map is a top line summary of the findings across the various drug and outcome domains. So along this left vertical axis are the various drugs and the indications. And then along this top horizontal axis are the various outcome domains that we graded. The text within each of the cells indicates the directionality of the evidence for that drug and outcome domain. For example, for Benralizumab, for improve symptom control, the results suggest the drug is more effective than placebo. And then the color of the cell represents the grade quality of evidence. So green is high quality, yellow is moderate quality, orange is low quality, and red is for very low quality. And you can see there's some bodies of evidence that have multiple outcomes that had varying strengths of evidence and that's represented by some different colors within the same cell. For harms, which is in this last column here, there's some interesting findings that we'll talk a little bit more about as we go through the presentation. We found fewer harms actually for Benralizumab and Mepolizumab compared to placebo, while no differences were observed for Dupilumab and Reslizumab and we'll talk about why that

might be a little bit later. So this is sort of the overall top line summary. And we'll kind of revisit it after we go back through some of the detailed findings. So before we move on to specific findings, I just want to call your attention to this slide, which is a reference for some of the abbreviations that we'll encounter along the way, along with estimates for minimally important differences on some of these outcomes and scales that have been established by the literature. I'll say a little bit more about some of these measures as we encounter them in the presentation. So first, we'll go through Benralizumab for asthma. There were six studies that we identified. All were multicenter studies conducted globally in more than one country. Five were phase three, one was a phase two study. Two studies enrolled persons aged 12 and over while four studies were conducted only among adults. Five of the studies enrolled persons exclusively or predominantly with allergic asthma, typically requiring a history of a positive skin prick [indistinct] testing or high levels of eosinophils at baseline or both. All the studies used a placebo comparator. Five of the studies used 30 milligram doses every four weeks, and three of them also included a study arm assessing every eight week dosing intervals. Just as a reminder, the FDA approved dose is 30 milligrams every four weeks for the initial three doses and then every eight weeks. Five of the six studies were designed to evaluate the add-on efficacy of Benralizumab to standard asthma controlling regimens, while one of the six was designed to evaluate the add-on efficacy of Benralizumab to standard regimens. That study also included a steroid tapering co-intervention in both the active and the placebo groups. In other words, the goal of that study was to improve or maintain asthma control while at the same time reducing the amount of steroids required. That type of study design was also used by other authors evaluating other biologics in this review and this type of design typically includes an initial period of between two weeks and three months where existing maintenance steroid doses are maintained, while the study drug, either the biologic or the placebo is started. And authors refer to this as the steroid stable phase. This is then followed by a steroid reduction phase where steroid doses, either oral or inhaled, are reduced by either percent of the patient's dose, or by a standard amount and a regular interval, for example, like every two weeks per protocol, until the dose is either eliminated entirely or until symptom control worsens. And then the lowest dose reduction achieved is then maintained for the final month or two of

the study. In the full report for this review and in the rest of this presentation, I'll refer to these kinds of designs as add-on efficacy with steroid tapering or as steroid sparing trials to distinguish them from the more traditional add-on efficacy RCTs where existing maintenance steroid doses were kept stable throughout the study. And the reason we are doing that is because the absolute magnitude of findings from the steroid sparing trials might not be directly comparable to the traditional add-on efficacy studies. And so we've sort of synthesize them separately. Okay, so now we're going to dive into the first outcome domain, which is symptom control. Let me just orient you to the slide as most of the subsequent slides will have a similar layout. So in the green header here at the top, the specific outcome, number, and type of RCTs, and the number of total participants is indicated. And just below the header is the grade rating that we assigned for the results shown. And below that will either be a forest plot, like as is the case on this slide, or they'll alternatively just be a text description of the findings. For the forest plots, I've gone ahead and put a green box around the headings for different estimates that are shown on the same plot. The plot includes the names of the studies, the time point for which the outcome is reported, and then the outcome values for the treatment and control groups are also shown on the plot. Each study's individual treatment effect estimate is shown in the middle of the plot on the graph. The black dot is the point estimate, the gray box surrounding it is proportional to the number of subjects in the study. And then the lines extending from the middle represent the 95% confidence interval. And then the numeric value of the estimate is over here on the right side of the plot. The vertical line here represents the null effect, which is zero for continuous measures, like a difference in mean change from baseline, which is the case for this measure on this plot. And it will be one when we're looking at relative measures of effects. This is risk ratios and rate ratios. The diamond represents the pool summary estimate. I've placed a green arrow for the most part next to the pool values on all the plots throughout the presentation to quickly call your attention to them as we move more quickly through the following slides. And then lastly along the x axis are labels to indicate the direction of effect. For example, for this measure, a pooled estimate to the left of the null effect represents a larger improvement among persons receiving Benralizumab compared to placebo. So, with that orientation, let me now just describe the finding on the slide. So we identified five add-on

RCTs that measured symptom control using the asthma control questionnaire, ACQ. As a reminder, the ACQ is a seven item questionnaire. The scale goes from zero, which means totally controlled to six which means severely uncontrolled. The minimally important difference also known as the MID for the ACQ is about half a point. As you can see here, four trials evaluated Benralizumab given every four weeks, in the upper panel. And the pooled mean change from baseline in the ACQ was .23 points. And then two RCTs evaluated at given every eight weeks. And the pooled estimate for that regimen was .27 points. So for both dosing intervals, there were larger improvements on the ACQ score observed for drug compared to the placebo. However, you'll note the magnitude of the pooled effect is smaller than the MID for this measure, which again is .5 of a point. In addition to these studies, we also identified one other RCT that could not be pooled, but it also reported a larger improvement in this measure, a difference of .1 point. So for this outcome, ACQ mean change for baseline, we graded the evidence as moderate quality. Okay. For some of the measures in addition to reporting on differences in mean change from baseline, studies often also reported differences in the proportion of participants who were able to achieve a minimally important difference on the measure. And we refer to this outcome as MID response. So in the top panel are the findings of the outcome of MID response on the ACQ. There were pooled estimates from two add-on efficacy RCTs demonstrating a significantly higher proportion of participants allocated to Benralizumab compared to those allocated to placebo. The risk ratio was 1.23. And as you can see, the confidence intervals of the pooled estimates do exclude a null effect. I do want to make note here that this estimate does include one study that included participants with both allergic and non-allergic asthma, and it didn't stratify its results. So we ended up rating this evidence as moderate quality. In the bottom panel, there was one phase three RCT that was a steroid sparing trial. The authors reported significantly larger improvements in the difference in mean change from baseline for the ACQ for the eight week dosing interval, as you can see here. The four week dosing interval also had improvement, but it was not as large as the eight week dose and it was also not statistically significant. And so we graded this outcome also as moderate quality. Moving on to quality of life domain, we identified three RCTs that measure quality of life using the asthma quality of life questionnaire. This is a 32-item questionnaire assessing disease

specific health related quality of life. The scale goes from one severely impaired to seven not impaired at all, which is the reverse scale of the ACQ. And that's why you see the labels along the x axis here reversed as an effect to the right of the null represents more improvement for the drug compared to placebo. The MID for this measure also happens to be half of a point. So there were three add-on RCTs that evaluated this outcome and as you can see significantly larger differences in mean change from baseline were observed for both the four-week and for the eight-week dosing intervals. But as you can see, again, the magnitude of difference here does not achieve the MID for this measure. There was also one steroid sparing trial that evaluated the quality of life. In this trial, the authors reported larger improvements in mean change in the AQLQ from baseline for both the eight-week and the four-week dosing intervals. But as you can see, neither finding was statistically significant, most likely due to just imprecision. So overall, we graded the evidence for AQLQ mean change for baseline is low quality. At the bottom of the slide, there was one add-on efficacy trial that reported MID response for the AQLQ. So 43% of persons receiving the active drug had an MID response versus 32% of the placebo for a risk ratio of 1.34. But again, the confidence intervals did not exclude a null effect. Also this happens to be the trial that enrolled persons with both allergic and non-allergic asthma and didn't stratify the results. So we graded this evidence as low quality. Moving on to the outcome of exacerbations. Before I describe the actual results, I wanted to say a few words about how studies defined this outcome as it varied somewhat across studies. A common component of all definitions of exacerbation was worsening symptoms that required systemic or increased doses of steroids on at least several consecutive days. Other components of the definition used by some studies included unscheduled physician visits, emergency room visits, hospital admissions, missed school or work, and then some also used objective measures of decline in lung function like FEV1 or peak expiratory flow. In the report and through this presentation, when we report data for exacerbations, it refers to exacerbations however defined by the study authors. And where possible, we've provided data separately relating to exacerbations requiring an ED or a hospital visit when specifically reported by authors in that way. So for Benralizumab, we identified three add-on RCTs that measured annualized rates of exacerbations. Among the two that we were able to include in the pooled analysis, there was a lower annualized rate of

exacerbation for both the four-week and for the eight-week dosing intervals, as you can see in the top and bottom panels of the plot. The pooled incident rate ratio happened to work out to be .59 for both dosing intervals. And as a reminder, a rate ratio represents irrelative effects. So the rate among Benralizumab participants was only .59, the rate that occurred among placebo participants. A rate ratio less than one means the drug results in a lower rate compared to placebo. The third RCT could not be included in the quantitative synthesis but it also reported a rate ratio of .55 so it was fairly consistent. So overall, we graded the evidence for this outcome as moderate quality. Several other exacerbation related measures were also reported including the incidence of exacerbations as shown here on the top of the slide. Two of the trials, one of which had two study arms, one for four week dosing interval and eight week and another for eight week dosing interval reported significantly fewer exacerbations with risk ratios ranging from .50 to .79, all of which excluded a null effect and we graded that evidence is moderate quality. Two trials also reported the annualized rate of exacerbations requiring ED or hospital visits. And a significantly lower rate of these exacerbations were seen with the four-week dosing interval. The rate ratio was .67. However, for the eight-week dosing intervals, significantly fewer exacerbations were seen in one study, but more exacerbations were actually observed in the second study. However, this study had pretty wide confidence intervals and cannot exclude a null effect. So overall, we graded this evidence as low quality. In the one steroid sparing trial, a significantly lower annualized rate of exacerbations was observed compared to placebo among participants receiving the eight-week dosing interval and the four-week dosing interval where the incident rate ratios were .3 and .45, respectively. We graded this evidence as moderate quality. With respect to steroid use, there's only one steroid sparing trial that reported this outcome for Benralizumab. So the proportion of participants who were able to reduce their oral steroid dose by 50% or more was significantly increased compared to placebo for both the eight-week and the four-week dosing intervals, as you can see here. The risk ratios were 1.76 and 1.79, respectively. Both excluded a null effect. And we graded this evidence as moderate quality. Moving on to key question two, harms for Benralizumab, pooled estimates for overall adverse events or total adverse events, and then serious adverse events indicated that fewer adverse events occurred in the Benralizumab group compared to placebo group, as you can see here

from these pooled estimates at the top and bottom of the plot. So we ended up grading the evidence for total adverse events as high quality and the evidence for serious adverse events as moderate quality. And primarily, that's because you can see there's much wider confidence intervals around the estimates for serious adverse events. So it's a less precise estimate and the confidence interval around the pooled estimate is also wider. It's worth pausing here just to discuss a little bit about what this finding of fewer adverse events actually means. If studies considered exacerbations as adverse events in addition to using them as the effectiveness outcomes, then this finding can really just be understood as reflecting fewer adverse events in the active drug group because symptoms were better controlled and participants then had fewer exacerbations. But we didn't see this finding universally across all the biologics in this review. And one reason may just be differences in how studies handled asthma exacerbations with respect to whether they also counted them as adverse events or not. And so that's probably the reason why we see this difference across the class. But another explanation for fewer adverse events may be that some of these agents may have off-target effects of the drug that just have yet to be elucidated. Okay, moving on to Dupilumab for asthma. We identified four studies. Two were phase two, two or phase three, one was conducted in the US and the rest were conducted globally in multiple countries. Two of the studies enrolled children and adults aged 12 years or older, and then two enrolled only adults. One trial enrolled only participants with allergic asthma. Two trials enrolled predominantly, more than 80% of participants had allergic asthma. And then one trial enrolls only about 42% of participants with allergic asthma, but they reported their findings separately, based on baseline eosinophil level. All of them compared Dupilumab to placebo. And the doses that were evaluated are the FDA approved doses of 200 milligrams or 300 milligrams sub Q are both with loading doses. Two studies were designed as add-on efficacy trials and two were designed as steroid sparing trials. And then the risk of bias for all of them was moderate. So starting with symptom control, you can see that Dupilumab was more effective than placebo for improving symptom control as measured by the mean change from baseline in the ACQ. Both the two add-on efficacy trials, which had a mean change of .28 and the two steroids sparing trials, which had a larger mean change of .55 excluded a null effect. And just as a reminder, the MID for this measure is half a point. And we graded

this evidence as moderate quality. One trial also reported the proportion of participants who achieved an ACQ MID response at 24 weeks. And there were significantly more participants who achieved this response for both the 200 milligram and the 300 milligram doses compared to placebo as you can see on the slide. Both of the estimates excluded a null effect. And we graded this evidence as moderate quality. With respect to quality of life, there were two add on efficacy trials that observed significantly larger improvements in AQLQ for Dupilumab compared to placebo. Again, the MID for this outcome is half a point. The point estimate here was .23 and this was at 24 weeks. One of the RCTs also reported findings, this particular measure at one year and the difference in mean change persisted. It was .29 for the 200 milligram dose and .26 for the 300 milligram dose. So that effect persisted up to one year and we graded over all this evidence as moderate quality. One trial reported the proportion of participants who achieved an AQLQ, MID response at 24 weeks. And again significantly more participants achieved this response for both the 200 milligram and the 300 milligram dose. As you can see, the risk ratios were 1.25 and 1.27, respectively and both excluded the null effect. And we also graded this evidence is moderate quality. Moving on to exacerbation outcomes. Across the add on efficacy trials, Dupilumab was more effective than placebo for reducing the annualized rate of severe exacerbations in two trials. The incident rate ratios ranged from .29 to .54 across all doses studied and all those estimates excluded a null effect. It was also significantly more effective at reducing the incidence of severe exacerbations. In one trial the combined dose groups 200 milligrams 300 milligram, only 10% of the participants had an exacerbation compared to the placebo group where 26% of the participants had an exacerbation for a risk ratio of .38. We graded that evidence as moderate quality. And finally, there was one trial demonstrated that Dupilumab was more effective at reducing the rate of exacerbations requiring an ED visit or hospitalization. The rate ratio in that trial, which went out to 52 weeks was .53. And we graded that evidence as low quality. Similar findings were found for the steroid sparing trials. In one trial, Dupilumab was more effective at reducing the rate of severe exacerbations, the rate ratio was .41. And in the other steroid sparing trial, which reported incidents of exacerbations, the risk ratio for incidents was .13. So we rated the first outcome is moderate quality and the second outcome is low quality. Across both steroid sparing

trials, Dupilumab was more effective than placebo at reducing steroid use. In one study significantly more participants were able to reduce their steroid use by 50% or more. From baseline, the rate risk ratio was 1.49. And significantly more were also able to completely reduce their usage. So 100% reduction. The risk ratio was 1.81. In the other study, fewer participants allocated to Dupilumab required the use of oral steroids during this study. So this particular study just measured steroid use in a different way. So 2% required additional steroid use during the trial versus 10% of the placebo group. And that risk ratio was .20. But as you can see, this was an actually fairly small study and the confidence intervals are quite wide. So we could not exclude a null effect. So overall, we graded the evidence for steroid use as moderate quality. So the same four trials that contributed to effectiveness outcomes also reported harm outcomes. Pooled analyses here indicated that there were no significant differences in the number of participants with adverse events, which we rated as high quality or serious adverse events, which we rated as moderate quality, similar to Benralizumab primarily because these events are rarer and that means the pooled estimate is more imprecise. Okay, moving on to Mepolizumab. We identified three phase three RCTs. All were multicenter conducted globally in more than one country. Two studies enrolled persons aged 12 or older and then one only enrolled adults. All studies enrolled all persons with eosinophilic asthma and they were all placebo controlled and used standard FDA approved doses, which is 100 milligram every four weeks. Two of the studies were designed to evaluate the efficacy of add-on Mepolizumab to standard therapy while one was designed to evaluate add-on efficacy in the setting of steroids tapering interventions, and they were all moderate risk of bias. So for symptom control, the two add-on RCTs reported using the asthma control questionnaire, the ACQ, which we've already talked about, but they also reported using something called the St. George's respiratory questionnaire. Because of differences in these two studies, we depicted the pooled analyses on the same plot using standardized mean differences. But I've also pasted in here the unstandardized mean differences to facilitate comparison to other drugs and to the MID for the measure. So as you can see here, people who got allocated to Mepolizumab had significantly larger improvements on the ACQ. The point estimate is .43, the unstandardized mean difference, and the effect excludes a null effect and is close to but not above the MID for this measure, which again is

half a point. And similarly, there's a similar conclusion if you look at the St George's respiratory questionnaire. ACQ was also reported by the one steroid sparing trial. The difference in mean change from baseline was .52 points, which you'll note does meet the MID threshold for this measure. None of the three studies reported quality of life so we'll move on here to the exacerbation domain, which we were not able to pool. All three studies reported significantly lower annualized rates of exacerbations, as you can see. The rate ratios ranged from .42 to .68. And we graded this evidence as moderate quality. Both add-on RCTs also reported on annualized rate of exacerbations requiring ED or hospital visits here in the middle and both studies reported significantly lower rates for Mepolizumab compared to placebo. As you can see the rate ratio is .32 and .30. And then lastly, the steroid sparing trial reported on the incidence of exacerbations requiring hospitalization. And as you can see, the risk ratio point estimate is .07. But it's an imprecise estimate. This is a rather small trial, only 135 participants. These events are rare. So the confidence interval is quite large and could not exclude a null effect. Thus, we graded the second two of the three outcomes on this slide as low quality. Moving on to steroid use. Only the steroid sparing trial reported on this outcome. And as you can see, significantly more participants on Mepolizumab were able to reduce their scarcities by 50% or more. It was 54% in the treatment group versus 33% in the placebo group for a risk ratio of 1.61. More participants were also able to completely reduce their oral steroid use. It was 14% versus 8% in the placebo group. The risk ratio here was 1.91 but again, this is a rare outcome. So the confidence intervals are wider, the estimate is not as precise and cannot exclude a null effect. Moving on to adverse events from Mepolizumab. So all three studies contributed data to this key question. As you can see, there were significantly fewer overall adverse events and fewer serious adverse events with Mepolizumab compared to placebo. So these findings are similar to what we saw with Benralizumab, where there's fewer adverse events with the drug compared to placebo. Moving on to Omalizumab for asthma now. So this graphic summarizes the characteristics of the 23 studies that were included for Omalizumab for asthma, five were phase two or three studies. Another six were indicated as phase four or post marketing studies. And there were another 12 that just did not specifically identify a phase. Six were conducted in the US and the rest were conducted globally. Nearly half of them enrolled persons aged

12 and older, four of them enrolled persons less than age 18, and then eight of them enrolled only adults 18 and above. All but three studies specifically enrolled persons with allergic asthma. All but three studies used a placebo control. No treatment was used in one study and then optimized. Asthma therapy was used in one study and best standard care was use in the last study. So those two really we would call sort of usual care, although if you look at what they did, they really actually optimize treatment during a run-in phase before the people started the active drug. So I'm not sure if that is really equivalent to usual care. Over half of the trials were designed to evaluate Omalizumab as add-on therapy to a person's existing asthma regimen and then six were designed as add-on therapy during a steroid tapering intervention. There was one study designed to reduce non-steroid treatment after an initial phase of active drug treatment. And then there was one study that we're calling a discontinuation study that randomized people already taking long term Omalizumab therapy and then randomized them to either stay on the biologic or to discontinue use. And then in this bucket of 23 studies, eight of them we rated as high risk of bias. The rest were moderate. So first we'll go through symptom control. There were five add-on RCTs that reported significantly higher proportions of either patient or physician ratings of global treatment effectiveness. So this is where the physician or the patient rates treatment effectiveness as either good or excellent. And the pooled risk ratio for physician ratings in five studies was 1.60 and the pooled risk ratio for a patient ratings of good or excellent among two studies was 1.34. So one thing I will note about the analysis using physician ratings is that it has a moderate to substantial amount of heterogeneity as you can see over here by the I squared statistic, which is 84. This is likely driven by this Bousquet study, which is a bit of an outlier. Its individual study estimate risk ratio is 3.2. This happens to be an open label trial, so it was not blinded. And the control group here was not placebo, it was optimized asthma therapy. And we rated the risk of bias as high for that particular study. And so we conducted a sensitivity analysis to remove that study just to see how it would impact the pooled estimate. The pooled estimate remained significant but decreased in magnitude down to 1.34, which is very similar to the patient ratings. So overall, we graded this outcome as moderate quality of evidence. This same outcome global treatment effectiveness was also reported among the three steroid sparing trials. As you can see, the pooled risk ratio for the patient

ratings was again somewhat smaller, magnitude 1.32 compared to the physician ratings, which is 1.48. And for the patient ratings, the confidence [indistinct] around the pooled effect actually does not exclude a null effect even though the two individual studies actually do exclude a null effect. And this is likely just due to our use of random effects model, which typically generates wider intervals than fixed effects models. And we rated the overall evidence for this outcome is moderate quality. Studies also reported several other measures of symptom control, which was consistent with Omalizumab being more effective than placebo. We graded the evidence as high quality for the outcome of number of days with asthma symptoms across three studies. The mean reduction in days was about half a day. For the outcome of mean change from baseline and the asthma control questionnaire, we were not able to pool findings. The range in this outcome went from zero, which was reported by one of the studies that enrolled persons with non-allergic asthma. And then at the other extreme, the other study reported a mean change of .87, which is probably amongst the highest in this bucket of evidence. And that happens to be that same unblinded open label, Bousquet study. And so as a consequence of this large variation in magnitude and problems with the risk of bias studies, we ended up grading this particular outcome as very low evidence. And then lastly, two trials reported using the asthma control test or the children's asthma control test, which is the same instrument, just modified for use in children. The pool difference in mean change on this estimate was .52. This particular estimate is reverse scored compared to the ACQ. So a positive increase means there was more asthma control. And the MID for this measure happens to be three points. So a change of .52 is improvement, but it doesn't meet the threshold for the MID. And we ended up grading this evidence as low quality. Moving on to quality of life. There were five add-on RCTs and one steroid sparing RCT reporting the AQLQ. We couldn't pool the findings but the range and difference in mean change from baseline went from .29 to 1.19 in the four RCTs. And findings were statistically significant in three of the four studies. The actual difference in mean change was not reported by the study, but they did say it was statistically significant. And so we ended up rating this evidence is moderate quality. Three of the add-on efficacy RCTs also reported on the proportion of participants achieving an AQLQ MID response, which again is about half a point. The pooled risk ratio for that was 1.15 and was significant. In the one

steroid sparing trial that reported this measure, a statistically significant risk ratio was observed across the steroid stable phase, the steroid reduction phase, and the double blind extension phase that lasted up to one year. Although the estimates range from 1.14 to 1.24, but they were all statistically significant. And so we ended up grading this particular outcome as high quality. Lastly, the pediatric asthma quality of life questionnaire was reported by two different steroid sparing trials. And these were trials that only enrolled children, which is why they use the PAQLQ. One trial found essentially no difference in mean change from baseline. The MID again is .5 in this study, found a mean change of .04. In this particular study, participants had their asthma regimens optimized during the run-in period prior to randomization. The other trial reported findings as a portion that achieved a large MID response, which they defined as 1.5 points. So participants allocated to the Omalizumab were more likely to achieve a large MID during both the steroid stable and the steroid reduction phase as seen here with risk ratios of 1.45 and 1.67. However, you'll note these findings are not precise. The confidence intervals are wide and the findings could not exclude a null effect. This happens to be a study that also did some converting of participants pre-study steroid doses to equivalent doses, but they didn't actually seek to optimize the treatment during the run-in period. Moving on to exacerbations, this analysis includes 12 add-on efficacy RCTs reporting on the incidence of one or more exacerbations during the study periods. Overall, you can see that compared to placebo, Omalizumab significantly reduced the incidence of exacerbations. The pooled risk ratio was .71 and we graded this evidence as high quality. There were four steroid sparing trials reporting on exacerbations. Similar significant rates of reduction were observed across the steroid stable phases, which is up here at the top of the plot, the stairway reduction phases, which is here in the middle. And then a couple studies had double blind extension phases. And so the point estimates are a little bit different but are all consistent with reductions in asthma exacerbations compared to placebo. A small [indistinct] reported on exacerbations requiring ED or hospital visits. There were three add-on efficacy studies that reported this outcome. We weren't able to pool their data, but the range of risk ratios or rate ratios was between .23 and .66. And three of the four estimates did exclude a null effect. We graded that evidence as moderate quality. Among the three steroid sparing trials reporting exacerbations requiring

hospitalization, participants allocated to Omalizumab had fewer of these types of exacerbations. As you can see, the risk ratio here is .23 during the steroid stable phase, the risk ratio was .18 during the steroid reduction phases. However, you can see that the estimates were not precise and the estimate during the steroid stable phase could not exclude a null effect. But the estimate during the steroid reduction phase does show a significant effect. We graded this outcome as moderate quality. Moving on to steroid use, only one add-on efficacy trial reported on steroid use outcomes. In the study, fewer participants allocated to Omalizumab required oral steroids during the course of the study compared to placebo and the risk ratio was .80 and excluded the null effect. And we graded that outcome as low quality. Three steroid sparing trials reported on the proportion of participants who achieved a 50% or more reduction in inhaled steroid use and the pooled risk ratio there was 1.39 during the steroid reduction phase and was 1.40 in the double blind extension phase. And we graded this outcome as high quality. And then four of the trials reported on the proportion of participants who were able to completely reduce their inhaled steroids. And the risk ratio was 1.79 during the steroid reduction phase and 2.63 during the double blind extension phase. But that was only from one study. And both of these excluded the null effect and we graded this evidence also as high quality. Now for harms for Omalizumab and asthma, this slide shows the findings from pooled analyses of 17 RCTs that had data that we could pool for the outcome of total adverse events. As you can see, most of the individual study estimates are very close to the null effect and the pool risk ratio was exactly 1.0 with quite narrow confidence intervals spanning .97 to 1.03. And we graded this evidence as high quality for no difference in adverse events. And in terms of serious adverse events, includes analysis from 16 trials that had poolable data. As you can see, there's more imprecision in the individual study estimates. The confidence intervals are wider. You would expect that because this is a rare outcome. The pooled estimate suggests fewer serious adverse events. The risk ratio was .76 and it just barely excludes a null effect. Moving on now to Reslizumab for asthma. We identified seven studies. One was conducted in the US, the rest were conducted in multiple countries. Give enrolled persons aged 12 and up, two enrolled only adults. Six of the seven studies enrolled persons with allergic asthma. And one study included both allergic and non-allergic asthma. All of the studies used placebo competitors. Five of

the seven studies evaluated the standard FDA approved doses of three milligram per kilogram IV. Two studies evaluated a subcutaneous dose of 110 milligrams. I'll say more about that later. Six of the seven studies evaluated add-on efficacy of Reslizumab and then one study used a steroid sparing design. So six add-on efficacy RCTs reported symptom control using ACQ mean change of baseline. And five of those reported outcomes at 15 to 16 weeks, which is shown here in the upper panel. And three reported at 52 weeks, which as you can see down here in the bottom panel. As you can see, both pooled estimates show significantly larger improvements for Reslizumab compared to placebo, though the magnitude again is smaller than the MID for this measure, which is half a point. One other thing I wanted to mention here is the trial reporting out at 52 weeks by Bernstein, this is the trial that used a dose of 110 milligrams sub Q, which is equivalent to about an IV dose of one milligram per kilogram for a 70 kilogram person, which is less than the FDA approved dose, and which may explain why the magnitude of that study is less than all the other studies. Five of the add-on efficacy trials also reported on ACQ MID response and the pooled risk ratios at 15 to 16 weeks into RCTs and at 52 weeks and different RCTs suggests significantly more participants who get Reslizumab are able to achieve an MID. There was a fifth RCT where the actual values were not reported. And the difference between groups was actually described as non-significant. But despite that, overall, we graded that this body of evidence is high quality. Three of the add-on efficacy studies also reported using the asthma symptom utility index. This is an outcome based on an 11 item interviewer administered questionnaire and the range of scores is from zero, which means worst possible symptoms to one, which means no symptoms and an MID on this measure is about .09 points. At both 16 and 52 weeks, the pool difference in mean change from baseline showed significantly larger improvements for participants allocated to drug compared to placebo, though, you'll note the pooled estimate of .05 here is less than the MID for the outcome, which again is .09. And then lastly, the one steroid sparing trial reported the mean change from baseline in the ACQ, which they reported as .17 but this was not precise enough to exclude a null effect. Again, this is the study that used the 110 milligrams subcutaneous dose. In terms of quality of life, four RCTs reported a mean change in baseline on the AQLQ. As you can see, the pooled estimates at 16 weeks and 52 weeks showed significantly larger improvements for participants allocated to

Reslizumab compared to placebo. The pooled estimates were .24 and .21 respectively, again, smaller than the MID for this measure. And we graded this evidence as moderate quality. In the only steroid sparing trial, the mean change from baseline, the magnitude of difference between groups suggest larger improvement for participants allocated to Reslizumab, mean change is .25, which was consistent with the add-on efficacy trials. However, you can See this estimate. It's a smaller study, only 177. The estimate is less precise and thus failed to exclude a null effect. Three of the studies reported in MID response for the AQLQ. One RCT at 16 weeks reported significantly higher proportion of persons achieving and MID for Reslizumab, 64% versus 48% allocated to placebo. The risk ratio was 1.35. And in a pooled analysis of the other two studies at 52 weeks, again, significantly more participants achieved an MID response. Three of the add-on RCTs reported annualized rates of exacerbations. The rate was significantly lower for participants allocated to Reslizumab compared to placebo. The pooled rate ratio was .53, as you can see here, also excluded the null effect. And we graded this evidence as high quality. Three add-on RCTs also reported the annualized rate of exacerbations requiring ED or hospital visit and the pooled rate ratio was .73. Because again, these events occur with less frequency, the estimate was imprecise and could not exclude a null effect. Thus we graded this evidence as low quality. Three trials also reported the incidence of exacerbations more generally, and significantly fewer participants experienced an exacerbation with Reslizumab compared to placebo. The pooled risk ratio is .63 and excluded a null effect. In the one steroid sparing trial, which was again the trial that used a dose lower than the FDA approved dose, the annualized rate for Reslizumab of exacerbation was 1.51 compared to 1.86 for placebo, for a rate ratio of .82, which is again, a bit smaller in magnitude than the add-on efficacy trials from the previous slide. But it was also not very precise and could not exclude a null effect. In terms of steroid use, there's only one steroid sparing trial that reported this outcome. The study reported the difference in mean percentage dose change between Reslizumab and placebo. And so the active group had a 17.8% difference in mean percentage dose change. Although this larger dose reduction was observed, the finding was imprecise and could not exclude a null effect. Thus, we concluded the quality of evidence was low for no difference between groups. Moving on now to harms for Reslizumab. All seven trials reported harm outcomes. A pooled estimate for total

adverse events and serious adverse events showed no significant difference between groups. The pooled risk ratio for total adverse events was .92 and the pooled risk ratio for serious adverse events was .94. Alright, we're in the homestretch now. The last major grouping here is Omalizumab for CSU. We identified 10 studies. One was conducted in the US, the rest were conducted either in European countries or across multiple countries globally. Five studies enrolled participants aged 12 and up and the other five enrolled only adults. All the studies used placebo controls. And the doses used were either 300 milligram dose every four weeks or 150 milligram dose every four weeks. And there was one study that use a single 300 milligram dose. Nine of the ten trials were designed to assess the add-on efficacy of Omalizumab to standard CSU management, which is typically antihistamines and in some cases also included [indistinct] receptor antagonists. However, there was one study, which was a phase four post-marketing evaluation, where Omalizumab was given open label to all participants for 24 weeks, and then participants [indistinct] in the final two weeks were randomized to either continue Omalizumab or switch to placebo through week 48. We rated this study as high risk of bias for a variety of reasons and although results from it are included in the full report, I'm not going to really spend any time on that study in this presentation, for lack of time. So in terms of symptom control, we identified five trials that measured the urticaria activity score, or the USA7, at 12 weeks and three studies that measured it also again at 24 to 28 weeks. As a reminder, the UAS7 is a diary-based patient reported  measure that assesses the key sign of CSU, hives, and the key symptom, itch, each day. And the weekly score ranges from zero, which means no activity, to 42, which means intense activity. And the MID for this measure is about nine and a half points. So the pool difference in mean change from baseline at 12 weeks was -8.85 points and at 24 to 28 weeks it was -7.79 points. So close but not larger than the MID for this measure, which again is about nine and a half points. We graded this evidence as moderate quality. UAS7 remission is defined as a score of six or less and significantly more participants achieve remission based on that threshold at both 12 weeks. The pooled risk ratio was 3.09 across four RCTs. And also at 20 to 24 weeks, the pool risk ratio was 1.98 across two RCTs. And then UAS7 complete response is defined as a score of zero and significantly more participants achieved a response at 12 weeks. The pool risk ratio was 6.82 across four RCTs. And at 20 to 28

weeks, the pool risk ratio was 3.16. So we graded both of these outcomes as high quality evidence for Omalizumab being more effective than placebo. Moving on to quality of life, there were seven RCTs reporting the mean change from baseline and the DLQI, the dermatology life quality index, which that's a measure that includes 10 self-administer items concerning the impact of skin disease on different aspects of their life with a one week recall. And the scale ranges from zero, which is no impairment, to 30, which is the highest impairment. And the MID for this measure is 2.2 to 3.2 points. At the bottom of this plot, you will note that the pool difference in mean change from baseline here was about 3.55 points from the five studies that reported the study. So that estimate is above the MID for this measure. There were also a couple studies we couldn't pool. In those studies, the DLQI scores were all more favorable for the intervention group compared to the placebo group. So we graded the evidence for the DLQI measure as moderate quality. This plot happens to have a couple of the other measures that we didn't grade but they're very consistent with the DLQI. In terms of anti-urticarial medication use, there were six trials that reported this outcome but the measures used varied widely. Sometimes studies reported number of tablets per day, sometimes studies reported the mean days of use per week. And then sometimes studies reported usage based on individual medications used, like specific anti histamines. Others aggregated across multiple drug classes or multiple types of medication. So it's very hard to sort of come away with a single takeaway for this outcome. Essentially, we kind of concluded mixed findings. There were two trials that reported significant reductions in antiurticarial medication use for participants taking Omalizumab. And then there were two trials that reported less use but the findings were not statistically significant. There was one trial that showed a significant reduction in use for people taking 300 milligram dose, but not any significant difference for people taking the 150 milligram dose. And then finally, there was one study that reported less use in the Omalizumab group but didn't have any data for us to be able to conduct significance testing and they didn't report significance testing. So overall, studies seem to point in the direction of reduced use, even if some of them were not statistically significant. And thus we concluded Omalizumab was probably more effective than placebo but graded the evidence is very low quality. In terms of adverse events, pooled analysis from eight trials indicated no differences

between active treatment and placebo groups in total adverse events. The risk ratio was 1.7, which we graded as high quality and then the risk ratio for serious adverse events was 1.17 but was less precise with confidence intervals spanning .66 to 2.10. So we graded this finding as moderate quality. Okay, that was a summary of the published evidence. Now this slide briefly summarizes ongoing studies in this area. We identified 15 ongoing studies. 13 were related to asthma, two are related to CSU. Most of the studies were placebo controlled. We identified only one head to head trial currently ongoing that's comparing Omalizumab to Mepolizumab. This is a study that's being conducted in France and it appears to be sponsored by a health system with multiple hospital sites. And to kind of summarize things up here, so this is back to the top line summary heat map of findings. As a reminder, the drugs are along the left vertical axis, the outcomes domains are across the top, and the colors of the cells represent the quality of evidence - green for high, yellow for moderate, orange for low, red for very low. So for asthma, between 12 and 52 weeks follow-up, Benralizumab, Dupilumab, Mepolizumab, and Omalizumab and Reslizumab were more effective than placebo for controlling symptoms, improving quality of life, and reducing exacerbations, though the quality of evidence, as you can see, varied from very low to high, depending on the outcome and the agent. All of them but Reslizumab down here also appear to reduce steroid use. So Reslizumab was the one where we actually concluded no difference with low quality of evidence. In terms of adverse events, there were either no difference in adverse events or serious adverse events, or there were fewer events with the biologics compared to placebo. So that's the case for Benralizumab and for Mepolizumab. And I discussed some of the reasons for this particular finding earlier in the presentation. And then for CSU, which is the second to last row here, outcomes were measured between 12 and 60 weeks of follow up. Omalizumab was more effective than placebo for controlling symptoms, which was moderate to high quality, depending on the outcome, improving quality of life, which was high quality of evidence, reducing antiurticarial medication use, which was very low quality of evidence, and no difference in adverse events and serious adverse events. So the last point I'll make about this heat map is that you will notice there are no head to head trials for either conditions. So all this is mostly placebo controlled evidence. A few comments about subpopulations that might be of interest for asthma. The biologic

agents appear more effective than placebo among children, among adolescents, and adults. We did not have enough studies in children for any given agent to conduct any formal subgroup analyses though. For CSU, the agents appear more effective than placebo among adolescents and adults. And of note, no trials enrolled participants younger than 12. This slide summarizes a few of the limitations of the evidence base on the left and a few limitations of the review on the right. First, as I've already mentioned, we didn't identify any head to head trials. Most trials were industry sponsored and that is what mostly contributes to their moderate risk of bias ratings. Few of the studies report outcomes beyond one year. There were many statistically significant differences in effectiveness outcomes compared to placebo. But the magnitude of those differences may not be so clinically relevant for some of the outcomes for some of the drugs. As you saw, many of the comparisons, estimates of the mean change from baseline was less than the MID for that measure. This should probably not be interpreted as the drug not working, but rather the drug probably works well for some people and not so much for others since the mean change really is just the adverse effect across the population. Most of the studies use passive run-in phases, meaning there was no drug or placebo administered. And this was done to establish baseline frequencies, various symptoms. But several studies did use those run-in periods to optimize asthma management. So the variation in effects that are seen across studies may also be partly explained by whether management was optimized prior to the study start, as you might expect that effects would be smaller in those kinds of studies. And then lastly, our review is limited to studies in English and didn't include data from press releases or conference abstracts or posters. We did not attempt to make any indirect comparisons across the placebo controlled studies. However, I did want to mention results from two relatively recent network meta analyses. As you may recall, this type of analysis allows for indirect comparisons of active agents through a specialized type of meta-analysis of placebo controlled studies. Both of these analyses were focused on biologics for asthma and they included Benralizumab, Dupilumab, Mepolizumab, and Reslizumab. And they looked specifically at the outcome of asthma exacerbation among persons with severe eosinophilic asthma. Ramonell was published in 2020, included a search through July 2019. It included nine RCTs and Edris was published in 2019, included a search through 2018 and included

30 trials. But many of those were for biologics still under investigation or not approved for use in the US. Both of these analyses found that all drugs were significantly more effective than placebo for reducing exacerbations and identified no statistically significant differences in the indirect head to head comparisons. Okay, last slide. Just a few things regarding applicability of biologics in practice. So for asthma, the bulk of the evidence in the review was for persons with allergic phenotype asthma. And this is part of the drug labels for these agents but might also be worth including in any criteria that are established for use for these agents in asthma. The evidence establish the effectiveness of these agents without increased harms, as both add-on therapy to standard asthma controllers, which includes a lot of the things most of the studies allowed participants who were taking inhaled or oral steroids or long acting beta agonists or leukotriene antagonists theophylline or allergen immunotherapy. So standard asthma controllers. The evidence also suggests effectiveness when trying to use these as a way to facilitate reduction in oral or inhaled steroids. In terms of CSU, the evidence in the review established effectiveness probably without increased harm, just add-on therapy to standard CSU treatment, which, in these trials and the review typically meant H1 or H2 antihistamines, and in a few studies that also included people who were taking leukotriene antagonists. Other considerations for practice include the route of delivery, so Dupilumab, Mepolizumab, and Benralizumab are available in prefilled syringes or auto injectors that can be administered by patients themselves or by caregivers. At the time I gave this presentation to DERO in February, Omalizumab was not yet available for home administration. But since then, it now has become approved in a prefilled syringe. And so that is also now available for home administration. So Reslizumab is only available as an IV infusion. So that definitely has different applicability concerns in terms of administration compared to the others. Alright, I'm happy to take any questions or clarify any part of the presentation at this point.

Ginni Buccola: Leila, this is Ginni. I just want to say thank you. That was really detailed and organized and just echo to the committee, are there any questions before we go to stakeholders?

Susan Flatebo: Yeah, this is Susan Flatebo. Excellent presentation. But I had a question in regards to the adverse events of these agents. Were their patients who had to discontinue the drugs in the clinical trials because of harms? [indistinct] symptom control. I just mean, harms that were specific to the agents.

Leila Kahwati: Yeah. There were discontinuations due to adverse events. And believe we captured that in the full report. We captured that data. We didn't grade that data. But it is available in the full report if that is something you'd like to dig in. And there were, I don't remember off the top of my head, but there were discontinuations due to adverse events. I don't believe there was a large signal and there being a difference between after drug and placebo though.

Susan Flatebo: Okay, thank you.

Alex Park: This is Alex Park. Leila, thank you. It's an incredibly comprehensive overview. And I wanted to ask about the asthma phenotypes that was seen across all of the studies for these various agents. And I'm asking that because I guess when I think about this class of drugs, I sort of think about the Omalizumab is primarily allergic asthma and then the other biologics [indistinct]. Of course, many patients have a lot of overlap. But just in thinking about what the committee is about to do in terms of therapeutic interchange recommendations and so forth, would you say that across the studies, the asthma phenotype was fairly similar? Or did they very specifically sort out particular phenotypes for specific biologics?

Leila Kahwati: Yeah, I would say they're more similar across the body of evidence. So the inclusion criteria for studies, either they would typically - I'm talking about more than 90% of the studies - specified people with asthma who also had one or more chronic allergies, like dust, not seasonal allergies, per se, but chronic arrow allergens. And some studies also went as far as requiring people to have positive skin prick testing or evidence of allergies [indistinct] testing. And then some studies went a little step further and may have required, like a certain level of baseline of blood eosinophils. Some studies measured blood eosinophils at baseline. It didn't exclude people from participating but then they stratified their findings based on lower or higher levels of eosinophils. But I wouldn't say one biologic used one approach versus

another biologic. They all used a similar menu of options for characterizing the phenotype, if that makes sense.

Alex Park: No, it does. Thank you. And when you look at Omalizumab, I think it's dosed by IGE level.

Leila Kahwati: Yes, by body weight and IGE level, yes.

Alex Park: Body weight and IGE level. And so were IGE levels known in the other non-Omalizumab biologic studies? I guess what I'm asking is, would it be okay to think of Omalizumab as interchangeable with the other biologics?

Leila Kahwati: The other studies were more likely, I think, to measure eosinophils, than to measure IGE levels, specifically. Now, some of them may have reported IGE levels, but I don't recall off the top of my head. But Omalizumab, it is dosed based on IGE levels. So in terms of effects, though, they appear to me to be interchangeable in terms of their impact. And so I would probably consider them to be interchangeable. But Omalizumab is a different mechanism of action, though. And I haven't seen guidelines that express preferences for one over the other at this point that I'm aware of.

Alex Park: You know, I think you're right on that. There was one interesting study that I ran across getting ready for the meeting where they put people in mepolizumab after they had not gotten control on Omalizumab. They did pretty well. I guess it's not really a head to head. It's sort of a head after head trial. But it seems to indicate to your point, maybe these biologics, despite having different targets, could be considered interchangeable. Okay. Thanks, Leila.

Ginni Buccola: This is Ginni again. Are there any other questions for Leila? Okay. We'll go ahead then and move to stakeholders. So we have two stakeholders for this asthma biologics section. We have Long Nguyen with GSK and then Brandon Yip with Sanofi Genzyme. I'll let Leta go ahead and unmute Long. And you'll have three minutes to share. And if you could please introduce yourself and of course your affiliation, would be great. And I just want to double check, if you are intending to speak or thought you were on the list but I didn't call your name please raise your hand. Thank you.

Long Nguyen: Good morning. My name is Long Nguyen from GlaxoSmithKline providing comments on Nucala or Mepolizumab. So, Nucala was the first IO5 antagonist approved for the treatment of severe asthma with eosinophilic phenotype in 2015. Today, Nucala continues to be the only anti IO5 agent that is preferred on the Washington PDL. Even though there are many asthma biologics indicated for asthma for different types of biomarkers such as IGE and eosinophils, they are all different based on other FDA approved use in eosinophilic disease and therefore they are not interchangeable with Nucala despite the fact that they are all reduced blood eosinophil levels in various degree. I ask the committee to keep Nucala as a preferred anti eosinophilic agent because one, Nucala has the longest safety profile compared to other anti-IO5 agents. Two, Nucala does not deplete the patient's eosinophil level completely. And that is important because eosinophil plays a significant role in defending the body against parasitic infections. Nucala is the only asthma biologic agent that is approved for patients between six to 11 years old and it is the only agent that is also indicated for other rare eosinophilic conditions such as Churg-Strauss Syndrome, or EGPA. And on September of last year, Nucala received an FDA approval for HES treatment for patients 12 years of age and older. Now the current HES treatment options such as steroids, cytotoxic, and immunosuppressant agents are associated with adverse events and doesn't target eosinophils since eosinophils are a key mediator of tissue damages and flares. The HES approval was based on a randomized phase three prospective trial comparing Nucala plus standard of care and standard of care alone result in a 50% fewer patients on Nucala experienced HES flare with a p value of 0.002. The study also showed Nucala reduces annualized rate of HES flare by 66% with a 92% reduction in blood eosinophils throughout the trial compared to the placebo group. And finally, there were no new signals or adverse events identified. Therefore, with these key points I've mentioned previously, I ask the committee to recommend that Nucala remain preferred agent on the Washington PDL. And thank you very much for your attention and I will be happy to address any questions at this time.

Ginni Buccola: Thank you, Long. This is Ginni again, committee chair. Are there any questions from the committee for a Long Nguyen? Okay, thanks very much. We'll move next to Brandon Yip with Sanofi Genzyme and

Brandon, as soon as you're unmuted, you'll have three minutes. If you could just introduce yourself and give us your affiliation. Thank you.

Brandon Yip: Thank you, Ginni. This is Brandon Yip. I am a manage medical director representing Sanofi Genzyme today. And I just thank the committee for giving me the opportunity to make some brief remarks, very brief comments, after very extensive and comprehensive presentation on biologics and asthma. I just wanted to add, specific to Dupilumab, we are expecting publication of some six to 11 results at ETS next month and a launch in October. And those study results would very much align with our adolescent and adult data, looking at primary endpoints of reduced exacerbations and the secondary endpoint in reduction of FEV one. So I'll keep it short. And if there's any questions I'd be happy to entertain any questions.

Ginni Buccola: Thank you, Brandon. Committee, are there any questions for Brandon? Okay, it looks like we're ready to move to the motion.

Leta Evaskus: Hang on, Ginni. This is Leta. We have some hands raised. We have three. So first, I'm going to go to Kyle Downey. If you can tell us your affiliation. And it looks like you are self-muted. There you go.

Kyle Downey: Good morning, Washington State P&T. My name is Kyle Downey. I'm a medical affairs executive director with Genentech here to talk to you today about Omalizumab or Xolair. Xolair is actually indicated for three different indications. One is moderate to severe persistent asthma in patients six years or older with a positive skin test or in vitro reactivity to [indistinct] allergens who are not adequately controlled with corticosteroids. The second is for CIU for patients who are adolescents aged 12 years or older who remain symptomatic despite h1 antagonists. And the third in December of 2020, a Nasal Polyps indication for patients aged 18 years older. From the questions from Dr. Park, subcutaneous administration is the route of administration for Xolair and for both the asthma and nasal polyp indication, it's a sub Q dose based upon IGE levels as well as body weight. But for the CIU indication is a subcutaneous fixed dose every four weeks. Also, as mentioned from Dr. Kahwati's very thorough review, we recently had a self-administration indication as of April 12, so just this last week for the prefilled syringe to be really determined in consultation of either self-administration or caregiver

administration with the oversight of a health care professional. So Xolair is the only asthma biologic approved for both allergic asthma and CIU that is available in a prefilled syringe formulation. As an overall warning, Omalizumab carries a box warning for anaphylaxis and should be overseen by healthcare provider oversight overall. And I refer the committee to our package insert around the thorough review of both our efficacy and indications. Lastly, we respectfully ask that the committee look for the nasal polyp indication at a future meeting in order to do a P&T review. And with Dr. Park's comment of the overlap between allergic asthma and eosinophilic asthma, there are overlapping patients but there are also differentiated patients who may have both eosinophilic asthma or one or the other or allergic asthma. So it's a really key clinician variable. And, overall, we'd like the committee to consider that. So thank you for your time. Xolair has a long history of treating patients with both moderate to severe asthma, CIU, and now most recently nasal polyps and can be administered in a health care provider setting or within the self-administration indication as of this last week. We respectfully ask that you keep Zoeller as a preferred agent on the Washington State PDL. And I will open it up for any questions.

Ginni Buccola: Thank you, Kyle. This is Ginni. Are there any questions from the committee for Kyle? Okay. Leta, I'm sorry, I'm not able to see the hands that were raised. Can you go ahead and --

Leta Evaskus: This is Leta. It looks like they put their hands down. So if anybody else would like to speak on asthma biologics, please raise your hand now. Otherwise, I'll assume those two did not want to speak. Okay, Maria Agapova, I will unmute you now.

Ginni Buccola: When you start you'll have three minutes. Thank you.

Maria Agapova: Good morning. My name is Maria Agapova and I'm a senior medical outcomes liaison at Teva Pharmaceuticals. I'm here to provide information about Cinqair Reslizumab injection. Thank you so much for the opportunity to provide comments today and for providing access to Reslizumab to Washington Medicaid patients. For the full overview of Reslizumab safety, please refer to the prescribing information. Just a brief comment relating to a systemic corticosteroid burden that was mentioned in the report, wanted to bring to your

attention a post hoc analysis of patients pulled from two of breath trials, looking at Reslizumab effect on systemic corticosteroid burden that didn't make it on board. This study was published in the Journal of Allergy and Clinical Immunology Practice in February of last year by narrative colleagues and found significantly fewer new prescriptions were issued to patients taking Reslizumab versus placebo. And then total and per person systemic corticosteroid burden was lower among Reslizumab treated versus placebo treated arms. And this difference was also statistically significant. For the complete benefit and adverse events and points evaluated in this analysis, please refer to the full publication. That's all I had for today. Again, thank you for the opportunity. Thank you for the access. If there is time, I'm happy to answer questions. Otherwise, I yield the remainder of my time to the committee.

Ginni Buccola: Thank you, Maria. Are there any questions from the committee? Okay, thank you again. Do we have an additional one?

Leta Evaskus: Yeah. Michael Noonan.

Ginni Buccola: Okay. As soon as you're ready, Michael, you'll have three minutes to speak.

Michael Noonan: Thank you very much. And Leila, that was a wonderful representative overview. And I'm an allergist in private practice and was asked just to speak. I also did clinical studies. And I did these studies with almost all the biologics. And the real thing that it comes down to is our patients are individuals and they don't all react to the same ones the same way. So somebody could do really well on one biologic and then not do very well on the next biologic. So you get the mean of one. From a practice standpoint, I just want to say it's easier if we can change, if we need to, for our patients. And that's all I wanted to say. Thank you.

Ginni Buccola: Thank you very much. Committee members, any questions before we go to the motion, which I think we're ready to do. Alright and again, this is Ginni Buccola, committee chair. My committee members, since I can't see you, I'll just give maybe what feels like a little longer than normal for us to read and ask questions.

Leta Evaskus: Okay, this is Leta. One thing I want to point out with this motion is Dupilumab, that's grayed out because it is categorized under two drug classes. And so we have it under a topic dermatitis on the Washington PDL. But it can be used for therapeutic interchange and asthma biologics. And if Ryan Pistoresi, if you could talk more about that.

Ryan Pistoresi: Yes, good morning, this is Ryan Pistoresi. Because Dupilumab was included in this report but it is originally part of the a topic dermatitis class on the Washington preferred drug list, we wanted to include it here because you are reviewing enough evidence to make considerations about its safety and efficacy. As you see in the previous motion, we did not address it. So that is something for you as the P&T committee to consider whether it would be available for therapeutic interchange, whether it would be available to be a preferred drug for this indication, whether it would not be allowed to be preferred for therapeutic interchange with certain drugs. So, really, we wanted to bring it up here because it was being reflected in the report. And it will be reflected in the cost analysis for these drugs. But it will still be included in the A topic dermatitis drug class. And one of the other reasons for including it in that drug class instead of bringing it over here is that we did look at the utilization. And it does look like most of our Dupilumab utilization is for that indication, though there is some use in both A topic and asthma together. So if you have any other questions about what this means, including it here or maybe about what you may think of for the motion, I can help guide you in that.

Alex Park: Thanks, Ryan. It's Alex Park here. So just to confirm, I would be in favor of putting Dupilumab on the motion for therapeutic interchange. But if we did that, would that affect its hierarchy level in the A topic dermatitis world?

Ryan Pistoresi: That's a great question. So this is Ryan again. We would be able to have the therapeutic interchange specific for this asthma indication. So you'd have to note that maybe one sentence after the other current therapeutic interchange where it says therapy, interchanging the Washington preferred drug list. You could then have a separate sentence following it saying, Dupilumab can be subject to therapeutic interchange or with other asthma biologics for the treatment of asthma on the Washington preferred drug list, or something to that nature to then make it very clear that we would not be able to

substitute another one of these asthma biologics when it is being approved for A topic dermatitis. And this other drug would not be approved for that.

Alex Park: Thank you. It's Alex Park again. Well, here's another question. I remember reading on the PDL therapeutic interchange guidelines the immunosuppressants are generally not felt to be a class that can be subject to interchange. Does that not apply to this class?

Ryan Pistoresi: So this is Ryan. Again, that's a good question. I think what you may have been reading, and we may have to confirm it, but those are protected drug classes. So that means that if someone were already started on a drug and this was a refill that they have their refill be protected. So if someone were already established on one of the refill protected drug classes, we wouldn't be able to do that substitute. That would only really occur at the initial one. If this were their first therapy, that therapeutic interchange may occur.

Alex Park: I see. So you're saying that if you're a patient and you've been on, let's say, Mepolizumab and you're new to an insurance that is under the auspices of the HCA here, for that first refill-- well, I guess I don't understand what you're saying. Could you explain it again? Sorry.

Ryan Pistoresi: Sure. So, there are certain drug classes that are considered refill protected on the Washington PDL. And I believe they're antidepressants, anti-epileptics, anti-psychotics, antiretroviral, chemotherapy, immunomodulatory for Hep C, and the immunosuppressives. And it just means that if someone were to be already established on it and then come into one of our health plans, that their refills would be protected and not subject to therapeutic interchange, meaning that if someone were started on a non-preferred drug, nonpreferred relative to the Washington, PDL, and then they came in and were subject to a drug class in which therapeutic interchange could apply, that it would be protected and that they would be able to continue with their non-preferred drug, not subject to therapeutic interchange.

Alex Park: I see. Okay. But if I were a patient who had always been under an HCA auspice insurance and newly developed allergic asthma then potentially, for one of these agents, I couldn't be subject to a

therapeutic interchange if I'm being prescribed by an endorsing provider.

Ryan Pistoresi: This is Ryan and yes, correct. That's how I understand it.

Alex Park: Okay. Thank you.

Ginni Buccola: And this is Ginni, committee chair. I just wanted to add that I support Alex's suggestion of that wordsmithing in terms of the Dupilumab being added. Are there other thoughts from committee members on that?

Leta Evaskus: This is Leta. Alex, did you want to add it as another sentence as a therapeutic interchange? Or do you want to just add it to this list of drugs right here?

Alex Park: Well, this is Alex Park, I think the motion would be cleaner if we added it to the list. But I think what I'm hearing from Ryan is that it would be useful for us to have it as a separate line item to protect HCA's ability to monitor that medication into the topic dermatitis indication. Is that what you're saying, Ryan?

Ryan Pistoresi: So this is Ryan. I know for other motions that we've done in the past for other drug classes in which we wanted to make certain things clear, we would add in a separate paragraph after and then include specific information. So one thing that you could do is really copy and paste that, remove the list of drugs and just make sure that it says that it's safe and efficacious for the treatment of asthma, rather than just saying the approved indications. Because then atopic dermatitis is an approved indication for that. And that's trying to be captured in the separate motion for that drug class and that review. But really I think that depending on the language that you use and how clear it is, I think we would be able to take the intent that you have for the policy and then apply it to the agency director's memo where we make the decision.

Alex Park: Okay, this is Alex Park. So what if we were to do in the last sentence Benralizumab, Mepolizumab, Reslizumab, and Dupilumab can be subject to therapeutic interchange in the Washington preferred drug list under the indication of biologic drugs of asthma urticaria.

Ryan Pistoresi: I think that would work.

Amy Irwin: Hey, Ryan, this is Amy. The motion already says for the treatment of asthma. So do we need to clarify that a second time?

Ryan Pistoresi: Oh, you're right. It does say that above. I just was looking for approved indications down below. We might need to put “urticaria” because I think this drug class was originally just for asthma and then we added urticaria. And then I can look to our DERP representative to confirm that.

Leila Kahwati: This is Leila. So the review we did included it for chronic spontaneous urticaria, specifically or chronic idiopathic urticaria, specifically, not urticaria broadly.

Ryan Pistoresi: This is Ryan. Great. Thanks for that. We'll add that into the motion to make sure that it's clear.

Alex Park: This is Alex Park. And to just be clear, I felt the data from Leila really was convincing that all of these drugs, including omalizumab, are basically -- the data is pretty effective for all them and safety wise, not a big concern. But I am thinking the committee previously did not include it in the TIP listing primarily because of the logistics involved with getting IGE levels and so forth. Am I correct in thinking that?

Ryan Pistoresi: So this is Ryan. I'm trying to remember. I'm not familiar with the last time this was reviewed back in 2019. I can see if I can do a little bit of digging right now. But I don't know if I'll be able to find it.

Leta Evaskus: This is Leta. The last time Dupilumab was grayed out because it said it couldn’t be considered for the PDL. So I don't know if at that time if it was not reviewed. And maybe Laila, you can confirm.

Ryan Pistoresi: This is Ryan. Yeah, yeah, it was a surveillance document. So the last time that we did this drug class at P&T, it was a surveillance document. We added Dupilumab to the class but we didn't have any evidence synthesis or evidence presentation at that time, since it was a surveillance document. As you know, those are typically saying, here's how many studies have been done. Here's where the evidence

is going. And then from that document that we had in 2019, we decided to commission the full report, which then was presented at this meeting. So this was really the first time that we've been able to look at the level of evidence, the quality of evidence, the quality of the effects of Dupilumab in relation to these indications. So that's why it's being added today.

Leta Evaskus: Okay, so then it is available to be preferred.

Ryan Pistoresi: Yes, yeah. This is Ryan again. So we have had enough of an evidence review so that it can be considered eligible to be preferred for these indications.

Leta Evaskus: Okay, so Alex, do you want to add it up above as well?

Alex Park: This is Alex Park. Sorry, guys. I may have misspoken. What I was asking about was why the committee did not put Omalizumab in the TIP list on the prior motion, not Dupilumab. And I'm thinking it was because of the logistics involved with IGE levels and so forth, making it a little bit tricky for pharmacists to just switch that out for a different IO five agent. And if that was the reasoning, I'm comfortable leaving that off the TIP, even though I feel the data is fairly bland on all of them being equal and safe.

Ryan Pistoresi: So this is Ryan again. Do you think it's between the allergic asthma versus the eosinophilic?

Alex Park: Right. I mean, as we've been talking about the phenotypes crossover a lot, so practically speaking, I think in terms of efficacy and safety, it seems okay to put it on the TIP list. But then thinking of it in terms of being a pharmacist, working with an endorsing provider, I could see why it would be hard for them to switch, say, Benralizumab, to Omalizumab because you might not have an IGE level and so forth for dosing. So if that's why the committee did not include it, I think that makes sense.

Ryan Pistoresi: This is Ryan again. I think we would have to look prior to that 2019 meeting, since that was just a surveillance. And we probably had the more in depth review at maybe a 2018 meeting on this. And so yeah, we would have to look through the transcript and try to find what the

discussion was for that. But I'm thinking you're probably along the right lines of saying that maybe the level of evidence wasn't as strong back then and really, that they didn't want to cross between the studies on the allergic versus the eosinophilic. So maybe that is a reason to be cautious today, given that it was in the previous motion.

Alex Park: Sure. And I feel ready to go ahead and make the motion and I'll let other committee members jump in or object if they feel that omalizumab should be included. But the motion as is I feel looks pretty solid.

Leta Evaskus: This is Leta. I have a question before we go on, Alex. If Dupilumab is going to be listed for therapeutic interchange, doesn't the committee need to say that it is safe and efficacious as well?

Alex Park: Oh, yeah, we probably should. I agree.

Leta Evaskus: Ryan, do you see any issues?

Ryan Pistoresi: This is Ryan. Yeah, I think you would want to add that in there just to make it clear that it is safe and efficacious. And also at the line above where it says, for the treatment of asthma, we may also want to add in that chronic, spontaneous urticaria as well. And then that way, we're just being very complete with this motion.

Alex Park: Is that in a good place now, Leta?

Leta Evaskus: I believe so. I'm trying to get this little thing off of here.

Ryan Pistoresi: This is Ryan. I think once you start typing by motion it will go away.

Leta Evaskus: Yep. There we go. Thanks.

Alex Park: Okay, this is Alex Park. I'm going to read this fast, Ginni, because I know we're behind schedule. So here we go. Alex Park here moving that after considering the evidence of safety, efficacy in special populations for the treatment of asthma and chronic spontaneous urticaria, I move that Benralizumab, Dupilumab, Mepolizumab, Omalizumab, and Reslizumab are safe and efficacious for the treatment of their approved indications. Benralizumab, Dupilumab,

Mepolizumab, and Omalizumab can be subject to therapeutic interchange in the Washington preferred drug list for asthma and chronic spontaneous urticaria.

Ginni Buccola: This is Ginni Buccola and I'll second. And thank you for saying all the drug names, Alex. If all the committee members have their microphones on, we'll go ahead and make a motion. All in favor, please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? Alright, the motion carries. So let's see, we're at 10:55. We're going to take a ten minute break.

Leta Evaskus: Yeah. Do you want to shorten it to five minutes or do you want ten minutes?

Ginni Buccola: Five minutes is fine. Anybody have any concerns with that? Alright, we'll come back at 11.

Leta Evaskus: Okay, thank you.

[break]

Ginni Buccola: This is this is Ginni. Are we all back and ready to reconvene? It looks like next on the agenda is the TIMs class with plaque psoriasis, psoriatic arthritis, Crohn's Disease, and ulcerative colitis and rheumatic arthritis and ankylosing spondylitis. And we have both Candi Wines and Shauna Durbin with DERP giving us presentations.

Candi Wines: Hello, this is Candi. Would you like me to get started?

Ginni Buccola: Yeah, that would be great, Candi, if you're ready to go.

Candi Wines: Okay, great. And you will be controlling the slides on your end, is that correct?

Leta Evaskus: This is Leta. Yeah, I have them unless you want to present them.

Candi Wines: Not, that's okay. Thank you.

Leta Evaskus: Okay. Just say next slide when you want me to go on.

Candi Wines: Sure. Well, good morning, everyone. I'm pleased to share with you the topic brief for targeted immune modulators for the plaque psoriasis and psoriatic arthritis indications. The aim of this topic brief was so briefly identify eligible randomized controlled trials and non-randomized studies published or registered in clinicaltrials.gov since the most recent full report on the subject was completed. Next slide, please. This slide shows the overview and flow for today's presentation. And I'll begin with a brief definition of the two conditions and the class of drugs you'll be hearing about. Next slide please. Plaque psoriasis and psoriatic arthritis are chronic inflammatory conditions and targeted immune modulators or TIMs are a group of medications that selectively block the mechanisms involved in the immune response associated with these conditions. The first TIM was FDA approved in 1998. Since then, many additional agents, including biosimilars have been approved. The most recent full DERP report on TIMs for plaque psoriasis and psoriatic arthritis was done in March of 2020. This topic brief identifies new publications since that full report. Next slide please. This slide and the next three slides describe the populations, interventions, competitors, outcomes, and study design criteria used to screen the literature for this topic brief. The populations were adults with plaque psoriasis or psoriatic arthritis. We considered TIM agents that are FDA approved for these conditions or that are in the pipeline for approval. The specific drugs we considered will be shown on the upcoming slide. For competitors, we selected studies that compared one FDA approved TIM agent to another agent in a head to head comparison. And for pipeline drugs, we also included placebo or standard of care comparisons. Next slide please. This slide shows the TIM agents that we considered for this topic brief. There are a total of 27 eligible agents. However, the biosimilar products are not shown on this slide. The agents that have biosimilars are indicated with an asterisk. The blue boxes show agents that are approved for use in both plaque psoriasis and psoriatic arthritis. The agents in the green boxes are approved for only plaque psoriasis. Those in the pale yellow boxes are approved for psoriatic arthritis. And the agents in the white boxes are not yet approved for either condition. I will note that Upadacitinib, a Janus kinase inhibitor is FDA approved for rheumatoid arthritis, not

yet approved for psoriasis or psoriatic arthritis. Next slide please. For outcomes, we selected studies that reported on measures of disease remission, clinical improvement, quality of life, adverse events, serious adverse events, and other health outcomes. Next slide please. And finally, for study designs, we selected randomized controlled trials of 12 weeks or longer duration. For harms, we also selected cohort studies at least 12 weeks in duration and with at least 1000 participants. Next slide please. This is a summary of the key questions for the topic brief. Key question one is about the comparative effectiveness of the TIM agents for plaque psoriasis or psoriatic arthritis. The second is about the comparative harms of the agents. And the third is about variation by subgroups such as age, race, gender, and patients with comorbidities. And we also collected characteristics on ongoing studies. Next, please. To conduct this topic brief, we use the standard DERP methods. We searched Medline, inclusive of May 2019 through March of 2021. We also searched clinicaltrials.gov for completed but not yet published and ongoing studies. All searches were limited to studies published in English and conducted with humans. And additionally, we conducted surveillance for new publications through March 31 of 2021. Next slide please. We will be moving on to the findings. Next please. With respect to randomized controlled trials, we identified a total of 16 new articles representing 13 unique studies. That's the prior report. Nine of the studies are new RCTs whereas four of them were included in the prior report, and additional data are now available. Seven of these RCTs aim to evaluate TIMs for plaque psoriasis. The remaining six evaluated TIMs for psoriatic arthritis. 11 RCTs evaluated head to head comparisons and two RCTs were placebo controlled trials. The sample size across all RCTs ranged from 54 to 1704. And the study duration ranged from 12 weeks to 52 weeks. 12 of the RCTs reported disease remission or clinical improvement outcomes. 10 reported safety outcomes and seven reported quality of life outcomes. Work productivity and function were reported in one study each. Next please. This slide and the next four slides are here for your reference. I will not cover them in great detail. But briefly, I'll describe what information is presented in this table. The studies are grouped according to indication starting with plaque psoriasis, followed by psoriatic arthritis studies. The information captured includes the author and year for each publication, the national clinical trials number, and the trial name in the leftmost column. The center three

columns convey study characteristics, such as drug and comparator, doses and frequencies, sample sizes and length of follow-up. On the far right column lists the eligible outcomes reported in each study. If we could go straight to slide 16, please. Thank you. Our search for cohort studies reporting harms outcomes yielded four eligible studies. Three of them evaluated TIMs for both conditions and one examined TIMs among plaque psoriasis patients. Three are new analyses from registries or data sources included in the previous report. One analyzes data from a new source, just multiple Swedish registries. The sample sizes ranged from 1955 to 69,873. And the outcomes, three of the studies analyzed the risk of infections and one study analyzed the risk of major cardiovascular events. Next please. This slide and the next one show the characteristics of the four cohort studies. As with the previous table, I won't go into great detail but I'll describe the information. In the far left column, you'll see the author and year and the study or registry name. The eligible drugs evaluated in this study are listed in the next column, followed by study characteristics then outcomes. And we can go to slide 19, please. Next I'll summarize the results of our search for ongoing studies. Among the ongoing studies, eight were randomized controlled trials of TIMs for plaque psoriasis. Completion dates listed for these studies ranged from January of 2020 through October of 2022. Sample sizes ranged from 180 to 1484. Half of the plaque psoriasis studies were head to head comparisons of pipeline drugs versus FDA approved drugs. Next slide please. We identified four ongoing RCTs of TIMs for psoriatic arthritis. The completion dates listed for these range from December 2021 to August 2022. The sample sizes ranged from 180 to 840. There were two head to head comparisons, one comparing a pipeline drug with an FDA approved drug and one comparing two FDA approved drugs. Next slide please. Before ongoing cohort studies we identified correlate data from either Germany, Korea, Spain, or multinational registries, and each study plans to analyze data for adverse events and/or serious adverse events. Next slide. The final slide provides an overall summary of the recently published literature on targeted immune modulators for plaque psoriasis and psoriatic arthritis. In summary, we identified 17 recently published studies, 13 RCTs, and four cohort studies. Four of the RCTs are included in the previous report and new data are now available for these studies. 11 of the 13 RCTs are head to head comparisons and two are placebo controlled trials. Three of the four cohort studies reported on rates of infection

and one reported on rates of major cardiovascular events. When added to the 38 studies included in the previous report, the cumulative body of published evidence for TIMs and plaque psoriasis and psoriatic arthritis is 51 studies. Then we also identified 16 ongoing studies, eight randomized controlled trials for plaque psoriasis, four RCTs for psoriatic arthritis, and four cohort studies. Among those RCTs, eight are head to head comparisons and four are placebo controlled trials. Next slide, please. Thank you for your attention. And I'll take questions if you have any.

Ginni Buccola: Thank you. This is Ginni. Committee members, are there any questions? Okay. Candi or Shauna, is that the end of that content or do you have another section of slides for us?

Leta Evaskus: This is Leta. There's three sets of slides and we're going to go through all of them before we hear stakeholders.

Ginni Buccola: Thank you. Okay.

[unrelated discussion]

Shauna Durbin: Hello, everyone. My name is Shauna Durbin. I'm a research associate at the Center for Evidence Based Policy. Today, I'll be leading you through our surveillance findings on targeted immune modulators for the treatment of Crohn's Disease and ulcerative colitis. This is the first two such presentations we'll be doing. Next slide please. So like Candi did in the last presentation, this will follow a fairly standard format for surveillance or topic briefs. I'll go over some topic history and some background, follow that up with the methods that we use to conduct this surveillance activity and then I'll present a summary of the findings. Next slide. So beginning on the bottom line of the table on this slide, you can see that the original systematic review for this topic was completed in 2005. Today's presentation marks the first surveillance report since the seventh and most recent update for Crohn's and ulcerative colitis that was completed and presented in February of 2020. And that included searches through August of 2019. This surveillance report includes information available from September 2019 through January of 2021. Next slide. I think Candi did a great job covering what targeted immune modulators or TIMs are. So I think we can just move past this slide and just say that they are

disease modifying drugs. So a little bit of background about Crohn's and ulcerative colitis, they're both chronic inflammatory bowel conditions. As you can see in the figure on the right hand side of your screen, they both affect the GI tract, but they do so in distinctly different ways. So in people with Crohn's Disease, inflammation can occur intermittently throughout the digestive tract involving full thickness of the bowel wall. In contrast, ulcerative colitis generally manifests as continuous inflammation of the colon and rectum and only affects the innermost lining of the bowel. Despite their clinical difference, treatment goals for both conditions include controlling inflammation, maintaining remission, preventing complications. TIMs are generally prescribed for people who have moderate to severely active Crohn's Disease or ulcerative colitis and who haven't responded to conventional therapies. Next slide. On slide five, we're going to begin our description to the PICOS that we use to conduct this review and guide our surveillance activities. The target populations report we're adults with Crohn's Disease or ulcerative colitis. I did want to note that both of these conditions occur in children and there are several TIMs that are approved for use in pediatric populations. [indistinct] you can see the two figures in the bottom of the slide from a longitudinal study of IBD incidents in Minnesota. The majority of people with Crohn's Disease and ulcerative colitis are diagnosed in early adulthood. Next slide. So slide six is the first of two slides that describe the numerous TIMs reviewed for this report. The table shows both generic and brand names of the drug followed by the mechanism of action and the route of administration, and then the approved populations relevant to this report and then the date of FDA approval. So as I explained earlier, TIMs work by selectively blocking mechanisms to be involved in the inflammatory response. So of the TIMs that we evaluated for use in Crohn’s Disease and ulcerative colitis, there are currently four primary categories of inhibitors. The largest group by far are TNF Inhibitors.. So this includes Adelimumab, Certolizumab Pegol, Golimumab, and Infliximab. And there are several biosimilars available for both Adelimumab and Infliximab. So our list of included interventions continues on slide seven. Next slide. Natalizumab and Vedolizumab are both FDA approved alpha for integrant inhibitors, Tofacitinib and Upadacitinib and Peficitinib are all Janus kinase inhibitors. Tofacitinib is FDA approved for ulcerative colitis, whereas Upadacitinib and Peficitinib are currently being evaluated for our target conditions. Finally, Risankizumab,

Ustekinumab, and the Pipeline drug with model number PF-04236921 are all selective interleukin cytokine inhibitors. Ustekinumab is currently FDA approved for the treatment of both Crohn's Disease and ulcerative colitis, whereas Risankizumab and the pipeline drug are currently being investigated for both conditions. Next slide. So now on to our comparators. So you can see [indistinct] drug approval status. Studies of FDA approved TIMs are only eligible for inclusion if they were compared with another one of the listed interventions for [indistinct]. In contrast, we included studies of pipeline drugs that were compared with another listed TIM intervention, placebo, or usual care. Next slide. Slide nine, you'll see research for a range of health outcomes and harms. Some included disease specific outcomes such as disease remission, flares, and disease specific mortality. They looked for some broader quality of life elements. And we also looked at harms and overall and some specific adverse events such as malignancies and opportunistic infections. Next slide. Finally, on slide ten you'll see that for comparative effectiveness, we limited study designs to randomized controlled trials with minimum 12 week study duration. For harms outcomes only we included retrospective and prospective cohort studies that compared one intervention to another in addition to these RCTs. So the cohort studies were required to have a study duration of at least 12 weeks and include a minimum sample size of 1000 participants. Next slide. So in scope, the past report included three key questions. The two questions one and two evaluated the comparative effectiveness and harms of TIMs for the treatment of Crohn's Disease and ulcerative colitis. And key question three assessed whether the effectiveness of the included interventions varied by subgroups. This could include things such as age, race, ethnicity, sex, comorbidities, or concurrent therapy with other treatment types. Although not included as a formal key question in the last report, the primary review update also summarized the characteristics, ongoing studies, which is also an important component of the surveillance report. So we did look at ongoing studies. Next slide please. Our surveillance search methods include three main activities. First, using drug names and keywords. We search clinical trial sites to identify proud numbers of potentially eligible ongoing studies. We used those trial numbers to search for newly published RCTs and comparative cohort studies of harm in OVID MEDLINE and Google Scholar. And then finally, we reviewed several websites and databases, primarily the FDA and IPD analytics

to identify new FDA actions such as approved drugs, formulations or indications or any new serious warnings or harms. Next slide. The next few slides are going to detail our surveillance findings including both clinical evidence and FDA action. Next. First we'll take a look at the clinical evidence. Next slide. So our searches yielded no new published eligible RCTs or observational studies of harms. However, we did identify 14 ongoing studies of TIMs for Crohn's Disease and ulcerative colitis. Ongoing studies included six head to head studies of approved interventions, four of which included comparisons with Ustekinumab and two included Vedolizumab. We also found eight placebo controlled studies of unapproved interventions, four that evaluated Upadacitinib and four that evaluated Risankizumab. Next slide. Now I'll review our FDA actions that occurred since the last review. Next slide. During this surveillance period, the FDA approved for new biosimilars, which were all TNF alpha inhibitors for the treatment of both Crohn's Disease and ulcerative colitis. Avsola, which was approved in December of 2019 is the fourth biosimilar, Infliximab and was approved in patients ages six and older. So there's a pediatric population. Hadlima, Abrilada, and Hulio are all biosimilars of Adalimumab that were approved for adults only between July of 2019 and July of 2020. It should be noted that there may be published clinical evidence on these biosimilars that we would include in a report. But we didn't search for studies on these drugs during the surveillance period because they weren't part of the previous scope. Finally, we didn't identify any new formulations, existing drugs. Next slide, please. We did, however, identify four new indications. In late 2019 the FDA added children aged six and older with ulcerative colitis to the list of improved indications for all infliximab biosimilars. At the time, this included Renflexis, Inflectra, and Ixifi but this also now applies to Avsola. In December of 2019, the extended release formulation of Tofacitinib or Xeljanz extended release was approved for treatment of adults with ulcerative colitis. In practice this means that certain individuals treated with twice daily Xeljanz may switch to once daily treatment with Xeljanz extended release. Next slide. Now we'll move into a discussion of harms that we identified, new harms and warnings. In March of 2020, the FDA issued new warnings for Vedolizumab regarding increased risk of progressive multifocal leukoencephalopathy, PML is how I refer to that, which is an opportunistic viral infection of the brain that can lead to severe disability or death. Warnings were also issued for infusion related and

hypersensitivity reactions, all for Vedolizumab. Second, in May of 2020, the FDA issued a contraindication for Infliximab and all biosimilars. This includes the newly approved Avsola and this is at doses greater than five milligrams per kilogram in patients with moderate to severe heart failure. This warning was prompted by an RCT that observed significantly higher rates of cardiac related adverse events and participants with heart failure who received either a five milligram per kilogram or ten milligram per kilogram dose of Infliximab compared with placebo. Next slide, please. So in June of 2020, the FDA updated and existing black box warning for Natalizumab with specific clinical risk factors for PML, including presence of anti-JCV, standing for John Cunningham Virus antibodies, treatment duration with Natalizumab of greater than two years and prior use of immunosuppressants. Finally, in December of 2020, the FDA issued a warning to monitor all patients treated with Ustekinumab for signs and symptoms of posterior reversible encephalopathy syndrome, PRES. And this is after two cases were reported in clinical trials. Next slide. So I'm going to summarize all of this information together pretty quickly. Next slide, please. As you'll recall, in terms of new clinical evidence, we found no new original published studies. We did, however, identify 14 ongoing studies that included six head to head studies comparing the effectiveness and harms of TIMs that are already approved for the treatment of Crohn's disease and ulcerative colitis. We also found eight placebo controlled studies of TIMs for agents that are not yet approved for our target conditions. Next slide. Finally, FDA activity was fairly robust during the surveillance period. We identified four new biosimilars, one for Infliximab and three for Adalimumab and we rerecorded for new indications, namely pediatric UC with three Infliximab biosimilars and extended release Tofacitinib in adults with ulcerative colitis. And our FDA summary continues on the next slide where we see that we found four new warnings issued during the surveillance period. And we did not identify any drug formulations. So this is our presentation today. There are three more slides that are DERP specific so if we could just skip through those to questions slide, I will take questions.

Ginni Buccola: This Ginni. Just want to say thank you for the report and make sure the committee has opportunity to ask questions. Okay, sounds like we're good ready to move to the third chunk of information.

Leta Evaskus: This is Leta. I'm pulling it up now.

Ginni Buccola: Thanks, Leta. Thanks, Shauna.

Shauna Durbin: Okay. So, same process, different target conditions. We're going to be looking at targeted immune modulators for rheumatoid arthritis and ankylosing spondylitis. This is a surveillance report. So next slide, please. Again, it's good to follow the exact same methodology as the last report. So let's move to the next slide where I will again say that this surveillance follows the seventh the most recent update of TIMs for rheumatoid arthritis and ankylosing spondylitis. It was completed and presented in April 2020 with searches through September of 2019. So this surveillance report includes information available for September 2019 through February of 2021. Next slide. Again, we've heard a lot about TIMs today so I think we can move past this. And then for a little bit of background of our target conditions, rheumatoid arthritis and ankylosing spondylitis are both painful chronic inflammatory disorders of the joints that lead to progressive disability. So as you can see on the right hand side of your screen, rheumatoid arthritis or RA is how I'll refer to this is an autoimmune disorder that attacks the tissues that line the joints that are called the synovial tissues, causing painful inflammation. Over time, the joint tissues thicken and fluid builds up, leading to bone erosion and joint misalignment. And this occurs most often in the hands and feet. So in contrast, ankylosing spondylitis is a form of inflammatory arthritis that primarily affects the spine. So in people with AS, joints in the spine become inflamed and stiff. And this often begins in the sacroiliac joints at the base of the spine. And this stiffness progresses throughout the body. In advanced cases, ankylosing or new bone formation in the spine can occur, and it can cause parts of the spine to actually fuse together. So despite their differences, treatment goals for both conditions include controlling inflammation and maintaining remission and then preventing complications often with medications like TIM. Next slide. Slide five, we'll begin our description of our PICOS that we used to conduct this review. The target populations for this report more of course, adults with rheumatoid arthritis, hereafter RA, or adults with ankylosing spondylitis, from here on out, AS. From the bottom half of the slide, I've provided figures that illustrate the effects of the advanced cases of these conditions. You can note the joint misalignment in the hands with RA on the left side, and then the

fusion in the spine with AS on the right hand side of the screen. Next slide. So, slide six is the first of two slides that will describe our TIMs that we reviewed for this report. Very similar to the table that I presented in the last presentation. So as I explained earlier, TIMs work by selectively blocking these mechanisms known to be involved in the inflammatory response. So of the TIMs that we evaluated for use in RA and AS, there are currently five primary categories of inhibitors. So the largest group and those that are primarily presented on this slide includes our tumor necrosis factor alpha inhibitors, which includes Adalimumab, Certolizumab pegol, Etanercept, Golimumab, and Infliximab. Of these, biosimilars are available for Adalimumab, Etanercept, and Infliximab. These make up the majority of the included interventions. Next slide please. So the second group are selective interleukin cytokine inhibitors, which include [indistinct], Sarilumab, and Secukinumab, and Tocilizumab. The third group would be Janus Kinase inhibitors, or JAK inhibitors, which include [indistinct], Tofacitinib, and Upadacitinib. And the fourth group [indistinct] inhibitors, which includes only [indistinct]. And finally as the last group, our CD 20 antibodies, which includes only Rituximab. Next slide. We also looked for information regarding four pipeline drugs. The first drug with the model number ABBV-3373 is a TNF alpha inhibitor that's currently being investigated for RA Bimekizumab is an interleukin cytokine inhibitor being investigated for RA. And then finally, Filgotinib and Peficitinib are both Janus Kinase inhibitors that at the time of the last report update were under investigation for RA and AS. Since that time, the manufacturer of Filgotinib has withdrawn their FDA application for RA and halted enrollment into AS trials. I'll discuss this at greater length in a few slides, but we wanted to make sure to note that there have been some changes to the TIMs landscape up front. Next slide please. So this follow the same competitors as the last reports. For FDA approved drugs, they must be compared with another TIM and pipeline drugs can be compared with another TIM, placebo, or usual care. Next slide. Again, we looked for a wide range of health outcomes and harms. Some disease specific ones specific to RA and AS would be swollen or tender joints or rebounds and flares and steroid withdrawal. Next slide please. Finally, on this slide, you'll see that for comparative effectiveness, we limited our study designs to randomized controlled trials with a 12 week study duration, same as the last two reports. And then we also included comparative retrospective and prospective

cohort studies for harms outcomes only. Next slide, please. This review has four key questions. The first key questions and I'm sorry, there is a typo on this slide. But I assure you that we looked for comparative effectiveness TIMs for RA and AS for both and then the comparative harms of TIMs for RA and AS, not Crohn's Disease and ulcerative colitis. The third key question was about subgroups. A subgroups could include age, race, ethnicity, sex, comorbidities, concurrent therapy with other treatment types, and disease progression. And then for key question four we summarized the characteristics of ongoing studies. Next slide. We already discussed what our main surveillance methods were but in summary, we searched trial registries for registered trials. We search for publications in OVID MEDLINE and Google Scholar. And then we look to some websites, mainly the FDA for new FDA actions. Next slide. Now we'll move into our actual findings and we'll detail both clinical evidence and FDA actions. Now we'll take a look at the clinical evidence. Next slide. So our clinical evidence searches yielded three new RCTs that were published since the last report update. The 24 week select choice trial compared the effectiveness of Abatacept and extended release Upadacitinib in 613 participants with moderate to severe RA. This is to our knowledge, the first published study of this comparison in RA and is therefore considered to be a meaningful study. Next, the 48 week R4RA trial compared the effectiveness of tocilizumab and rituximab in 164 participants with RA, who all had an adequate response to at least one prior TNF alpha inhibitor. Again, we've determined this to be the first study of this comparison RA and consider it to be very meaningful. The final RCT that we identified was the 52 week Finch 3 trial which evaluated the effectiveness of Filgotinib in combination with methotrexate compared with Filgotinib or methotrexate monotherapy. And this was performed in 1,252 participants with RA. This is the fourth published trial of Filgotinib in this population. Next slide. So in terms of ongoing studies, we identified 24 ongoing studies of TIMs for RA or AS. 16 studies are head to head trials of FDA approved TIMs, four studies are placebo controlled trials of pipeline drugs, and then four are harms only comparative cohort studies. The majority of studies, that would be 18, include only participants with RA, five studies included participants with AS only, and then one study included participants who had either RA or AS. Some sample sizes in the ongoing studies ranged from 20 to nearly 10,000 participants and are slated for primary completion

between 2019 to 2025. In our estimations, seven of these studies are likely to publish sometime in 2021. Next slide please. We'll now review our new FDA actions that occurred since the last review. Next slide. During the surveillance period, the FDA approved six new biosimilars for the treatment of both RA and AS. Hadlima, Abrilada, and Hulio are the fourth, fifth, and sixth biosimilars of Adalimumab respectively, and were approved between July of 2019 and July of 2020. All Adalimumab biosimilars are approved for adults with RA or AS. Eticovo is the second biosimilar of Etanercept and was approved for adults with RA or AS in April of 2019. Avsola, that I described in the last presentation, is the fourth biosimilar for infliximab and was approved for adults with RA or AS in December 2019. And finally Truxima is the first biosimilar for Rituximab. And although it was approved by the FDA in 2018, it was only just approved for the treatment of RA in adults in 2019. Again, it should be noted that there may be published evidence on these biosimilars that we would include in a report. But we didn't search for studies on these drugs during the surveillance period because they were part of the previous scope. And finally, we didn't identify any new formulations or indications of existing drugs. Next slide. So the next few slides will describe new harms and warnings that we identified during the surveillance period. In May of 2020, the FDA issued a contraindication for infliximab that I described in the prior presentation. Basically, infliximab is contraindicated for patients with moderate to severe heart failure. And that also includes the new biosimilar Avsola. And then in June of 2020, the FDA issued a warning of increased risk of infections and malignancies due to T-cell inhibition with an abatacept treatment. And then in July of 2020, the FDA issued a warning for increased risk of hypersensitivity reactions including angioedema, urticaria, and rash with Baricitinib treatment. Next slide. So I said that we would circle back around the Filgotinib and we have arrived. So although Filgotinib is not approved for the treatment of RA or AS, major FDA actions have occurred during the approval process of this drug that we thought were best classified as a new harm or warning. So in August of 2020, the FDA rejected Gilead's new drug application Filgotinib in moderate to severe RA. And this is citing concerns over potential testicular toxicities that were shown in animal trials. Mainly we're looking at decreased sperm concentrations. And they also had concerns over the overall safety profile of Filgotinib at doses of 200 milligrams. So before moving forward, the FDA requested results from

two ongoing trials evaluating testicular toxicities. And these are the MANTA trial for people with inflammatory bowel diseases and MANDA-RAy for people with RA. So preliminary results from the randomized phase of these trials are expected in 2021. And I do believe since I did this presentation the first time, interim results have been presented to the FDA, though they are not made publicly available. However, in December of 2020, Gilead announced that it would no longer seek FDA approval for Filgotinib in RA. And then they suspended enrollment in two trials of Filgotinib with participants with AS, and that would be the SEALION1 and SEALION2 trials. At the moment, Filgotinib's future and US markets remains unclear. But we do want to note that despite the concerns raised over potential toxicities, NICE went ahead and approved Filgotinib for the treatment of RA in the UK in January of this year. That makes it the third market to do so after Japan and the EU. Next slide. So now to summarize and pull all of this information together. Next slide. In terms of clinical evidence, we found three new original published RCTs including two that we deemed to be meaningful publications of first time TIMs comparison. We also identified 24 ongoing studies including 16 head to head studies comparing this admits and harms of already approved TIMS, four placebo controlled studies of TIMs not yet approved for our target conditions, and then four comparative studies of harms. Next slide. Again, FDA activity was pretty robust during the surveillance period. We identified six new biosimilars, three fur Adalimumab, one each for Etanercept, Infliximab, and Rituximab. We also identified four new harms and warnings including the rejection of Filgotinib to NDA for RA due to potential testicular toxicities. Finally, we did not identify any new indications or formulations for any of our included interventions. And then again, the last three slides of this presentation are DURP specific, so we can move into questions.

Ginni Buccola: This is Ginni Buccola. Thanks a lot, Shauna and Candi for those presentations. Any questions from the committee? Okay, I have four stakeholders listed and I'm going to go ahead and list them. If you don't fit your name called and you expected to give testimony, please raise your hand to let us know. So I have Anthony Wheeler with Eli Lilly, Anthony Hager with Bristol Myers Squibb, Margaret Olmon with AbbVie, who is presenting on three separate drugs and will have six minutes, and Piao Chang with Pfizer. So we will go ahead and start with Anthony Wheeler. And as always, with each presenter, if you

could state your name, your affiliation with any pharmaceutical company. And once you start speaking you'll have three minutes to share. Thanks.

Anthony Wheeler: Alright. Well, thank you. My name is Anthony Wheeler. I'm an employee of Eli Lilly and Company, which manufactures a drug called Taltz. This is also known as ixekizumab. It's part of the IL 17 inhibitor class of drugs and it was originally approved for the treatment of plaque psoriasis. It's since been approved in more recent years for psoriatic arthritis and ankylosing spondylitis, and then was most recently approved for pediatric psoriasis and non-radiographic axial spondylarthritis. And you've reviewed this drug a few times before, so I just want to provide a couple of updates of research that's been finished since your last review. The first is the completion of a study called XOR-R. This was a randomized controlled trial that compared Taltz with Tremfya, that's also known as guselkumab in participants with plaque psoriasis. In this study, Taltz showed superiority to Tremfya on the primary outcome measure, which was PAZI 100, or complete clearance of skin lesions. The other research update is the completion of a different trial. This was known as spirit head to head and this compared Taltz with Humira, or at adalimumab in participants with psoriatic arthritis. In this study, Taltz demonstrated superiority to Humira on the primary outcome measure, which was the simultaneous achievement of ACR 50 for a 50% reduction in disease activity, and PAZI 100 or again, complete skin clearance. So thanks for letting me provide these updates. And please see the package insert for all of the safety details on Taltz. I'm happy to try to answer any questions that you may have.

Ginni Buccola: Thank you, Anthony. Committee, are there any questions for Anthony Wheeler? Okay, we'll move on to Anthony Hager.

Anthony Hager: Thank you for the opportunity. Good morning, almost afternoon, everyone. I'm Anthony Hager. I'm a pharm D and medical liaison with Bristol Myers Squibb. I work in immunology and rheumatology and I'm very happy to provide testimony today in support of consideration for Orencia, abatacept. So, a little bit of background here. So Orencia's label indications for rheumatoid arthritis, psoriatic arthritis, polyarticular JIA have not changed recently. Orencia continues to have no black box warnings on its label. It also remains

the only molecule in its mechanism class T-cell co-stimulation modulation. That's quite a mouthful. The most commonly reported AEs for Orencia occurring in at least 10% of Orencia treated patients are [indistinct] TI, nasal pharyngitis and nausea. And today, I wanted to share some new data with you regarding Orencia's efficacy and value that you may find interesting. So, a little more background here. Bristol Myers, in collaboration with the rheumatology community have uncovered evidence of a clinically meaningful serum biomarker predicting treatment or response to Orencia in adult patients with RA, rheumatoid arthritis. This biomarker, ACPA or anti citrullinated peptide antibody and the related CCP test. It's an auto antibody commonly utilized for its diagnostic and prognostic value in rheumatoid arthritis. However, it's recently been shown to correlate with enhanced treatment response to Orencia. So we have some data to support this. For example, the ample study, this is a head to head randomized controlled non inferiority study, of abatacept versus Adalimumab, which is a TNF inhibitor. In biologic naive, methotrexate and adequate responder RA patients. In this study the sub Q, Abatacept cohort with the highest ACPA concentrations, meaning that they have higher auto antibody levels in [indistinct] had higher treatment responses than those with lower concentrations in [indistinct] one through three. And this association was not observed with the [indistinct] cohort. And that was published in 2015. Similar results were found in a subsequent clinical trial in which numerically greater urgency treated patients achieved an ACR 50 response versus Humira, 70% versus 45% in this early, dual seropositive. So here we think about ACPA and rheumatoid factor RA cohort. And that was published in 2019. There's also been some consistent data published from the Corona Registry, so real world data. This is an independent prospective study of RA patients. And this also found that ACPA positivity was associated with greater improvement in response versus ACPA negative status for abatacept but not for TNF inhibitors. In closing and given the unique mechanism of Orencia as a co-stimulation modulator, as well as its differential treatment response in seropositive RA patients, I ask that you evaluate coverage policy in this class to allow access to Orencia by adding it to a preferred position in the Washington Medicaid PDL as a unique and targeted option in RA patients not responding to anti TNF inhibitor therapy. Thanks so much for your time and I will take any questions.

Ginni Buccola: Thank you, Anthony. Any questions from the committee for Anthony Hager? Okay, thanks very much. Margaret Olmon and again, Margaret's with AbbVie. You have several drugs you're presenting on. So we have you down for six minutes.

Margaret Olmon: Thank you very much. So, hello, everyone. My name is Dr. Margaret Olmon from Medical Affairs at AbbVie. I want to thank you so much for the additional time since I'm going to cover three medications today. AbbVie now has three targeted immunomodulator medications available. I'd like to briefly review Skyrizi, Rinvoq, and Humira and answer any questions that you might have. It is going to be a short review so please see the full prescribing information available at rxabbvie.com for comprehensive safety and efficacy data. Skyrizi was not mentioned I don't believe in the review that we just heard. That's Risankizumab. It's an IL-23 inhibitor that's indicated for the treatment of moderate to severe plaque psoriasis in adults and is given as a subcutaneous injection at week zero, week four, and every 12 weeks thereafter, which means four doses per year for maintenance treatment. The phase three clinical program was conducted in four trials with over 2000 patients and it met all primary and ranked secondary endpoints in all trials. Skyrizi showed superior efficacy to Stelara in both PASI 90 and PASI 100 responses at week 16 and 52 weeks. After two doses, 75% of patients had at least a 90% reduction in their psoriasis severity index score, and that proportion of patients increased to 83% after one year of treatment. Skyrizi also showed significance versus Humira in PASI 90 at week 16, and after a switch from Humira, intermediate responders. In clinical studies, treatment for one year provided complete skin clearance to over 50% of patients. The incidence of adverse reactions in the integrated analysis was similar for Skyrizi, Humira, and Stelara through 16 weeks. The incidence was similar in both short term and in the long term studies. There was no unexpected safety findings and there are no contraindications for treatment with Skyrizi. Rinvoq, upadacitinib, is an oral drug inhibitor indicated for the treatment of adults with moderately to severely active rheumatoid arthritis. It is taken as a 15 milligram tablet orally once daily with or without food. Rinvoq may be used as mono therapy or in combination with methotrexate or other nonbiologic [indistinct]. The phase three clinical program consisted of six studies in almost 5000 patients. Individual trials included RA patients who were methotrexate naïve, conventional [indistinct]

inadequate responders, or biologic inadequate responders. Rinvoq met all primary and all ranked secondary endpoints in all six clinical trials, and significantly more patients achieved [indistinct] 28 remission and low disease activity versus controls in each of their trials. Rinvoq is the only approved JAK inhibitor to demonstrate inhibition of joint damage in its approved population of methotrexate IR patients. It is also the only targeted immunomodulator to show clinical superior to Humira plus methotrexate. The most common adverse reactions in the [indistinct] trials were upper respiratory tract infections, nausea, cough, and fever. All anti TNFs, including Humira, carry similar box warnings regarding serious infections, tuberculosis and malignancies. JAK inhibitors also include a warning about thrombosis. Patients starting any of these medications should be screened for TB and carefully monitored for serious events. Humira has 11 currently approved indications and in three of these conditions, Humira can treat children as well as adults. Humira has recently just been approved by the FDA for the treatment of pediatric patients in UC. The 11 currently approved indications include rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and now pediatric ulcerative colitis, adult and pediatric Crohn's Disease, plaque psoriasis, Hidradenitis suppurativa, and intermediate posterior and panuveitis. With long standing safety data, 71 global clinical trials, 18 years of on market experience, and over 1 million patients exposed, Humira has a well-defined published benefit to risk database. In summary, I respectfully urge the committee to maintain preferred status of Humira on the PDL and to add Skyrizi and Rinvoq as available treatments for the Washington Medicaid patients. Thank you so much for your time and I'd be happy to answer any questions that you might have at this time.

Ginni Buccola: Thank you, Margaret. This is Ginny, committee chair. Are there any questions from my committee members? Okay, thank you very much. Next we have Piao Chang with Pfizer.

Piao Chang: Thank you, Ginni. Hello everyone. I'm Piao Chang with Pfizer Medical Affairs team. Thank you for allowing me to provide medical information on Tofacitinib, brand name Xeljanz and Xeljanz XR for your consideration for Apple Health preferred drug list. Tofacitinib is indicated for the treatment of adult patients with moderately to severely active RA, who have had an inadequate response or

intolerance to methotrexate. It may be used as a monotherapy or in combination with methotrexate or other [indistinct]. The recommended dose of Xeljanz is five milligrams twice daily. The recommended dose of Xeljanz XR is 11 milligram once daily. A 12 month double blind head to head non-inferiority randomized control trial was conducted to assess the comparative efficacy of tofacitinib five milligrams twice a day monotherapy, tofacitinib 5 milligram twice a day plus methotrexate, and adalimumab 40 milligrams sub q every other week plus methotrexate for the treatment of RA in patients with a previous inadequate response to methotrexate. This study was published in The Lancet in June 2017. The primary efficacy endpoint was 50% improvement in ACR 50 at month six. At this time point, ACR 50 responses rates for tofacitinib five milligram twice a day monotherapy was 38%. Tofacitinib 5 milligrams twice a day plus methotrexate was 46% and [indistinct] 40 milligrams every other week plus methotrexate was 44%. Using a non-inferiority margin of 13%, non-inferiority of the ACR 50 response at six months were shown for tofacitinib plus methotrexate versus [indistinct] plus methotrexate, but not for tofacitinib monotherapy. A 2012 study of the corona registry showed there was 71% to 85% non-responders to first and second anti-TNF biology after 12 months. In addition, it was shown that a gradual reduction in efficacy was observed with subsequent therapy steps. Tofacitinib is included in the ACR RA treatment guideline post methotrexate in established RA. According to the ACR guidelines, if the disease activity remains moderate or high despite the monotherapy, the recommendation is to use combination traditional [indistinct] or an anti TNF or a non TNF biology or tofacitinib rather than continuing the [indistinct] mono therapy. In closing, heading a medication that is administered orally or offer an additional treatment option for patients with RA in Apple Health population. Based on the efficacy of tofacitinib, we ask the committee to add Xeljanz and Xeljanz XR to Apple Health preferred drug list. Thank you for your attention and happy to answer any questions.

Ginni Buccola: Thank you, Piao. This is Ginni, committee chair. Are there any questions from the committee? Okay, I did see a hand raised by Shirley Quach.

Shirley Quach: Hello?

Ginni Buccola: Hello. Is that Shirley?

Shirley Quach: Yes, it is.

Ginni Buccola: I'm sorry, Shirley. I can't remember your affiliation. If you could go ahead and let us know. And then you'll have three minutes to speak.

Shirley Quach: Yes. So I'm with Novartis pharma. So good morning, Washington, P&T committee members. Again, my name is Shirley Quach. I'm a population health MSL at Novartis. I want to first thank you for your thorough and very thoughtful review of the targeted immune modulators class. And for this opportunity to provide some updates regarding Cosentyx, Secukinumab, the first and only fully human interleukin inhibitor that's indicated for plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondylitis arthritis, a group of related diseases driven by interleukin 17 A. Pediatric psoriasis beta for Cosentyx was presented at the American Academy of [indistinct] in June 2020. And both doses of Cosentyx demonstrated high and sustained efficacy up to week 52 in clearing skin and improving health related quality of life with a favorable safety profile in pediatric patients with severe chronic plaque psoriasis. The maximized study for Cosentyx was published in December of 2020 in the Annals of Rheumatic Disease Journal and it is the first randomized clinical trial that evaluated the efficacy of a biologic and the management of axial disease manifestations in patients with psoriatic arthritis. Cosentyx provided rapid and significant improvement in [indistinct] 20 response through week 12 with continued improvement through [indistinct] study at least 52. Cosentyx provides comprehensive psoriatic care across all [indistinct] domains, which includes skin, peripheral and axial joins, and the most challenging areas such as the scalp, nails, palmoplantar, and disease joints and spine with proven dedicated clinical trials across these disease manifestations as well as proven inhibition of joint structural damage progression. To date, Cosentyx has been prescribed to over 400,000 patients worldwide since it was launched with over five years of consistent long term efficacy and safety data, over 100 clinical studies, and a comprehensive head to head clinical trial program. Novartis respectfully requests the committee consider adding Cosentyx as preferred to the Washington Medicaid PDL. And thank

you for your time and consideration, and I'd be happy to answer any questions you have for me. Thank you.

Ginni Buccola: Thank you, Shirley. Any questions from the committee? Leta, are there any additional stakeholders that I missed?

Leta Evaskus: No, I do not see any.

Ginni Buccola: Okay. Are we ready to go to a motion then?

Leta Evaskus: We are. So first, this is Leta, I'll need you to accept the surveillance. So we're treating surveillance reports like we did scans where new drugs are not available to be preferred on the Washington preferred drug list. So by accepting a surveillance, you're saying that it's an adequate update. If not, you can request that a full update be done.

Alex Park: This is Alex Park. And before we do that, can I just ask Candi and Shauna, on most of the classes that you reviewed, the ITS rating was maybe. So does that mean that you're coming back to us with a further developed summary? Or are you feeling that the summary as is, is adequate for the time being?

Ryan Pistoresi: So this is Ryan. I just wanted to say, so that rating at the end of those slides is mainly presented to us as the DURP states, for us to then help understand whether we want to go ahead and commission a full report at the time. And then we go through our voting and then determine how does that report look. Are there certain elements -- do we change the scope at all? So we go through that. And I believe that these will be eventually developed into full reports by the next time that we review these in 2022. So I don't think you need to spend too much time thinking about that. That was mainly more for us to kind of get an idea of how does this level of evidence compare to when we typically commission a full report.

Alex Park: Thank you, Ryan. In that case, this is Alex Park, am I making a motion here, Leta? I guess I am. I would move that the reports, which we're treating as scans be considered adequate at this time.

Ginni Buccola: Do we need a second to accept the motion or we just need to go ahead and agree?

Leta Evaskus: You can do a second.

Nancy Lee: This is Nancy. I second the motion.

Ginni Buccola: Thank you, Nancy. So this is Ginni Buccola, committee chair. All committee members in favor of accepting the scan as adequate, please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? Alright, the motion carries.

Leta Evaskus: Now move on to the motion.

Susan Flatebo: This is Susan Flatebo. Can I just reiterate the prior motion?

Leta Evaskus: This is Leta. If the committee doesn't want to make any additions or subtractions to it.

Ginni Buccola: Susan, this is Ginni and I'm in support of you reiterating the motion but I'd be interested to hear from other committee members as well.

Alex Park: This is Alex Park. I don't think we heard anything in the scan today that would move us to amending the motion, which was made relatively recently. So I'm in favor of your proposal, Susan.

Susan Flatebo: So then this is Susan Flatebo. I reiterate the prior motion.

Catherine Brown: Catherine Brown. I second.

Ginni Buccola: This is Ginni Buccola. All committee members in favor of this decision, please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And the decision carries. So that should take us to the end of our P&T committee meeting tasks for this morning and adjourn this portion of the meeting. We were scheduled to go to

the DUR board before lunch, but I want to check in with Leta about time.

Leta Evaskus: Yeah, no, let's take lunch. Let's take half an hour and then when we come back, we'll start with the DUR.

Ginni Buccola: Great, thank you.

Leta Evaskus: Okay, so we'll come back at 12:35.

[break]

Ginni Buccola: Hello everyone, this is Ginni Buccola, committee chair. I hope you all had a good lunch. If everybody is on and ready, we're going to reconvene as the DR board and start on the next agenda item, which is ADHD, anti-narcolepsy agents and Umang Patel with Magellan will give us a presentation. Whenever you're ready, Umang.

Umang Patel: Okay, thank you so much. Just to remind the committee on the next slide here, we'll kind of review the significant clinical information in the last one year plus or minus a week or two, for each subclass. And some of these classes are stratified by a specific mechanism of action as well. And so there are a few subclasses here that do not look at the entirety of the disease state but look at a specific mechanism of action. So on the next slide here, as you can see, the first class we'll look over is ADHD, anti-narcolepsy agents as well. On the next slide, we have a little bit of background information. So ADHD, the most common use of stimulants is for the treatment of ADHD for which they're considered first line. It has been diagnosed in approximately 15% of children four to 17 years of age, and 4% of adults. And it's a chronic condition with core symptoms of inattention, hyperactivity, and difficulty controlling behavior. It may also be accompanied by internalized disorders such as sadness, anxiety, as well as aggressive and oppositional disorders. And it is broken down into three subtypes of primary hyperactive, primary inattentive, and mix. A little update in terms of guidelines, the medical letter last year in 2020, suggested that school aged children, adolescents, and adults begin with an oral stimulant, noting that none of the agents have shown to be more effective than another. However, some patients may respond better to amphetamines than to methylphenidate and vice versa. They advise

that the use of long acting formulations which generally contain both immediate and extended release components have become standard clinical practice and the addition of short acting stimulants may improve symptom control early in the morning or to prolong the duration of action in the afternoon. While the alpha agonists, clonidine and guanfacine and the selective norepinephrine reuptake inhibitors, like atomoxetine, can reduce ADHD symptoms, these agents are considered less effective than stimulants. And the use of pitolisant and solfiamfetol were not addressed for the drugs of ADHD. On the next slide here, so hypersomnolence is an excessive sleepiness. It is the primary and often debilitating symptom experienced by patients with narcolepsy, obstructive sleep apnea, hypopnea syndrome, and shift work sleep disorder. The defining characteristics of hypersomnolence is 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 complain of fatigue, tiredness, lapse of attention, lack of energy, low motivation, difficulty concentrating, disrupted sleep, snoring, or difficulties at work. On the next slide here, now to pivot over into updated clinical information. The first one we'll look at is Wakix. It's a new medication here. In October 2020, the FDA approved an expanded indication for the treatment of cataplexy in adults and narcolepsy. Again, just to remind P&T committee members, if existing medications just has updated information like expanded indications, I tend to bold what the change is. That way it's easier for you and anyone else watching to kind of get the takeaway points. So it already had an indication for treatment of excessive daytime sleepiness and now it has a an additional one of cataplexy in adult patients with narcolepsy. All of their information has remained the same, such as warnings, precautions, dosage, and availability. Therefore, I will not go over those but they're here for the committee's leader. And on the next and final slide here we have Azstarys. It is a combination medication of serdexmethylphenidate and dexmethylphenidate. So in March of 2021, FDA approved this medication for ADHD in patients six years of age or older. There are a few different warnings and precautions to keep in note here. First being there as a black box warning. CNS stimulants have a high potential for abuse and dependence. So it's important to assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy, and another for serious cardiovascular reactions. Sudden death has been reported in

association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, or MI have been reported. Avoid use in patients with a known structural cardiac abnormality, cardiomyopathy, serious heart arrhythmia, or CAD. The dosing is stratified as one can imagine by age. So there's a pediatric dose for six to 12 years of age and then adult and the second half of the pediatric dosing is together for 13 years to 17 years and adults. And it is important to note that it is not recommended to substitute this medication for other methylphenidate products on a milligram per milligram basis, as a sort of combo product here. The availability are capsules in various strength, stratified by its sub products. In terms of special populations for this medication, women who are pregnant, there is no available data to evaluate a drug associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. And lastly, if a patient has hepatic or renal impairment, there is no experience or studies in patients with renal and/or hepatic impairment for this medication. Now, I'll pause right there as that is the end of updated clinical information for ADHD class and narcolepsy agents. And I'll answer any questions the committee may have.

Ginni Buccola: This is Ginni. Thank you, Umang. Are there any questions? It looks like we have one stakeholder. I see Deb Profant with Jazz Pharmaceuticals listed on my agenda.

Deb Profant: Yes, I'm here. Are you ready for my testimony?

Ginni Buccola: Yeah, thank you, Deb. You can go ahead and introduce yourself and your affiliation and you'll have three minutes to share. Thank you.

Deb Profant: Okay, thank you. I'm Deb Profant, Director of Global Value from Jazz Pharmaceuticals. I am a full time employee of Jazz. I'm going to speak to you today about Xywav, which is calcium, magnesium, potassium, and sodium oxybate. Xywav was approved in July of 2020 for the treatment of cataplexy or excessive daytime sleepiness in patients seven years of age and older with narcolepsy. The recommended dosage for Xywav in adults is six grams to nine grams per night orally. For our patients transitioning from sodium oxybate or Xyrem to Xywav, you initiate at the same gram for gram dose and then optimize titrate as needed. At the maximum recommended dosage of nine

grams per night, sodium intake with Xywav is reduced by 1,509 milligrams or 92%. In comparison with sodium oxybate, exposure to all the other cat ions in the formulation is within the adult recommended daily allowance. So distinct from sodium oxybate, or Xyrem is Xywav does not have a warning regarding high sodium content or the subsequent precautions around monitoring patients with heart failure, hypertension, or impaired renal function. So why is sodium intake important? Sodium intake may be particularly relevant for patients with narcolepsy due to their increased risk of cardiovascular disease based on their disrupted nighttime sleep and their lack of nocturnal blood pressure dipping. Studies have demonstrated a diagnosis of narcolepsy is associated with increased prevalence of cardiovascular, metabolic, and psychiatric comorbidities. In the general population, it has also been well established that chronic excessive sodium consumption is associated with increased risk of hypertension and cardiovascular disease. As well, excessive sodium consumption is associated with stroke even in the population that does not have existing hypertension. In the Xywav phase three clinical trial, the most common adverse events in adults were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting. Xywav is a schedule three controlled substance and has a black box warning associated with central nervous system depression and abuse and misuse. Xywav and Xyrem are only available through the restriction program under the rems called Xywav and Xyrem rems. Please refer to the full prescribing information for more details on Xywav. So in conclusion, Xywav is the lower sodium formulation of oxybate without the cardiovascular warnings or precautions that are in the label for Xyrem. Xywav allows patients with narcolepsy to benefit from oxybate therapy, while providing a clinically relevant reduction in daily sodium intake. I respectfully request that the prior authorization criteria for Xywav be the same as the prior authorization criteria for Xyrem so that patients with narcolepsy can have access to the treatment, which is the optimal oxybate formulation for them. And I'm happy to take any questions.

Ginni Buccola: Thank you very much. Committee members, do you have any questions for Deb? Are there any stakeholders that I've missed? Alright, I don't think so. So I think we're ready to look at the motion then for the ADHD anti-narcolepsy agents.

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

Nancy Lee: This is Nancy. I second that motion.

Ginni Buccola: This is Ginni Buccola, committee chair. All committee members in favor please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And the motion carries. And we will move to allergy, allergenic extracts and biologicals with Umang.

Umang Patel: Perfect, thank you. On the next slide, we'll look at a little bit of background. I do want to mention for the P&T committee members, There's also an appendices that I've made at the end of this slide deck that you have access to and that essentially has older clinical recommendations. There are guidelines in there over a year old that are not reviewed here, as I mentioned, because it's not within the last 12 or 13 months. But I keep it in there as a little bit of a reference guide for anyone on the committee that wishes to take a look at that. Having said that, we'll pivot over to allergies, first being allergic rhinitis or hay fever. This is with or without allergic conjunctivitis and it affects approximately 8% of adults, 9% of children in the US. Allergen avoidance and medication therapy can provide significant symptom relief, but for many, symptoms remain. For some of these patients, allergen immunotherapy is a reasonable alternative. Subcutaneous immunotherapy or SCIT moving forward has proven to be effective in the management of allergic rhinitis and asthma since the early 20th century. However, it requires regular injections typically over a period of three to five years and it carries the potential of serious systemic allergic reactions in response to the

treatment itself. Now, peanut allergies is specific. In 2010, an electronic survey of us homes estimated about 8% of children have food allergies, estimated that peanut allergies specifically affect almost 1 million children in the US and only 20% of those that have it will outgrow their allergy. Previously, food allergy treatments primarily consisted of avoiding the allergen and promptly treating any accidental exposure. Reaction to peanut exposure varies from mild skin and/or GI symptoms to severe angioedema and anaphylaxis. When accidental peanut exposure occurs, antihistamines can manage mild to moderate reactions but patients must carry an epi autoinjector to treat severe reactions. In January of last year, the FDA approved the first treatment for oral immunotherapy, OIT, Palforzia. OIT involves feeding an increasing amount of an allergen to a person allergic to that specific allergen. OIT does not cure food allergies, rather it induces a level of tolerance that prevents allergic reactions. Although Palforzia is an OIT agent, it has many similarities to the SLIT products in regards to safety, tolerability, and administration issues. Current guidelines on peanut allergy management from key stakeholder groups have not been updated yet to include Palforzia. On the next slide, to continue the discussion about Palforzia. In January 2020, FDA approved this medication for the mitigation of allergic reactions including anaphylaxis that may occur with accidental exposure to peanuts for use in patients with a confirmed diagnosis of peanut allergy. As you can see, the indications are listed in front of you. The limitation of uses, it is not indicated for emergency treatment of allergic reactions, including anaphylaxis. There is a black box warning here. It can cause anaphylaxis, which may be life threatening and can occur at any time during therapy. It is recommended that prescribers prescribe an injectable epinephrine and instruct and train patients on the appropriate use and instruct patients to seek immediate medical care upon use. Do not administer to patients with uncontrolled asthma. And it's available through the Palforzia rems program. The dosing is very specific here because they go into depth of escalation, up-dosing, and maintenance and that can be found in the PI and TCRs that the committee has access to. And the availability of that powder for oral administration, which is supplied in .5, 1, 10, 20, and 100 milligram capsules, or a 300 milligram sachets. In terms of special populations, specifically women who are pregnant, there's no human or animal data available to establish the presence or absence of risk due to Palforzia in pregnant women. And in terms of other

specific subpopulations, carcinogenesis, mutagenesis, impairment of fertility, it has not been evaluated for these three in male or female fertility in animals. I'll go ahead and pause right there and take any questions this committee may have.

Ginni Buccola: Thank you, Umang. This is Ginni, committee chair. Any questions? I don't see any stakeholders listed. And I think we can go right to the motion.

Diane Schwilke: This is Diane Schwilke. I moved that all products in the Allergy: allergic extracts, biologics-oral drug class are considered safe and efficacious for their medically accepted indications that are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require trial of two preferred products with the same indication before non-preferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

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

Ginni Buccola: This is Ginni Buccola, committee chair. All those in favor please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? The motion carries. And we will go to anticonvulsants. Back to Umang.

Umang Patel: Great, thank you. So the next being anticonvulsants. Epilepsy is one of the most common disorders of the CNS. It's defined when a person has two or more seizures. It affects approximately 2.2 million Americans with 150,000 diagnosed cases each year. The risk is estimated to be 1% from birth to 20 years of age and 3% at age 75. Isolated seizures may also occur during febrile illness, after head trauma, or as a result of withdrawal from alcohol or sedative hypnotics. A seizure is traceable to an unstable cell membrane or cluster of cells, and excessive excitability spreads either locally, which is defined as a partial seizure, or more widely, a generalized seizure. Partial seizures begin in one hemisphere of the brain and unless they become

secondarily generalized, they can cause alternations in motor functioning, sensory symptoms, or automatisms. If there's no loss of consciousness, they are called simple partial. If there is loss or impairment of consciousness, they're called complex partial. About 70% of patients with epilepsy can be maintained on one drug. However, noncompliance and evolving refractory epilepsy are common reasons for treatment failure. If control is not achieved with one drug, an alternative medication should be attempted before others are added to current therapy. On the next slide here, we'll kind of break down a few other sub anticonvulsant disease states, first being Lennox-Gastaut syndrome. It's one of the most severe forms of childhood epilepsy and is one of the hardest forms to treat, characterized by mental retardation and multiple seizure types. Patients have seizures daily, sometimes experiencing several seizures within a day. Patients may also experience what are called drop attacks, which is defined as a loss of muscle control causing the patient to abruptly fall to the floor. The second sub disease type is infantile spasms, primarily consists of a sudden bending forward of the body with stiffening of the arms and legs. West Syndrome is characterized by infantile spasms, developmental regression, and a specific pattern on the EEG called hypsarrhythmia or chaotic brainwaves. The onset is usually within the first year of life, typically between four and eight months and usually stops by age five but may be relapsed by other seizure types. Next, we have Dravet Syndrome. It’s a rare catastrophic form of epilepsy that presents in the first year of life and is characterized by frequent prolonged seizures. Patients may experience multiple seizure types during their lifetime. Infants with Dravet Syndrome often experience multiple comorbidities over their lifetime related to the persistent seizure activity, including behavioral and developmental delay. Dravet Syndrome is also associated with a 15 to 20% mortality rate due to sudden unexpected death in epilepsy. The goals of treating epilepsy are to reduce the frequency of seizure occurrence along with providing the best possible quality of life for the patient. Treatment will depend on the specific type of seizure. Many different classes of drugs are available to treat the different forms of seizure and some patients will require more than one drug to control. On the next slide here we have our first medication for review being Fintepla. In June of 2020, FDA approved Fintepla for the treatment of seizures associated with Dravet Syndrome in patients two years of age or older. There are

some black box warnings here to take note, first being there is an association with serotonergic drugs, with 5-HT2BH receptor agonist activity, including fenfluramine, the active ingredient in Fintepla and valvular heart disease and pulmonary arterial hypertension. The second black box warning being echocardiogram assessments are required before, during, and after the treatment. And this medication is only accessible through a restricted program called the FINTEPLA REMS program. As you can see, the initial starting and maintenance dose is .1 milligrams per kilogram twice daily, which can be increased weekly based on efficacy and tolerability. Patients not on concomitant stiripentol, the maximum daily dose is .35 mg per kg twice daily max of 26 milligrams. And if the patient is taking stiripentol concomitantly, plus clobazam, the maximum daily maintenance dose decreases to .2 mg per kg for the maximum daily dose of 17 milligrams. The availability is an oral solution of 2.2 mg per milliliter. In terms of special populations, women who are pregnant, it is recommended to advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during Fintepla therapy. There are no adequate human or animal data on developmental risk associated with the use of Fintepla in women. If a patient does have renal impairment moderate or severe renal impairment is not recommended with this medication. And administration with any form of hepatic impairment is not recommended as well. On the next slide, we'll move over to Epidiolex. In August 2020, FDA approved an expanded indication for the treatment of seizures associated with Lennox-Gastaut Syndrome, Dravet Syndrome, or tuberous sclerosis complex to include in patients one year of age or older. Previously, this is only indicated in children two years of age or older for only Lennox-Gastaut and Dravet Syndrome. So increase in age and increase in disease state indication. All of the warnings, dosage, and availability have remained the same so I won't go over them. Again, in terms of special populations, women who are pregnant, based on the animal data this may cause fetal harm. Dose adjustment is required for renal impairment and it is necessary in patients with moderate or severe hepatic impairment as well. The next slide here we have Vimpat. In November 2020, FDA approved and expanded indication for the injunctive use in treatment of primary generalized tonic-clonic seizures in patients four years of age or older. This was previously only indicated for treatment of partial onset seizures in patients four years of age or older. As you can see, no changes to the warnings for

the dosage because of the expanded indication in adults 17 years or older. The new adjunctive therapy indication, the dose recommended as 15 mg twice daily. For pediatric patients, this is stratified by body weight, and it's found in the TCR PI that is put in the web portal for the committee members. No changes in availability here. Similar to the previous medication based on animal data, this may cause fetal harm. There is no dosage adjustment required in mild or moderate renal impairment but there is in severe renal impairment. And in terms of hepatic impairment, there is dosage adjustment required in mild to moderate hepatic impairment and it is not recommended in patients who are severely hepatically impaired. On the next and final slide, we have Spritam. So in January 2021, FDA approved and expanded indications for the treatment of partial onset seizures in patients four years of age or older when greater than 20 kilograms. It was previously indicated as an adjunctive therapy in patients with epilepsy four years of age or older, weighing over 20 kilograms. As you can see, no changes or updates to the warnings, dosing, or availability. In terms of special populations, dose adjustment is required for mild, moderate, and severely renally impaired patients, and there's no dosage adjustment for hepatically impaired patients here. I'll go ahead and pause right there for any questions from the committee.

Ginni Buccola: Thank you, Umang. This is Ginni. Committee members, do you have any questions? Okay, I see four stakeholders listed. Bill O'Neill with Sunovion, Debbie Sheppe with Neurelis, Stephanie Kennedy with Greenwich Biosciences, and Patrick Harvey of Supernus Pharmaceuticals. If there are any here to give testimony that I did not list just make sure your hand is raised. And we'll go ahead and start with Bill O'Neil if you're ready.

Bill O’Neill: Hi, yes, this is Bill O'Neill. I'm director of health economics and outcomes research with Sunovion Pharmaceuticals. Thanks for the opportunity to provide information supporting the adding of Aptiom to the Washington State Medicaid preferred drug list. Aptiom is indicated for the treatment of partial onset seizures in patients four years of age and older and Aptiom is contraindicated in those who have hypersensitivity to eslicarbazepine acetate or oxcarbazepine. Aptiom is not a controlled substance. It is just once daily and maybe taken crushed or whole with or without food. So Aptiom has had three

recent publications I would like to make the committee aware of. One was this past month in March of 2021 in the publication Epilepsy Research. This was results from an open label 24 week phase four study of Aptiom which demonstrated Aptiom was effective and well tolerated as the first adjunctive therapy to [indistinct]. So these are two of the most prescribed first line agents and also in treatment resistant patients. The 24 week retention rates were at 81.8% and 63.8% respectively in the two arms of this study. There were no new safety signals. There were no worsening and behavior, mood, or health related quality of life. The second study in December of 2020, was published in neurology and Therapy. And this was an analysis using these same early initiator patients, those using Aptiom's first adjunctive treatment [indistinct]. And they were studied in a claims database. They showed better economic outcomes potentially driven by the better efficacy and tolerability observed in that phase four study. These real world patients experienced significant reductions in all cause inpatient and all cause and focal seizure related outpatient visits. Although there was the expected increase in prescription charges, the increase was less than the reductions observed in the total medical charges. And then the third publication, it was this week actually in Clinical Economics and Outcomes Research. And this was a retrospective analysis of Aptiom studied as first line drug therapy compared to current standard of care generics. Patients on Aptiom experienced statistically significant greater reductions in all cause and focal seizure related emergency room and outpatient visits. And again, in this study, the increase in prescription charges were of lower magnitude as compared to the reductions in the medical charges. So this data from real world studies using you know, Aptiom, both first line and as adjunctive treatment would imply the use of Aptiom a preferred agent among these adult patients with focal seizures could help conserve these scarce healthcare resources, and hopefully reduce the overall burden on healthcare budgets. So please take this research into consideration as you select products in this class for your preferred drug list. And please consider adding Aptiom to your PDL as a preferred agent. And thank you. If there's any questions on Aptiom, I'm happy to take them.

Ginni Buccola: Thank you, Bill. Any questions from the committee? Okay, we'll go next to Debbie Sheppe with Neurelis. And Debbie, when you're ready, you'll have three minutes.

[unrelated discussion]

Debbie Sheppe: So today we respectfully request Valtoco be placed on a preferred position without restrictions. Valtoco is an intranasal [indistinct] and its indication is for the acute treatment of intermittent stereotypic episodes of frequent seizure activity like seizure clusters and is the first and only intranasal rescue medication for patients with epilepsy age six years and older. It is used for emergency treatment while the patient still continues on a stable regimen of anti-seizure medications. This efficacy is based on the relative bioavailability compared to Diastat. And it was designated clinically superior to Diastat by the FDA for orphan drug exclusivity on the basis that intranasal route of administration provides a major contribution to patient care. The FDA stated that in the context of when this drug is given, which is typically in the middle of a seizure event, it is easier to administer the drug to a patient intranasally than rectally. Valtoco is ready to use out of the package by simply depressing the plunger. If you can access the nose, you can give the medication. Valtoco has a half-life of 49 hours and that allows coverage within expected six to 24 hour timeframe that the majority of seizures within a cluster occur. In our clinical trials, the safety findings were consistent with what we already know about diazepam and the rate of somnolence in our trials was 1.5%. It contains a proprietary excipient called intervale and that increases drugs often across the nasal mucosa and that resulted in 97% bioavailability relative to IV diazepam. The Cmax and AUC parameters were two to four times less variable than for Diastat. In our exploratory analysis, subjects with epilepsy and their caregivers reported treating over 4000 seizure events. 94% of these events were able to use a single dose of Valtoco over a six hour period, and 86% used a single dose over a 24 hour period. Survey data from this trial suggested that subjects were more comfortable being treated in a public space with intranasal than rectal diazepam, and a majority of the subjects were able to quickly return to their usual cells. As with all benzodiazepines, Valtoco has a box warning regarding [indistinct] use with opioids abuse, misuse, and addiction, and dependence and withdrawal reactions. The most common local ease were nasal discomfort, congestion, epistaxis, and dysgeusia. In summary, Valtoco provides a noninvasive on hand rescue treatment for seizure emergencies and is the only nasal spray indicated in patients to the

age of six. In the midst of a seizure event, the FDA indicated that Valtoco provides a substantial advancement in patient care by providing a less invasive route of administration and was determined be clinically superior to Diastat. Access to rescue medications easily administered at home or at the hospital have the potential to decrease unnecessary utilization of healthcare resources, break the cycle of seizures, and prevent progression to status Epilepticus. Thank you very much for this opportunity to speak with the board today.

Ginni Buccola: Thank you. Any questions for Debbie? Okay, and we'll go to Stephanie Kennedy with Greenwich Biosciences. Are you there Stephanie?

Stephanie Kennedy: Hello, my name is Stephanie Kennedy. I am a health outcomes liaison manager from Greenwich Biosciences and I'm here to speak about Epidiolex, the first and only FDA approved prescription cannabidiol indicated for the treatment of seizures associated with Lennox-Gastaut, Dravet, or tuberous sclerosis complex, in patients one year of age and older. The recommended maintenance dose for LGS and Dravet is 10 to 20 mg per kg per day, and the maintenance dose for TSC is 25 mgs per kg per day. As Mr. Patel stated in 2020, we had a third indication of TSC added to our label. So I'm just going to provide you with a little information on TSC. TSC is a highly variable genetic disorder that is characterized by the formation of benign hematomas in virtually every organ of the body. Patients with TSC commonly experience treatment resistant epilepsy that can begin in infancy and persist throughout life with multiple seizure types. Efficacy and safety of add on Epidiolex for the treatment of seizures associated with TSC was evaluated in a 16 week randomized double blind placebo controlled multicenter trial. Doses of 25 mg per kg per day and 50 mg per kg per day equally and significantly reduced seizures at 49 and a 48% mean reduction compared to placebo, a 27% reduction in the intention to treat analysis. While the TSC clinical trial included a 15 mg per kg per day arm, greater efficacy was not observed compared to the 25 mg per kg per day. However, greater incidence of the AEs was observed, thus we did not seek approval for the 15 mg per kg per day dose. Most common adverse reactions in patients receiving Epidiolex greater than 10% than placebo include transaminase elevation, somnolence, decreased appetite, diarrhea, [indistinct], vomiting, fatigue, malaise, [indistinct], rash, sleep disorders and infections. hematologic abnormalities were also observed. Details

regarding the contraindication for hypersensitivities warnings and precautions are provided in the Epidiolex full prescribing information. In summary, Epidiolex has been demonstrated as effective for the treatment of seizures associated with Lennox-Gastaut, Dravet, or tuberous sclerosis complex in patients one year of age and older with a well characterized safety profile. Thank you for your time and consideration and allowing appropriate patient access for those living with these severe forms of treatment resistant epilepsies. Thank you.

Ginni Buccola: Thank you, Stephanie. Committee, do you have any questions? Okay, going to Patrick Harvey with Supernus Pharmaceuticals. Are you there?

Patrick Harvey: Yes, thank you. My name is Patrick Harvey and I am in medical affairs at Supernus Pharmaceuticals. And I thank you for allowing me today some time to talk on behalf of Trokendi XR, which is [indistinct] extended release. I do not have any new indication study for trials. But I would like to make just a couple of points that I hope you will consider when making a decision as to whether it should remain on the PDL. As you know, and the reason why we're reviewing it today is because it has indications for children and adults for monotherapy and adjunctive therapy for partial onset or primary generalized tonic-clonic seizures as well as adjunctive therapy in the treatment of Lennox-Gastaut Syndrome. I'd like to point out it also has an FDA approved indication and much more utilization in the prevention of migraine headaches in children 12 and older. The once a day dosing makes it a very attractive option for those patients that they prefer that and increases in adherence and compliance over immediate release products. Also in the control state, Trokendi XR produced significantly fewer cognitive deficits that the immediate release[indistinct] as measured by the control oral association test of verbal fluency. Cognitive related side effects are one of the most common reasons for the discontinuation of immediate release [indistinct] product. The other point I hope that you will consider is if it is removed from the PDL, those patients that have been taking it for migraine prevention will more than likely be switched to other therapies which might include newer agents, which in some studies have not proven to be much more effective than the older products such as Trokendi XR. It’s for these reason, I respectfully ask for you to keep Trokendi XR on the preferred drug list. I yield back the rest of

my time and I'll be glad to answer any questions the committee might have.

Ginni Buccola: Thank you. Committee, do you have any questions? Okay, I see with the hand raised and in the question box, Sibin Stephen with Zogenix. Okay, go ahead. You'll have three minutes to speak.

Sibin Stephen: Perfect. Thank you, everyone. My name is Sibin Stephen. I'm the medical science liaison with Zogenix. Fintepla oral solution, or Fenfluramine was approved by the FDA on June 25th of 2020 and is indicated for the treatment of seizures associated with Dravet syndrome in patients two years of age and older. As was mentioned earlier, Dravet syndrome is a rare and severe form of epileptic and developmental encephalopathy that is highly refractory to existing anticonvulsant therapy, and has significant morbidity and mortality, including an increased risk of sudden unexpected death in epilepsy. Fintepla it can be taken with or without food. The initial starting dose is point one milligrams per kilogram twice daily, and the max daily dose is 26 milligrams per day. And if in combination with [indistinct] plus [indistinct], then it's 17 milligrams per day. There is a box warning related to the association between serotonergic drugs with 5-HT2B receptor agonist activity, and valvular heart disease on pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment, and Fintepla is available only through a restricted program called the FINTEPLA REMS. The effectiveness of Fintepla was established in two rigorous clinical trials. Study one compared a 0.7 milligram per kilogram day dose and a 0.2 milligram per kilogram per day dose of Fintepla with placebo in patients who were not receiving [indistinct]. Study two compared to a .4 milligram per kilogram per day dose of Fintepla with placebo in patients that were receiving [indistinct]. In study one, the difference in the monthly convulsive seizure frequency relative to placebo was 32% for the low dose arm and 70% for the high dose arm. In study two, the difference in the monthly convulsive seizure frequency relative to placebo was 60%. A profound seizure reduction of 75% or greater was observed in 58% of patients in study one and 40% in study two. Patients who participated in the randomized controlled trial had the option to continue into an open label extension study. And the magnitude of effects observed in the clinical trials was maintained, with a median treatment duration of 631 days during the

open label extension study, with an overall median change in seizure frequency of 65%. The most common adverse reactions were decreased appetite, somnolence, sedation, lethargy, diarrhea, and constipation. Valvular heart disease and pulmonary arterial hypertension were evaluated in both the pivotal trial and the open label extension for up to three years. And no patient developed echocardiographic findings consistent with either valvular heart disease or pulmonary arterial hypertension. Thank you for your time. The benefit of the Medicaid patients in Washington State, Zogenix requests Fintepla remain on the preferred drug list with criteria to label for the treatment of seizures associated with Dravet syndrome in patients two years of age and older. Thank you very much.

Ginni Buccola: Thank you. Committee members, do you have any questions? Alright, and I see Raj Sandhar requesting to give testimony. I'm sorry, I don't know your affiliation, Raj.

Raj Sandhar: Yeah, so Good afternoon. My name is Raj Sandhar and I'm the MSL for UCB. I would like to discuss UCB's product Nayzilam, the first FDA approved midazolam intranasal spraying. However first important introduce the burden of seizure clusters and the significant unmet need for intranasal rescue therapy. In the US there is 3.4 million Americans living with epilepsy, around 5% experiencing seizure clusters. Washington has 74,600 residents currently living with epilepsy. As you could anticipate, around [indistinct] seizure clusters. So seizure clusters are acute episodes of consecutive seizures that occur with [indistinct] periods. Real world evidence studies show individuals suffering from seizure clusters at five times higher rates of hospitalization, not related to status Epilepticus, and three and a half times higher mortality risk compared to individuals with non-clustering seizures. Additionally, 30 to 40% of this population utilize ER over a one year period. Seizure cluster emergencies require rapid intervention to break the cluster and prevent progression to prolonged seizures or status Epilepticus. Until 2019, the only FDA approved treatment seizure clusters was diazepam rectal gel, but less than 10% of patients reported using. [indistinct] of these rescue therapies leads to potentially preventable increased risk of emergency care. Using seizure rescue therapy may also decrease or prevent neurological damage and improve the quality of life of the patient and potentially their caregiver as well. Nayzilam is indicated for a

treatment of intermittent stereotypic episodes of frequent seizure activity, i.e. seizure clusters and acute repetitive seizures that are distinct from patient's usual seizure pattern in patients with epilepsy 12 years of age and older. It is the only midazolam based option approved for the treatment of seizure clusters. Nayzilam demonstrates efficacy in stopping seizure clusters in a phase three double blind placebo controlled study of 292 patients in which significantly more patients receiving a single dose of Nayzilam experienced treatment success compared to placebo, 53.7% of Nayzilam patients versus 34.3% for placebo. Nayzilam treated patients experienced statistically longer time to next seizure and have fewer individuals experiencing seizure within 24 hours compared to placebo. Patients could have received a second dose of Nayzilam if needed as early as 10 minutes after the first dose. Open label extension trial for 161 seizure cluster patients 12 years of age and older reported sustained efficacy after repeated intermittent acute treatment with Nayzilam. Median time to document to return to full base and functionality was 1.2 hours. Nayzilam has a [indistinct] use with opioids as well as other important warnings and precautions including [indistinct] and CNS pression [indistinct] with other CNS depressants. Most common ADRs are [indistinct] headache, nasal discomfort, throat irritation, and [indistinct]. Please consider ensuring access to [indistinct] including Nayzilam for appropriate Medicaid patients with epilepsy. Thank you.

Ginni Buccola: Thank you very much. Committee, are there any questions? And I believe those are all the stakeholders. Again, please raise your hand if you've been missed. Okay, I think we can go to the motion.

Alex Park: It's Alex Park. I have a question. Leta, could you go back one slide? [unrelated discussion] Don't we have more anticonvulsant categories than this or are we separating out certain anticonvulsant categories for this motion? This is Leta. Marissa, do you want to speak to that?

Marissa Tabile: Hi, this is Marissa. So, Dr. Park, we do have other anticonvulsant classes on the AH PDL. But either they were archived or scheduled to be reviewed at another DUR meeting. So we are only reviewing the four that are listed here on slide seven.

Alex Park: Got it. Thank you very much.

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

Nancy Lee: This is Nancy. I second that motion.

Ginni Buccola: This is Ginni Buccola, committee chair. All those in favor, please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And the motion carries. And we'll move to antidementia agents with Umang.

Umang Patel: Okay, great. This one is a quick one. There are no significant clinical updates either in medications or guidelines in the last year. So there is nothing to report here. So I'll pause right there.

Ginni Buccola: Okay and this is Ginni. Again, we don't have any stakeholders and so we'll just need to take care of the motion.

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

Jordan Storhaug: This is Jordan Storhaug. I second.

Ginni Buccola: This is Ginni Buccola, committee chair. All those in favor please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And the motion carries. And we will move to neuromuscular agents for spinal muscular atrophy.

Umang Patel: It's actually antidepressants.

Ginni Buccola: I am sorry, I think that is missing off of -- my apologies. Please go ahead and I'll figure out why I'm off.

Umang Patel: So for the next one, it's a similar to its predecessor for the antidepressants, GABA receptor modulator, neuroactive steroid specific mechanism of action. There are no significant clinical updates in this subclass of antidepressants. And so I'll go ahead and pause right there for the committee.

Ginni Buccola: This is Ginni, thanks. Getting myself back on track with the right copy of the agenda. We have no stakeholders, I believe. I'm sorry if I'm incorrect.

Leta Evaskus: This is Leta. There are no hands raised.

Ginni Buccola: Okay, thank you. I'm off now. Yes, we're going to go ahead and take a look at the motion and I'll let the committee move forward when they're ready.

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

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

Ginni Buccola: This is Ginni Buccola, committee chair. All those who are in favor please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And the motion carries. And next is antiparkinson's agents with Umang.

Umang Patel: Alright, so again, to give a little bit of background, Parkinson's disease is a progressive neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity. The disease affects approximately 1% of individuals older than six years and the incidence increases significantly with age. The term parkinsonism describes the motor syndrome of bradykinesia, rigidity, tremor, and balance and gait disturbances. Secondary parkinsonism which has a different ideology and pathology than Parkinson's is the predominant clinical manifestation of a number of disorders including brain tumors near the basal ganglia, cerebral atherosclerosis, head trauma, and progressive supranuclear Palsy. Secondary parkinsonism can also be caused by toxins and drugs, especially antipsychotic agents. Despite advances and treatments over the years, there's no cure for Parkinson's. Symptomatic therapy can provide benefits for quite some time but the continued, however slow progression of Parkinson's eventually results in significant disability. Patients may not require treatment in the early stages of PD, if symptoms do not cause functional impairment. As the disease progresses, however, therapy becomes more complex requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments. Moving onward, restless leg syndrome. I'll give a little bit of background about this because there is overlap in terms of medications. So, on the next slide, restless leg syndrome is a neurological sensory disorder in which patients experience irrepressible sensations in the legs or arms will sitting or lying still to cause them to move their arms or legs. Providers will need to rule out other movement disorders with similar symptoms to RLS such as periodic limb movement disorder or PLMD, antipsychotic adverse drug effects, and dyskinesis to correctly diagnose and treat the symptoms. Studies suggest that RLS is associated with dopamine symptom and depletion of iron stores.

Historically, RLS has been treated with opioid benzos, anticonvulsants, iron replacement, and dopaminergic agents. Prior to 2000, levodopa was the dopaminergic agent most studied in RLS. Mirapex, Requip, Neupro are approved for an indication of RLS and there has been increased focus on the use of dopamine agonist in the treatment of this disorder. Horizant is also FDA approved for RLS. So, on to the first new medication. In April 2020, FDA approved Ongentys, which is a COMT inhibitor. It was indicated for adjunctive treatment to levodopa carbidopa in patients with Parkinson's experiencing off symptoms. As you can see on the next slide, the warnings. There are cardiovascular effects with concomitant use of drugs metabolized by COMT, falling asleep during activities of daily living may occur, hypotension and syncope, based on animal data, it may cause fetal harm to women who are pregnant, and it is recommended to avoid in patients with severe hepatic impairment and in patients with end stage renal disease. The dosing here is 50 mg once daily and it is available in capsule form of 25 and 50 milligram strength. On the next slide here we have Kynmobi. In May 2020, the FDA approved this sublingual film for the acute intermittent treatment of off episodes in patients with Parkinson's. The warnings include nausea and vomiting, again similarly to its predecessor on this slide set, falling asleep during activities of daily living, may cause hallucinations and psychotic like behavior, may cause impulse control and impulsive behaviors, withdrawal emergent hyper pyrexia and confusion may occur and based on animal data it may cause fetal harm. In terms of dosage, treatment with concomitant antiemetic is recommended three days prior to the initial dose. The dose ranges 10 to 30 mg per dose administered sublingually and maximum of five doses per day or a single dose of 30 milligrams. As mentioned, it's available in sublingual film, 10, 15, 20, 25 and 30 milligrams. Safety and efficacy has not been established in pediatric use, and there's no dosage adjustment and mild to moderate renal or hepatic impairment and it is not recommended in severe renal or hepatic impairment. On this slide here, in August 2020, Milan received FDA approval for its first generic versions of Orion’s Stalevo 50, Stalevo 75, Stalevo 125, and Stalevo 200. Generic versions of Stalevo 150 and 100 were already approved. On the final slide we have Gocovri. In February 2021, the FDA approved expanded indication for adjunctive treatment of levodopa carbidopa in patients with Parkinson's experiencing off episodes previously approved for dyskinesia in patients with Parkinson's or

levodopa. In terms of warnings, very similar to its predecessors in this topic, it's contraindicated in patients with end stage renal disease. It may cause falling asleep during activities of daily living. Suicide and depression are a warning for practitioners to keep an eye on. Based on animal data, it may cause fetal harm. It is not recommended to use during live attenuated influenza vaccine in patients receiving this medication. And it is not recommended if the patients have concomitant alcohol use. In terms of dosage, it is 137 milligrams and after one week, you can increase it to 274 milligrams taken at bedtime. Availability is an extended release capsule of 68.5 and 137 milligrams. In terms of pediatric use, safety and efficacy is not established. And there's a dose adjustment required for moderate to severe renal impairment. I'll go ahead and pause there as that concludes the antiparkinson's agent.

Ginni Buccola: This is Ginni. We have two stakeholders, Bill O'Neill with Sunovion and John Deason with Merocrine Biosciences. And we'll start with Bill. Can you hear me? And are you there?

Bill O'Neill: Yes. Hi, it's Bill O'Neill, director of health economics and outcomes research at Sunovion. And I'm speaking today on behalf of Kynmobi. As you just heard Kynmobi is a sublingual film indicated for the acute intermittent treatment of off episodes in patients with Parkinson's disease. You can think of this as an on demand treatment or rescue when Parkinson's patients are experiencing particularly troublesome off episodes. Then there are actually different types of off episodes, which include morning offs, wearing offs, delayed ons, and unpredictable offs. And the reasons for these off episodes vary and can include things like gastric emptying problems, absorption issues, trouble with drug metabolism, disease progression. And the thing is that not having a non-oral route of treatment is very beneficial in these patients. All of these types of off episodes can be treated with an on demand therapy, such as Kynmobi, however, only the wearing offs that are typically treated with on extenders or these adjunctive treatments, such as [indistinct], they're not effective in all types of wearing offs or off episodes. It may be necessary over the course of treatment for some Parkinson's patients to need carbidopa levodopa and on demand treatment and an on extender all at the same time. However, it would be best for the neurologists to decide the order in which these are added. I think [indistinct] just do a good job of

interviewing the patients around the types of off episodes. They are experiencing and know which treatments to prescribe. I think that one of the asks that we have today is that you please consider possibly a separate category within the antiparkinson's disease state for on demand treatments, as they treat different types of off episodes. And we would request that Kynmobi be selected as a preferred product within this category of on demand treatments. And thanks and I'll take any questions if there are any.

Ginni Buccola: Thank you, Bill. Any questions from the committee? Okay, we'll move to John Deason with Neurocrine Biosciences. You'll have your three minutes.

John Deason: My name is John Deason. I'm a senior managed care liaison with Neurocrine Biosciences in the medical affairs department and appreciate the opportunity to speak to you today about Ongentys or generic opicapone capsules, indicated as an adjunctive treatment to levodopa carbidopa in patients with Parkinson's disease experiencing off episodes. Although levodopa is the most effective therapy for managing PD motor symptoms, PD progression and pharmacological limitations of levodopa are associated with unpredictable motor fluctuations. And this leads to more frequent and unpredictable off periods between doses. As such, the control of motor fluctuations eventually becomes a key clinical need for almost all patients. And they weren't the addition of adjunctive therapies. The International Parkinson and Movement Disorder Society conducted an evidence based medicine review, providing an update on treatments for the motor symptoms of Parkinson's disease and concluded that opicapone is efficacious and clinically useful for the treatment of motor fluctuations. Out of respect for the board's time, I'll refer you to the TI for the safety and efficacy data from our two double blind randomized parallel group placebo and/or active controlled studies B part one and B part two, along with the warning and precautions associated with Ongentys use. But I would like to take the opportunity to share data from our 52 week open label extension study where all participants who completed the double blind phase of the B Part 1 and 2 were eligible to participate. Regardless of prior treatment, all participants entering the open label phase received opicapone 25 milligrams once daily for the first week, followed by individually tailored levodopa and/or opicapone dose adjustments. At the open

label endpoint, the main change in off time in participants that had previously received placebo during the double blind phase was reduced by 2.19 and 1.68 hours versus baseline in the B part one and B part two trials, respectively. And the mean off time in participants that previously received opicapone 50 milligrams during the double blind phase was two hours and 2.64 hours versus baseline in B part one and two, respectively. B part one participants that had previously received the active comparator entacapone during the double blind phase had reduced off time of 2.24 hours versus baseline, which represented an additional 42 minutes of reduced off time versus open labeled baseline treatment with entacapone. A [indistinct] safety analysis determined the most common adverse reactions were dyskinesia, constipation, blood creatine kinase increased, hypotension syncope, and weight decrease. Bodily fluid discoloration was not reported with onset disease. As mentioned, the FDA recommended dosing for Ongentys 50 milligrams administered orally once daily at bedtime. And as exposure is increased in patients with hepatic impairment, the recommended dosage in patients with moderate hepatic impairment is 25 milligrams and those with severe hepatic impairment should avoid using Ongentys. In summary, we respectfully requested the committee make Ongentys available for patients with PD taking levodopa carbidopa experiencing off episodes. I appreciate your time and welcome any questions the committee might have.

Ginni Buccola: Thank you very much. Are there any questions from the committee? Okay, let's go ahead and look at the motion.

Susan Flatebo: This is Susan Flatebo. I just had a question. Are these newer agents that are for these so-called off episodes of Parkinson's, are they considered a different class than the classic dopamine precursors like the levodopa, carbidopa medications? Could they be interchanged? How does that how does it work for preferred status?

Marissa Tabile: Hi, this is Marissa. Did you have a particular drug in mind? Because some of them, like the ones that were mentioned from the stakeholders and by Umang, like the Gocovri for example, that is in the antiparkinson’s agent dopaminergic. So it is lumped together with the other amantadine products. And then like the apomorphine. Was there another product that you had in mind that you wanted me to

check on because it might be in a different class that might be archived. But off the top of my head, I'm not entirely sure. I'm just looking at what I have pulled up right now.

Susan Flatebo: So yeah, I guess my question is if something like the apomorphine, I'm assuming it can be given in conjunction with the carbidopa levodopa. Correct?

Marissa Tabile: This is Marissa. Off the top of my head, I'm not quite sure if it can. Umang, do you happen to know by chance?

Umang Patel: I'm sorry. Can you repeat that question, please?

Susan Flatebo: So the apomorphine indication says it's for the intimate treatment of these off episodes, which I'm assuming they're having off episodes because they're carbidopa levodopa is not controlling their tremors. And so as far as preferred status, if you have a patient that's on carbidopa levodopa and the doctor wants to prescribe this apomorphine in addition, what does that look like? Is that something that's going to be preferred? I'm assuming it could be using them in conjunction.

Umang Patel: Correct. So if we're looking at the Gocovri, that is an adjunct treatment to the to the [indistinct], the carbidopa levodopa. It would not be like replacement treatment.

Susan Flatebo: Yeah, I just wondered like when they talk about preferred status, how that fits into it. So, thank you. I move that all products listed in the drug classes on slide 14 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require a trial of two preferred products with the same indication before a non-preferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

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

Ginni Buccola: This is Ginni Buccola, committee chair. All those in favor please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And that motion carries. And we'll move to atopic dermatitis agents.

Umang Patel: Thank you. So for atopic dermatitis, a little bit of background. It is a chronic noncontagious inflammatory disease of the skin resulting from a combination of genetic and environmental factors. Approximately 70% of patients diagnosed have a positive family history of atopic diseases. The odds of developing are two to three times higher in children with one atopic parent and increases to three to five times higher if both patients are atopic. It's often referred to as eczema. It affects approximately 18 million Americans and accounts for 10 to 20% of all visits to the dermatologist. Although it can develop at any age, it has been established that 60% of patients develop symptoms in the first year of life while 90% develop symptoms before the age of five and a half. It's characterized by extreme dry, itchy skin on the inside of the elbow, behind the knees, and on the face, hands and feet. In response to the intense itching, patients may scratch or rub the affected area, which can lead to further irritation and inflammation. As the skin loses moisture from the epidermal layer, it becomes increasingly dry and may begin to crack, weak, crust, and scale. The damage to the integrity of the skin renders it less protective and more prone to infection. Despite the chronic nature of this dermatologic 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 may exacerbate or cause flare ups. On the next slide here, there was an approved indication for the medication Eucrisa where it now has an indication for topical treatment of mild to moderate atopic dermatitis in patients three months of age or older, whereas previously it was only two years of age or older. Again, no changes to any of the precautions and warnings, the dosage, or the availability. And the only thing to note is for women who are pregnant there is no available data on its effect on fetal embryo. On the next and final slide here, we have Dupixent. And so there were two updates to

Dupixent in June 2020 that I've kind of stratified although the date is the same here, you can see underneath it the update is different. So firstly in June 2020, the atopic dermatitis indication has now been expanded to include the treatment of patients six years of age or older with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapy or when those therapies are not advisable. It can be used with or without topical corticosteroids. Previously, it was only indicated for patients 12 years of age or older. Secondly, in June 2020, a new formulation of a new single dose prefilled pen presentation in the strength of 300 milligrams per two milliliter solution was now available. No other changes in the dosage as it is stratified by indication age and weight, which is available in the TCR package insert. And as I mentioned earlier, there was an update to the availability which is now a single dose prefilled pen. In terms of special populations, women who are pregnant, available data from case reports and case series with Dupixent use in pregnant woman have not identified a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In terms of renal hepatic impairment, there is no formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of this medication that was conducted. I'll go ahead and pause right there for any questions from the committee.

Ginni Buccola: Thanks again, Umang. Any committee member questions? We have one stakeholder, Brandon Yip with Sanofi Genzyme. Are you there, Brandon?

Brandon Yip: Thank you, Ginni. Again, my name is Brandon Yip. I spoke earlier during the asthma section on Dupilumab. And again, I am from Sanofi Genzyme. Thank you to the committee for allowing me to give some remarks. I'll keep it brief. That was a great summary of a topic dermatitis and just a few points I wanted to add. We have completed a real world evidence study that includes 12 months of data in adults with atopic dermatitis, some data that shows discontinuation rates, adherence rates, effects on flares, and concomitant use of other medications. And there are ongoing studies to look at the same conditions of that particular study in the adolescent and pediatric population as well. So, a lot of new data and if the committee is interested in hearing that I would love to bring it to you guys. And thank you for your time. And I'll take any questions.

Ginni Buccola: Thank you very much. Are there any questions? Okay, I guess we'll be ready then to look at the motion.

Alex Park: This is Alex Park and I move that all products listed in the drug classes on slide 17 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require for trial to preferred products with the same indication before a non-preferred product will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Nancy Lee: This is Nancy. I second that motion.

Ginni Buccola: This is Ginni Buccola, committee chair. All those in favor, please say aye.

All: Aye,

Ginni Buccola: Any opposed? And the motion carries. And we'll go ahead and go to neuromuscular agents for spinal muscular atrophy.

Umang Patel: Thank you. So the next will be specifically spinal muscular atrophy agents in the subgroup of neuromuscular agents. To give a little bit of background on spinal muscular atrophy, it's a rare, debilitating neuromuscular disease characterized by motor neuron degeneration, muscle weakness, and atrophy. The disease mainly affects the motor neurons in the spinal cord and it is not believed to impact the person's capacity to think, learn, and build interpersonal relationships. It is the leading monogenic cause of infant mortality and is the second most common autosomal recessive inherited disorder, with an incidence ranging from four to 10 per 100,000 live births. It is more common in males than females, particularly with the early onset forms. Patients experiencing motor function decline with disease progression and morbidity and mortality rates are inversely correlated with the age of onset. Mortality due to FMA is most commonly related to respiratory infections and complications. Genetic testing is used to establish diagnosis in patients with suspected SMA based on symptoms and

universal newborn screening for FMA is a part of the federal recommendation uniform screening panel. Clinical classification is typically based on age of onset and maximum motor function achieved, which you can see below. The chart here stratifies it based on the SMA type, categorizes type zero, type one, type two, type three and four. As mentioned it's age of symptom onset where we have at birth or prenatal being type zero, zero to six months for type one, six to 18 months for type two, greater than 18 months for type three, and late onset, which is typically the third decade of life being type four, in the highest motor function achieved and respective correlated life expectancy for these five classifications. Now while type zero and one are the most common types, type two, three, and four, count for approximately 20%, 30%, and less than 5% of all FMA cases, respectively. On the next slide here, we look at some of these guidelines. Because normally I don't go over guidelines that are over a year of age in clinical updates for spinal muscular atrophy, so I will not review this. But again, it is here for the committee's reference. On the final slide for spinal muscular atrophy, in terms of Evrysdi, in August 2020, FDA approved this new medication for an SMN2 splicing modifier for the treatment of spinal muscular atrophy in patients two months of age or older. In terms of warning and precautions, based on animal data it may cause fetal harm and is recommended to avoid in patients with hepatic impairment. The dosage again is age and weight based, as you can see. It's stratified for two months to less than two years of age two years of age or older weighing less than 20 kilograms and two years of age and older weighing greater than or equal to 20 kilograms. It is an oral solution of 60 milligrams as a powder for constitution that provides .75 milligrams per milliliter solution. And in terms of special populations, I've already mentioned hepatic impairment in pregnancy. One thing to note is clinical trials did not include patients 65 years of age or older. So there is limited information on geriatric patients. I'll go ahead and pause there for any questions from the committee.

Ginni Buccola: Thanks, Umang. This is Ginni. First of all, a true pause for questions from the committee. Okay, thank you. And then we have two stakeholders. I see Jill Gardner with Novartis Gene Therapies and Lynda Finch with Biogen. Possibly I have the name Ivory Bickham. I see a hand raised. I don't know if that's also a stakeholder that would like to present. But we'll start with Jill Gardner with Novartis.

Leta Evaskus: This is Leta. I don't see Jill's name, but Ivory is also from Novartis. So Ivory, I'm going to unmute you. Are you speaking for Jill Gardner.

Jill Gardener: Yes, I'm here. Thank you. Good afternoon. My name is Jill Gardner, Regional Medical Director with Novartis Gene Therapies. I'm here to provide a brief update on Zolgensma. As you know, Zolgensma was approved in May of 2019. So it's been about two years. Approximately 1000 babies have been treated so far, over 500 in the US. It remains the only FDA approved gene therapy for SMA, which treats the underlying root cause of spinal muscular atrophy. Currently, we have about six years of long term follow up. And by that we've been able to note that there's been no loss of motor milestones achieved and no treatment related safety issues. It is indicated in SMA in pediatric patients under the age of two - I know you know that - it is administered as a one-time IV infusion over 60 minutes, usually in the outpatient setting. The SMN1 gene is delivered to the alpha motor neurons through vector cell transduction, which crosses the blood brain barrier. The vector is trophic towards the CNS. And so it's able to establish an episome, a trans gene that will now be able to synthesize the survival motor neuron in each of these cells. And that is essential, of course, for motor neurons just to thrive and function. The most common side effect of Zolgensma treatment was transient elevated liver enzymes and vomiting. Now there's an urgency that in order to avoid functional loss of motor neurons during the newborn period of life. That's obviously for the type one in the more severe forms. Now we have an interim analysis of this French study recently shared at MDA. And this is data on newborns treated. They were treated pre-symptomatic, meaning less than six weeks of age, 15 children with B copies of SMN2 and 14 with two copies of SNM2. These babies during the post treatment follow up, which was up to 18 months, showed -- obviously, they all survived, they were free of ventilation support. They were all able to feed orally and they were able to thrive, meaning they were able to maintain their weight, able to sit, stand, or walk independently depending on their age. And the median age was 15 months. So this is in stark comparison to the natural history as we know of SMA in which less than 10% by the age of 20 months. That's for the type one. So early diagnosis and treatment provides this opportunity for the greatest patient outcomes with no serious adverse events. Now in the state of Washington, it is

estimated that approximately six children are likely to be born with SMA. That's an instance of about one and 14,000 based on 87,000 live births. So it's great to know that SMA has been added to the panel in Washington. And it's an opportunity that we at Novartis Gene Therapy sees as the ability to diagnose early and therefore follow up with treatment early. Are there any questions?

Ginni Buccola: Thank you. I agree. Any questions committee? Okay, we appreciate that. Next, we have Linda Finch with Biogen. You'll have three minutes.

Linda Finch: Thank you. Good afternoon. My name is Linda Finch. I'm a medical liaison with Biogen. And I'd like to share some new data for nusinersen that's relevant to your discussion today. So as you know, nusinersen was the first treatment approved for SMA in December 2016. We now have over four years of real world experience, and it has been used to treat over 10,000 patients worldwide with 3000 of those in the US. And this includes babies as young as three days old and adults up to age 80. Nusinersen was approved after a robust multicenter sham controlled clinical trial program, and it has a broad label with no age restrictions. And then recently, there have been several well designed real world studies in adults with SMI that have been published that further support the efficacy and safety of nusinersen in these age groups. And in these studies, clinically meaningful improvements in motor function were documented and no new safety signals were seen. Nusinersen has also been studied in pre symptomatic infants. And these were in patients considered most likely to develop type one or type two SMA. And the results of this study indicated that after up to 4.8 years of continuous treatment, 100% of pre symptomatic infants are alive and free of permanent ventilation. And the majority of the patients achieve their motor milestones within timelines consistent with normal development, so development of normal children, reinforcing this importance of early diagnosis and treatment of SMA. And as the previous speaker mentioned, Washington State began a newborn screening program for SMA in August of last year. So now all newborns in the state are screened for SMA and can begin early treatment. The Washington State newborn screening program recommends immediate treatment for infants with three or fewer copies of the SMN2 gene. There's one group of patients however, that haven't had the opportunity to benefit

from treatment. These are SMA patients that are ventilator dependent. And the Washington Medicaid nusinersen policy currently excludes these patients from treatment. In our study, infants that required permanent ventilation were excluded because one of our primary endpoints was tied to permanent ventilation. They weren't excluded because we believed that they wouldn't benefit, just that they'd already met that primary endpoint. But what we saw during the trials that some patients did unfortunately become ventilator dependent, but they remained on treatment. So we now have sham controlled clinical trial data on nusinersen treatment of ventilator dependent patients. And what we've seen is that these patients who required permit ventilation, actually still achieved motor milestones. They achieved more motor milestones and exhibited higher motor function scores than those who were on sham treatment, and none of the treated patients were sent on the Hammersmith infant neurological exam. 61% of them actually improved. This is despite being permanently ventilated. And on the top and 10 score, 78% of the treated patients improved, whereas 82% of the sham treated patients worsened. The treated patients also required less time on ventilation and had a reduction in their serious respiratory events during the study. I'm out of time here but I just wanted to ask that you consider allowing these patients to receive the benefits of nusinersen as well as maintaining the current open access to treatment that you have. Thank you very much.

Ginni Buccola: Thank you, Linda. Committee, do you have any questions? Okay, let's look at the motion.

Leah Marcotte: This is Leah Marcotte. I move that all products listed in the drug classes on slide 20 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require trial to preferred products with the same indication before non-preferred drug will be authorized unless contraindicated, not clinically appropriate, or one product is preferred.

Susan Flatebo: This is Susan Flatebo. I second.

Ginni Buccola: This is Ginni Buccola. All those in favor please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? The motion carries. And Leta, shall we go to a break?

Leta Evaskus: That's what I was thinking. Let's take a ten-minute break. We'll reconvene at 2:15.

[break]

Ginni Buccola: This is Ginni. Welcome back from break. We are at sleep disorder agents. Umang, whenever you're ready.

Umang Patel: Thank you. My next new final update is for sleep disorder agents. So moving right along, a little bit of background about insomnia, it's a complex system that comprises difficulties falling asleep, staying asleep, or non-refreshing sleep in combination with daytime dysfunction or stress. The symptom complex can be an independent disorder defined as primary insomnia or the result of another condition, which is secondary. Insomnia is commonly divided into three types based on duration: transient insomnia, which lasts up to one week and is often referred to as Adjustment Sleep Disorder because it's caused most often by an acute situational stress such as a test or deadline. And it's often recurrent with the same or similar stresses. The second is short term insomnia. By definition, it lasts one to six months and is usually associated with more persistent stressful situations such as death or illness or environmental, such as noise. And finally, chronic insomnia, which is insomnia lasting more than six months. In children, the incidence of insomnia ranges from one to six percent. And in children with neurodevelopmental or psychiatric comorbidities, the incidence is as high as 50 to 75%. And insomnia in children may result in irritability, restlessness, lack of concentration, suicide risk, and poor memory. On the next slide here, there's also non 24 hours sleep wake disorder, or non-24 moving forward, a chronic circadian rhythm disorder that causes problems with the timing of sleep and sleep patterns. It occurs in approximately 55 to 70% of people who are completely blind but can be experienced in sighted people. Prevalence among people with sight is unknown. It states that

the condition is characterized by failure a person's biologic clock is synchronized to a 24 hour day light/dark cycle in people who are completely blind, defined this no perception of light. This is due to their eyes' inability to register light signals. In sighted people, non-24 may be due to a number of factors such as altered sensitivity of light on circadian rhythm, self-selected changes in light exposure late in the day, and hormonal factors. Those with disorders may have difficulty falling or staying asleep and may wake up feeling as if they need more rest. People with non-24 may find their sleep patterns reversed where they need to sleep during the day and be awake at night. And the onset most often occurs in late teens or early 20s but can occur at any age and appears to be a lifelong effect. On the next slide, according to the US Department of Veteran Affairs and the DOD, last year in 2020, they published a guideline on management of patients with chronic insomnia disorder and obstructive sleep apnea. It provides three one-page algorithms and 41 recommendations around diagnosis and assessment of OSA and chronic insomnia disorder, treatment and management of OSA, and treatment and management of chronic insomnia disorder. For OFA, positive airway pressure is recommended as well as caution or avoidance of opioids and sedative hypnotics. And for chronic insomnia, cognitive behavioral therapy is recommended first line. There are weak recommendations given for low dose doxepin and zolpidem, zaleplon, or eszopiclone at the lowest effective dose for shortest possible duration. There is insufficient evidence to recommend for or against ramelteon or suvorexant. And they recommend against use of herbal supplements, antipsychotics, benzos, and diphenhydramine. On the next slide here, in December 2019, FDA approved Dayvigo, which was indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. In terms of limitations, there are a few here - CNS depressant effects and daytime impairment, sleep paralysis, hypnogogic or hypnopompic hallucinations and cataplexy light symptoms, complex behaviors, and compromised respiratory function. The recommended dose is five milligrams taking no more than once a day. Dosage may be increased to ten milligrams based on clinical response and tolerability with the max dose being ten milligrams. Availability is in five or ten milligram tablets. In terms of special populations, patients who have hepatic impairment, there is a dose adjustment for moderate hepatic impairment, but it is not recommended for severe hepatic impairment. And there is no dose

adjustment required in patients with mild, moderate, or severe renal impairment. For pregnancy, it is recommended to advise patients that there is a pregnancy exposure registry that monitors outcomes in women who are pregnant taking Dayvigo. On the next and final slide of my presentation we have Hetlioz and Hetlioz LQ. So on December 20, FDA approved a new indications for the treatment of nighttime sleep disturbance in Smith-Magenis Syndrome in pediatric patients three years to 15 years of age. As you can see, it already had a previous indication. No changes in any of the precautions warnings or limitations. The dosing is stratified by indication age, which can be found in the TCR or the TI. And it is available in 20 milligram capsules and four mg per ml oral suspension. In terms of special populations, it was noted in the studies that Hetlioz exposure was decreased by about 40% in patients who smoke compared to non-smokers. There is no dosage adjustment for patients who have renal impairment. And there was insufficient data to evaluate a drug associated risk in women who were pregnant. That concludes the sleep disorder agents. I'll go ahead and pause there for any questions.

Ginni Buccola: Thank you, Umang. Committee, do you have any questions? I do not see any stakeholders listed. So I think we can go right to the motion. This is Ginni Buccola and I will make the motion. I move that all products listed in the drug classes on slide 23 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require a trial of two preferred products with the same indication before a non-preferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Catherine Brown: Catherine Brown. I second.

Ginni Buccola: And this is Ginni Buccola again. All those in favor please say aye.

All: Aye.

Ginni Buccola: Any opposed. And the motion carries. Thanks, Umang. We'll move on to Apple Health Policy focusing on Radicava Ryan Taketomo.

Leta Evaskus: And I'm going to make Marissa the presenter now.

[unrelated discussion]

Ryan Taketomo: Good afternoon, DUR board. This Ryan Taketomo and I'll be presenting the Radicava clinical policy. So a brief background. Radicava is indicated for the for amyotrophic lateral sclerosis. It's a neurodegenerative disorder characterized by loss of cortical and spinal motor neurons. This leads to weakness, muscle atrophy, and cognitive impairment. As the disease progresses, it eventually leads to the inability to control muscle movement, eventually leading to paralysis. Currently, there's only one other drug that is indicated for the treatment of this disease called riluzole and it's the only drug shown to have provided a survival benefit. So going into the clinical trials for Radicava briefly, the first study looked at a broad population of ALS patients. They had a disease duration of three years, a forced vital capacity of 70%. And this broader population, one compared to placebo found no significant benefit for slowing of the progressive disease when compared to placebo. They did find in a post hoc analysis that in a particular population, which was in an earlier stage of disease, these are patients who had a score of two or more on all ALS functional rating scale revised. A fourth vital capacity of 80% and a disease duration of at most two years that there might be benefit and so they conducted a second study. And this study eventually showed that there was a slower decline in patients with Radicava versus placebo. Since then, there has not been any new randomized controlled trials published. So looking at the clinical criteria. Number one is to ensure that the patient has met the age threshold. Currently, it's only indicated for adults. Criteria number two ensures that the patient has an appropriate diagnosis using one of the three criteria that had been used to diagnose ALS. Criteria three is ensuring that the drug is prescribed by or in consultation with a neurologist which would be the primary doctor that would typically manage this disease. And criteria four, which is new from the previous iterations of this policy is to have the providers submit the following four criteria which would be if known the date of disease onset, if known, the date of initial diagnosis, and then to provide their most recent forced vital capacity. And with the pandemic, there may be instances where a patient may not be able to have this assessment done. And so in this case, it's still important to monitor the patient's respiratory function

given the progressive nature of the disease. And so in these special circumstances, we would ask that they provide a plan of how they would be monitoring their respiratory function over time using consistent metrics. So for example, maybe they can use a peak flow meter over the counter to assess that over time. And lastly is to provide their most recent revised ALSFRS score. To note, compared to previous iterations, there were certain thresholds that patients had to meet in order to have this drug approved. And based off of the feedback we've received, we've decided to remove all those thresholds and just to have the prescribers report the information listed in criteria four. Lastly, with criteria five is just to ensure that the patient has been on riluzole or provide documentation of why they cannot be on that drug. Moving down to the authorization criteria. Essentially, we would like the drug to be prescribed by or in consultation with neurologists from number one, with number two to provide a statement that the drug is working and showing a slowing of the disease versus if they were not on therapy. And three is to again, provide the most recent forced vital capacity and if they're not able to do that specific assessment, to provide their alternative that would have been supplied in the initial authorization criteria. And lastly, the most recent ALSFRS score. Again, there are no thresholds that the patient needs to meet. And as we moved down the policy, we just have the dosage and quantity limits which reflect the labeling. And we have definitions and then references. So with that, we can move on to the pen form. So this pen form is used to help facilitate the prior authorization process with the prescriber to ensure that the process runs as smoothly and efficiently as possible. So I'll give the committee a few moments to review the pen form and think about the clinical criteria. And if there are any questions. I'll open it up.

Ginni Buccola: Thanks, Ryan. Any questions, committee members?

Alex Park: This is Alex Park. Would you mind scrolling back up to criteria number four I think it was? Thank you. I know this is a policy that we have spent considerable time looking over. I think it was at -- no it wasn't the last meeting, it was the one before that I believe. And I appreciate your hard work on this, Ryan and everyone at HCA. I know we had a forced vital capacity requirement of 80% before and then we had that ALS score of 20-something, 24 I think it was. So I appreciate

the clinical practicality that's been brought into this policy now, which seems reasonable to me the way you worded it.

Ryan Taketomo: Thanks for your feedback, Dr. Park. This is Ryan Taketomo. And just to add that with criteria number four. When we've reviewed these cases for Radicava in the past, many of these items were pretty much always provided in the clinical documentation submitted. So it will not be adding to the workload that the providers are already doing, since it does appear to be good standard of practice for managing patients with this disease.

Ginni Buccola: Any other questions? I see we have I have one stakeholder listed, William Gittinger with Mitsubishi Tanabe Pharma. I also see a hand raised with the name Christine Flynn.

Leta Evaskus: Yeah, I've just unmuted William.

Ginni Buccola: Okay, wonderful. William, when you're ready, please go ahead. You'll have three minutes.

William Gittinger: My name is Bill Gittinger. I'm the director of government accounts for Mitsubishi Tanabe Pharma America. We are the manufacturer Radicava. I've had the pleasure of speaking to this committee to two previous Radicava discussions, primarily centered around the forced vital capacity scores and the ALSFRS readings. Ryan, you have done a great job of capturing the language that we discussed previously. So thank you for that. And the FEC language, it is now much safer for physician offices and staff to be able to report in this area based on the language that you've provided there. So thank you for that while we're still in the National Health Emergency. On the ALSFRS scores, we agree with that, too. So for the committee, when it comes to the motion in the voting, the manufacturer in these two areas, we agree with everything that Ryan has said here. It is a much safer set of coverage, language, and it's much fairer to the patient. So we appreciate that. I only have one sidebar question for the committee or Ryan. With trying to get the initial dose and then with retreatments, you're still asking for ALSFRS score to be reported, regardless of whether it's a high score, which qualifies or a very low score. And just in wondering, is that something that you intend to keep track of in the long term and use? Or is that in there just as a reminder to the

physicians, that it is a viable tool for them to use in diagnosis? And maybe they score everybody. But instead of just well, regardless of the score, everybody qualifies. I'm just going to send everybody through. Or is it a little bit more for the physician's discretion to see if they have somebody that scores very low that's not a good candidate that they're not even -- it may cause them to think I'm not even going to send this patient in? Or is it being used for something else? And that was our basic question. But Ryan, you did a great job with capturing everything. So thank you.

Ryan Taketomo: This is Ryan Taketomo. I can answer that question. So the purpose with that ALSFRS score is yes, to have the prescribers provide that as a baseline measure. Given the limited, strong clinical data that's available to us at this time, we do plan to use this to kind of monitored the use of Radicava over time as we move into the future and continue to assess the appropriate use of the drug.

William Gittinger: Okay, great. I appreciate the answer. Thank you, sir.

Ginni Buccola: Okay, thank you. Do we have a second stakeholder?

Leta Evaskus: Yes, Christine Flynn.

Ginni Buccola: Okay, go ahead, Christine. You'll have three minutes.

Christine Flynn: I'm sorry. I raised my hand on accident.

Ginni Buccola: Oh, okay. We'll move on. We'll go ahead then and go to the motion.

Alex Park: This is Alex Park. We waited for this one for a while. But I think we're feeling good about where this policy is now. So I move that the Apple Health Medicaid program implement the clinical criteria listed on policy 74.50.90-1 as recommended.

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

Ginni Buccola: This is Ginni Buccola. All those in favor, please say aye.

All: Aye.

Ginni Buccola: Are there any opposed? And the motion carries. And we'll move to the next Apple Health Policy on Spinraza.

Marissa Tabile: So this is Marissa. I'm from HCA. And I will be leading the Spinraza policy for Apple Health. So just to give some background, well, I won't give quite the clinical background. I think Umang did a great job going over of the disease state. But just to give you some background on the Spinraza policies, it is an update from the current policy that we currently implemented on August 1 of 2018. And what triggered the update for this policy was some feedback that we received from some of our medical reviewers here at the agency who review the Spinraza cases and SMA cases, and we thought it would be helpful to have just kind of an annual update for this particular product. There was also, like Umang had said, a new product, Evrysdi that gained FDA approval in August of 2020. Both Spinraza and Evrysdi share somewhat of a similar mechanism of action. So we wanted those two policies to really align together. So that was also something that triggered the update as well. So I'll just go ahead and get straight into the clinical criteria, and kind of make some mentions of some updates that we made to the criteria. So number one, the patient must have a documentation of a confirmed diagnosis of spinal muscular atrophy, homozygous SMN1, homozygous SMN1 gene deletion, SMN1 gene mutation, and compound heterozygous SMN1 gene mutation. That is still the same with the current policy that we have implemented. So that has not changed there. For number two, we did kind of change this wording around. So previously, we had criteria about having specific numbers of copies of SMN2 gene, but we thought it would be a little bit better to change the criteria to be just that the patient is symptomatic with a phenotype of SMA1, 2, or 3. So we did make updates to that criteria just to be a little bit more broader. And we did also add these criteria number three and number four currently on our Spinraza policy that's posted online. We don't have any mention that they can't take it simultaneously with the new product Evrysdi. So we have made note of that, as well as that the patient has not been previously treated with Zolgensma. So that is now included in our clinical criteria. And that is included because the evidence using those simultaneously are previously being treated. It hasn't really been studied very well, the evidence is not really available yet. So we did add that to our criteria. We did make some adjustments to criteria number five, as far as the baseline motor exams that we would be

examining. And we did change the duration or the look back for what documentation we would consider. So it would be documentation of one of the following baseline motor exams for the patient age and motor function within the last 90 days. I believe currently, that is 60 days. But just from pre-Covid, we were finding that with the cases that we were reviewing, the 60 day look back was too soon. So we extended that out so then it gives a little bit of leeway and allows for less frequent testing compared to every two months. We did have some feedback from one of our medical reviewers here as far as the tests, the documentation for the baseline motor exams. So these were the ones that she recommended. And she did specialize in physical medicine and rehabilitation. And these were the particular baseline motor exams that she found particularly helpful and meaningful. So it would be the six minute walk test, the CHOP INTEND, the HINE, the HFMSE, and the revised upper limb module. And then we did make a little bit of updates to number six. So we would want baseline documentation of at least a neurological exam, a manual muscle test, and pulmonary function tests if available. We did add this if available in here, due to Covid restrictions that we have right now. So that is the reason why that's in there. We did also add criteria number seven, where the patient does not require tracheostomy or invasive ventilation. This was made by recommendation by one of our MCOs. We do collaborate pretty intensely with our MCOs as far as reviewing this policy. And we thought this was a reasonable recommendation to add this particular criteria in, just because it's based off of the clinical trials, as well as some other clinical policies that we were reviewing did have this as well. So we thought it would be a reasonable recommendation to add in. And then for number eight, this is still the same compared to our current criteria. So prescribed by a provider with expertise in treating and managing SMA. We did add this blanket statement right here, much like we're doing with our current policies, where if all criteria are not met, but there are documented medically necessary or situational circumstances based on the professional judgment of the clinical reviewer, requests may be approved on a case by case basis up to the initial authorization duration. I think in the last two policy reviews that we've done, this statement has been added to pretty much all of our updated policies. So that was just added into this Spinraza policy for an update. For the continuation approval criteria, we did make a couple of changes to this particular section as well. So how we currently have it on the website, it lists all of these

particular baseline motor tests, motor exams, like five A through E, with particular point definitions. And we found the wording of that kind of confusing, so we simplified it just to make it more concise and a little bit clearer. So for the continuation approval criteria, we would just need documentation of one of the following. So it would be disease improvement or stability as demonstrated by at least one of the functional skills or motor milestones listed above, evaluated in the previous 90 days. That duration has changed as well. This used to be 60 days and we change that to be 90 days. Or that the disease progression is slower than what would otherwise be expected. And we did move those particular definitions or the point values that we will be looking for documentation down below in the definition section. So here, these are what we would consider improvement for the particular motor milestones. And these point values were derived from the clinical trials and what they defined in the clinical studies as a responder. And then stability is defined as the function of scale. It did not worsen from baseline. And then we also added the blanket statement here as well, about cases being reviewed on a case by case basis. And then here are the dosage and quantity limits. Like I mentioned, the definitions for the different motor baseline exams. And then we have the coding and the references. So I'll go ahead and switch over to the authorization form. And then we can go over any questions on the policy. So this is the authorization form much like you saw previously that helps guide the provider as far as authorizations for this medication and the criteria. So I'll go ahead and let the committee review this. And then I can answer any questions that you might have. So I'll go ahead and pause for a minute.

Ginni Buccola: This is Ginni. Thanks, Marissa. Just opening up to the committee making sure we get our questions answered. If there aren't any questions, we can go ahead and go to the motion.

Marissa Tabile: This is Marissa. I will pull the motion now. Okay. And it is already when you are.

Ginni Buccola: This is Ginni Buccola. I'm just going to pause. I see a hand raised by Lynda Finch. I don't have any stakeholders listed, but am I missing someone?

Lynda Finch: Yeah, so I had requested to provide testimony for spinal muscular atrophy and I work for Biogen representing Spinraza nusinersen. Can I make a couple comments? So I actually, I gave most of my testimony earlier but with regard to the policy, it looks as if you are excluding pre-symptomatic patients from treatment based on this. The criteria say the patient has to be symptomatic. Is that correct?

Marissa Tabile: Hi, yes, that is correct.

Lynda Finch: Okay. I guess that contradicts current good clinical practice, as well as the wealth of data showing the importance of treating this condition as early as possible. If you treat pre-symptomatically these babies can develop normally. And so to wait until they develop symptoms means that you're condemning them to have significant motor function deficits for the rest of their life. So I think this is something that should be open for discussion by the committee if you're going to change this criteria. As I mentioned in my earlier testimony, Washington State has newborn screening now implemented since August, and they are recommending immediate treatment with patients that have three or fewer copies of SMN2 gene. And that's pre-symptomatic SMA.

Ginni Buccola: Thank you for bringing that to our attention, Lynda. I appreciate that. Where can we go next with this discussion?

Marissa Tabile: I was going to say the reason why we have excluded pre-symptomatic patients was based off of the evidence that was currently available. I know that there was some interim results for pre-symptomatic patients that was released for the nurture trial. But we were only considering the evidence that was available right now for the symptomatic, which was the basis of the approval for Spinraza by the FDA. So that was the rationale for not including pre-symptomatic patients.

Lynda Finch: Yeah, the nurture trial has been published in a peer reviewed journal quite some time ago. So I think that you'll find that commercial policies reflect that. So that might be something worth considering. It's been over a year ago that that was published.

Marissa Tabile: Hi, this is Marissa. We can take into consideration removing criteria number two or altering that to maybe include pre-symptomatic, if we

go back and review the evidence for it. So I can take that into consideration. I don't know if the DUR board has any thoughts or feedback?

Ginni Buccola: This is Ginni Buccola and I would support that pause to review the evidence and consider what's been brought up in terms of allowing access to care. Are there other thoughts from the committee?

Alex Park: This is Alex Park. I agree with you Ginni. And as I think we've done with some of our other policies, because this is a condition that I don't think any of us on the committee have experience managing, I would appreciate having an expert opinion, either summarized for us or I'd be open to having them come to a future meeting. As we think about pre-symptomatic treatment, I would guess that we would have to come up with some criteria for that as well, probably mostly based on the genetic screening that's been mentioned. But it would probably be good to have some expert guidance, in addition to the wonderful work that HCA has already done.

Ginni Buccola: That's a great point, Alex. That could be helpful to all of us, especially as things are moving quickly in terms of genetic identification. And it sounds like that change has happened very recently, at least in terms of Washington State newborn screening.

Nancy Lee: This is Nancy. I would echo that, and maybe, as Dr. Park was saying maybe just more of an idea of a separate kind of pathway for pre-symptomatic because that could potentially be its own checklist of things to consider.

Alex Park: This is Alex Park. I agree, Nancy. And I guess the other thing I'd be looking for is what's being done in practice by those experts with that genetic counseling data. And we may not have to reinvent the wheel, I mean, I'm sure they have a protocol that they use that we could look at.

Marissa Tabile: Hi, this is Marissa. This is great feedback. I can definitely try to reach out maybe to another specialist and get their thoughts and have them review this policy as well for any feedback, specifically with the pre-symptomatic treatment. So I have made note of that on the side. And I will take that back.

Ginni Buccola: Thanks very much, Martha. So we will not consider this motion at this meeting. And we'll table that for after we get that feedback. Is that right?

Marissa Tabile: Yep. That sounds good.

Ginni Buccola: Thanks, everybody. Let's go ahead then and go to the next policy. Evrysdi, I believe I'm maybe saying it right.

Marissa Tabile: [unrelated discussion] Alright, Luke, the policy should be displayed and whenever you're ready, if you want to go ahead and get started, the floor is all yours.

Luke Dearden: This is Luke Dearden, HCA and the purpose of this is to present the new Apple Health policy regarding risdiplam or Evrysdi, which is indicated for spinal muscular atrophy or SMA. This policy is very similar to the one Marissa just presented on Spinraza. But a little bit of background specific to Evrysdi. It was approved by the FDA in August of 2020. It is the first orally administered medication used to treat SMA. It was evaluated in a two part clinical trial. The first evaluated 21 infants with type one SMA and demonstrated that 90% were alive and did not require permanent ventilation at 12 months. 81% were alive and did not require permanent ventilation at 23 months. While there was no comparator here, the authors did note that only approximately 25% of infants with type one SMA [audio dropout] permanent ventilation. Second part was a randomized, double blind placebo controlled trial conducted in patients from two years of age to 25 years. Participants taking Risdiplam achieved statistically significant change from baseline in the motor function measure 32 or the MFM 32 score relative to placebo. Also, a larger proportion of the participants in the treatment group achieved clinically meaningful improvement in the MFM 32 defined as a greater than 3% increase from baseline. Diarrhea, rash, mouth ulcers, arthralgia, and urinary tract infections were recorded more in the treatment group relative to placebo. So we can scroll down to the clinical criteria here. It's largely based on clinical trials and the product labeling. It also is nearly identical to the Spinraza clinical criteria, which includes number one, diagnosis of SMA, number two is the exact same criteria as you were all discussing with the Spinraza policy. So patient is symptomatic with

a phenotype type of SMA1, SMA2, SMA3. And then three, though, which is different than the Spinraza policy, the patient has to be at least two months of age or older. So it may not be the type of thing where you would start right after -- not use simultaneously when Spinraza five has not been treated with Zolgensma. And then number six here, just like the Spinraza policy, completion of one or more of the following functional scales that is appropriate for patient age and motor function within the last 90 days. I won't list them all out again. Number seven is similar to Spinraza, baseline documentation of all of the following, same as Spinraza, and does not require tracheostomy or invasive ventilation. And finally, prescribed by providers specializing in the treatment of SMA. We go down to reauthorization, it's the exact same as the Spinraza policy. Disease improvement or stability, 1A or 1B disease progression, is slower than what would otherwise be expected. And we have the dose and quantity limits. It is weight based dosing with a maximum dose of five milligrams orally once daily. And the definitions that inform what an improvement would be and stability. And then we have a brief summary of the clinical trials and then the references. And we can head over to the pen form as well here. And feel free to read through this. And I'd be happy to accept any questions or feedback.

Ginni Buccola: This is Ginni. Do we have any questions?

Alex Park: This is Alex Park. I guess we're going to be in the same situation with this as the prior policy. Is that right?

Luke Dearden: Yes, I would say that is correct. The difference here is that it is approved for -- it does have that two months or older limit. And then phenotypes two and three was studied in a two year old to 25 year old population. But that may leave us where we are with this Spinraza policy.

Ginni Buccola: This is Ginni. So again, I think I'm just echoing what Alex just asked. But it sounds like the question is similar to the previous motion. Is it type one if I'm using the term correctly, but under two months and pre-symptomatic, right? And if we don't need to put that into details, I think I'm just thinking out loud here.

Alex Park: This is Alex Park. If we go with what we did on the last policy, in terms of requesting expert consensus opinion, I'd be curious to know if there's a mechanism for pre-symptomatic treatment starting at two months. I'm not familiar with what the cadence of that screening and timeline is. And meeting the FDA requirement of being two months of age with this, it may be a moot point to Luke's point. I'm guessing we'd feel more comfortable as a committee having that information in front of us. Just taking this policy together with the one before it.

Ginni Buccola: This is Ginni. I would agree with you, Alex, I would feel more comfortable with that information from an expert.

Alex Park: This is Alex Park. While we're on this, because I'm actually glad we got another chance to look at the policy on this topic. Looking at that Zolgensma requirement. So it really seems like you guys are hot on the idea that you really want people to have been on that first before moving to one of these other two agents. Is that right?

Luke Dearden: This is Luke. Are you asking if we want them to start Zolgensma first?

Alex Park: Yes.

Luke Dearden: No, I don't think that's our intention.

Marissa Tabile: This is Marissa. I can confirm that that's not the intention. Because Zolgensma is a once in a lifetime, pretty much treatment, there's really no evidence showing that if you're treated with Zolgensma first and then transitioned over to these therapies, like the efficacy of it. So it would require a more in depth evidence review, which the evidence really isn't quite available, or even really there yet. So that's really the intent of that particular criteria.

Alex Park: This is Alex Park. Okay, I see. It’s a one-time treatment. Okay, I get it. So if they've been on that it kind of eliminates relevance of subsequent treatment with the other agents. Okay, that makes sense. Thank you.

Marissa Tabile: Could we just scroll down to see how six is worded with that clarification. Should there be any details around that? Just clarifying that it's not excluding. Because I agree with Alex. The way it’s written tends to seem like people need to be treated. But maybe this is just

moot considering that the physicians who will be [indistinct] prescribing this will have that context.

Luke Dearden: This is Luke. So, to clarify, you are referring to question number six on the pen form?

Marissa Tabile: Yeah.

Luke Dearden: Okay. Yeah, not that there's necessarily a correct answer but in order to be approved for either Spinraza or Evrysdi, the provider here would check no.

Alex Park: This is Alex Park here. I wish there was a way and I'm not an expert on the word smithing to be able to come up with what I'm asking for. I wish there was a way to eliminate the impression that a provider might have looking at this, thinking, oh, boy, I'm going to have to go and do Zolgensma first, whereas I was originally thinking of giving a patient [indistinct]or something like that. Though, I guess if you were an expert in the field, you would know that Zolgensma is one and done and maybe you would understand the point of that question.

Luke Dearden: I see what you're saying. I think there is a way we can switch that question up and wordsmith it so it kind of changes to an affirmative instead of a negative, if that makes sense.

Alex Park: Yeah, that'd be cool. I mean, I totally get why it needs to be there. But we just don't want providers to think that that's a step they have to take.

Catherine Brown: This is Catherine Brown. I think that's a good idea, because I have had one situation where I got the question if they'd already had Zolgensma and were not improving to the degree that the provider would like, if one of these other agents would be an option.

Alex Park: You might be our SMA expert on the panel here.

Ginni Buccola: This is Ginni. I was just going to add that. Thank you, Catherine, for sharing your experiences. And then we're going to hold over this motion just as we did the previous one, correct?

Marissa Tabile: Hi, this is Marissa. I think that's what it's sounding like, Ginni, just to hold off on Spinraza and Evrysdi.

Leta Evaskus: Yeah, Ginni. There's two hands raised. So I'd like to go to the stakeholders. [unrelated discussion]

Anton Nguyen: Thank you. Good afternoon, committee members. My name is Anton Nguyen. I'm a medical liaison with Genentech speaking on behalf of Evrysdi. Thank you for the opportunity to speak with you today. We appreciate your thorough review and publishing of the policy for Evrysdi. Particularly thank you, Luke and Umang for your presentation today. It was very thorough and very appropriate. So we appreciate that. As you know, Evrysdi is an SMN2 splicing modifier indicated for the treatment of spinal muscular atrophy in patients two months of age and older. We would like to address two points from the policy that's being reviewed. First, ventilated patients and secondly tying to recertification of therapy. So firstly, in regards to ventilation, we respectfully asked you consider the [indistinct] part to study as Luke mentioned where four patients did in fact meet the definition of permanent ventilation and continue to improve on the CHOP INTEND score. We're certainly happy to send this information to you. Second, we further ask you consider recertification of therapy every 12 months to lessen the burden on patients with SMA. We appreciate the need to assess the patients in a timely manner and offer to you our clinical trials have the primary endpoints at one year. Lastly, we continue to follow safety as a top priority and have ongoing collection with full safety data from the trials shared periodically at congresses and through journals. And again as Luke and Umang mentioned, based on animal data, Evrysdi may compromise male fertility. As for the common adverse reactions previously stated, such as upper respiratory tract infections, fever, rash, diarrhea, and arthralgia, these AEs have not changed in incidence over time and are well characterized. Thank you again for this opportunity and your consideration. I'll pause here and take any questions.

Ginni Buccola: Thank you, Anton. Do we have any more questions from the committee or any questions from the committee for Anton? Okay, and then Lynda Finch.

Leta Evaskus: This is Leta. Linda put her hand down. If you still want to speak, Lynda, could you raise your hand again? Okay, she does. There you go.

Lynda Finch: Hi. Yes, thank you. Thank you for the opportunity to speak again. Just wanted to reinforce and we didn't get to this topic because of the other topic about pre-symptomatic treatment, but my request for the committee today was to consider nusinersen treatment for patients who've been permanently ventilated. Just as I spoke to with the Evrysdi data, we did see improvements and we now have long term data from our clinical studies that demonstrates that patients who are treated with nusinersen that reach the need for permanent ventilation have clinically meaningful improvements in their motor function over time despite needing permanent ventilation. And so that's something that we didn't discuss. But that is also an exclusion in the HCA policy for both [indistinct] as well as for nusinersen. Thank you.

Ginni Buccola: Thank you, Lynda. Committee, do you have any additional questions for Lynda? Okay, do we need more discussion around or to look at additional recommendations since we're not going to be entertaining the motion today?

Alex Park: This is Alex Park. Since we're having the experts, or we're reaching out to specialists in the field, I'm open to having them address the ventilatory requirement issue in the policy as addressed by the stakeholders.

Ginni Buccola: I would agree with that. Alright. If there are no other thoughts or discussion from committee members, then we can go ahead and move to the next and our last policy of the day, imidazotetrazines oral agents.

Marissa Tabile: Hi, this is Marissa. I just wanted to make a note that I am going to take that down as a takeaway as well to have a specialist review for the permanent ventilation criteria that we've put in. So just wanted to let the DUR board know that I am taking a note of that. So with that, I will go ahead and pull up the last policy.

Ryan Taketomo: Good afternoon again, committee. This is Ryan Taketomo. I'll be presenting the anti-neoplastic and adjunctive therapies for imidazotetrazines oral agents. And kind of similar to previous

oncology policies presented in the past, we have a blanket set of criteria which helps us to gather the information we need to properly make a determination efficiently without having much back and forth with additional requests for information. So looking at the medical necessity, currently, there's only one drug in this class, which is Temodar or temozolomide. And we would be reviewing the drug when it's used for any of the standard labeled indications that are supported by compendia recognized by Medicaid. Moving to the clinical criteria, number one, to ensure that the prescriber provides the appropriate diagnosis and staging of the cancer. And if this drug is to be used in combination as part of a regimen that they provide the other drug names as well. And that kind of fulfills criteria number one. And to talk about 1C really quickly, if the drug is not part of a first line regimen and is being used second line, they provide the history of what drugs the patient has tried and failed in the past and if there any reasons that are available to provide that information. We can move down to criterion number two. So criteria two focuses on any related tests that may be related to that specific diagnosis, any labs, et cetera. And that just helps again to ensure we have all the information available to provide an accurate story of how the drug is going to be used. With criteria number three, to ensure that the drug is being described by an appropriate provider with criteria four to ensure that the patient doesn't have any contraindications to the medication, or any of the other medications in the regimen for safety. And then with criteria number five, to ensure that the requested dose and quantity are within the limits of how the drug is used and how it was studied. And lastly, for number six, just to provide a plan of when their next follow-up will be in to ensure that the patient will be monitored appropriately. And so with the authorization criteria, we typically just ask to provide all the clinical documentation to show, is the patient's cancer progressing? Or is the drug working? And are we seeing some type of positive clinical response that would fulfill number one? And with number two, if again, the medication is a part of regimen, that related information is supplied as well, so that we have the full picture when making the determination for one of these imidazotetrazines. And that wraps up the clinical criteria. Then we have the dosing quantity limits, which reflected the dosing in the labeling. And then just some references so we can move on to the pen form. Again, this pen form is used to facilitate the prior authorization process and to ensure that it goes as smoothly and efficiently as possible. So I'll give a

few moments for the committee to review the pen form and open it up for questions. Thanks.

Ginni Buccola: This is Ginni. Thanks, Ryan. Committee members, thoughts, questions?

Susan Flatebo: This is Susan Flatebo. I just had a question under number two. The patient's diagnosis ICD code plus description, indicate stage, and then disease type. What does that mean? Because wouldn't that be answered in your diagnosis and description? I guess I don't understand what that means.

Ryan Taketomo: This Ryan Taketomo. That is a good question. And I would agree that the intent is that that ICD or that first part of the question would answer it. So I'd be open to removing that disease type.

Alex Park: This is Alex Park. ICD 10 codes get pretty specific. But they might miss things like initial onset of disease versus recurrence versus refractory versus et cetera. Is that what you guys were going for when you wrote disease type?

Donna Sullivan: Hi, Dr. Park, this is Donna. Sorry, for the long delay. I really don't remember. We kind of made this generic policy over a year ago. So I don't really remember the conversation about why we put this in here.

Alex Park: I'm only bringing that up because I was just going through the FDA indications for this drug and for glioblastoma and man, we've been talking about some really ugly diseases today guys. SMA and this. Anyway, it looks like it's considered off-label for recurrent or relapse, glioblastoma, but it is FTD indicated for newly diagnosed high grade glioblastoma. But I honestly don't know if the ICD 10 codes for glioblastoma capture that. So if you were to need that disease type or not.

Donna Sullivan: Ryan, do we have that statement that says, is there additional information that you would like to send? Maybe we could just ask, you know, additional clinical information that they would like to share related to the diagnosis instead of saying disease type.

Ryan Taketomo: And this is Ryan Taketomo. So after thinking about question number two, I think, really the purpose of that is to get the full diagnosis. And as Dr. Park was referring to with the type, if it is refractory, if it is a new diagnosis. And I also wonder about the usefulness of the ICD10 code part of the question. It makes sense but I think really the purpose of number two is to capture what type of cancer are we treating and the details around it. So if it's new, if it's refractory, that's what I would want number two to provide us.

Susan Flatebo: This is Susan again. So at the bottom of this page, did it ask for chart notes? So wouldn't that be included in the chart notes as far as you know, initial therapy, or is this for progression?

Ryan Taketomo: This is Ryan Taketomo. Yes, that information is usually included with the chart notes. Just having that information on the form when we receive it helps our initial frontline team to triage it quicker so that they can send it to our clinicians and review it. And it just makes our process internally more efficient.

Susan Flatebo: And then I have just another quick question. This is Susan again. Scroll up on number three. Is this being used in combination with other chemotherapeutic or adjuvant agents? And I'm assuming this includes radiation. So they would check yes for radiation? Because for initial diagnosis, high grade, GBM, it's used in combination with radiation. So I'm just questioning, would that include adjuvant agents? Does that include radiation?

Ryan Taketomo: This is Ryan Taketomo. Would it be helpful to add the radio therapy in addition? So maybe word it as, is this being used in combination with other chemotherapeutic, radio therapeutic, or adjuvant agents?

Susan Flatebo: Yeah, just because I think that would probably make it easier for you to approve it if you saw the dosing for newly diagnosed and it's being used in radiation, which is indication.

Ryan Taketomo: That makes sense to me.

Susan Flatebo: Yeah. Otherwise, I think it might be harder for them to think, is this radiation considered an adjuvant agent.

Alex Park: This is Alex Park. Why are we asking that question? I mean, if they are on other chemotherapeutic agents, wouldn't there be an instance where temozolomide would not be approved?

Ryan Taketomo: And so at least right now, because temozolomide is the only drug in this class, it may not make sense, but because we're looking at this policy at a drug class level, if other drugs are added then that question might become more relevant. And I think because this is taken from of our other oncology policies where they have multiple agents, that question might have been more relevant. But because this policy only has one agent right now, at least for temozolomide, specifically, it initially does not make sense in some cases.

Alex Park: Okay. So it sounds like this question for the time being wouldn't really influence approval, but it's part of the, I don't know, paperwork streamlining process. Okay.

Ryan Taketomo: Yeah.

Susan Flatebo: It just seems like a really in depth form for a drug that's reused pretty much on label most of the time. I rarely see it given off label. But anyway.

Ginni Buccola: So this is Ginni just chiming in to see where the committee is on this. It looks like there are enough questions to again, hold this.

Susan Flatebo: This is Susan. I'm fine with the form. It just seems really detailed to me. But I mean, it's fine by me. I figure if the oncologist is sending chart notes to specify the diagnosis and how it's being used, that would probably answer all these questions, I'm sure.

Ginni Buccola: Any other considerations or do we feel ready to entertain the motion or wait?

Alex Park: This is Alex Park. So, Susan, are you saying you are okay with the form the way it looks? Or do you want us to think as a committee about eliminating that one part of number two, and then rewording number three?

Susan Flatebo: Well, this really is a detailed form for a pretty straightforward -- this drug isn't used that often. But like I said, if you can leave everything in like it is, as long as they're attaching chart notes anyway, all that information will be included.

Ginni Buccola: So this is Ginni. I just want to add that I think it is a great observation that it seems overly detailed. And I just want to reflect your words because this is certainly outside of my practice area. And in terms of again, making care accessible, your feedback sounds very valid. I don't know what at the HCA have to say about that.

Susan Flatebo: And this is Susan again. And I have to be honest. We don't really have any issues with Temodar not being covered under Medicare or Medicaid insurance. That really hasn't been an issue in my experience. So I don't know if having this form is necessarily going to keep patients from getting their therapy. It just seems like it's a form that you have to take the form to fill out. And that's probably the biggest time constraint. But as long as they have chart notes, everything is going to be included on that so I'm fine with it.

Ginni Buccola: Okay, this is Ginni again. I'm fine moving to the motion as long we feel comfortable with this or if we want to see those changes that Marissa has highlighted there, that's also great. We can ask them to bring it back. So I hear that Susan's okay moving to a motion. Anybody else have any reservations?

Alex Park: Can I just see the first part of the policy again? Could you scroll up? Thank you.

Susan Flatebo: And then can I just ask the Health Care Authority, as far as this form being utilized by oncologists, are they pretty straightforward as far as, you know, are you having to deny patients therapy because maybe the form wasn't filled out correctly? Just because I see that adjuvant agents in there, I don't know if, not always the oncologist is filling out these forms. Sometimes it's the front office person or the MA or somebody that may not know how to answer these questions correctly. And so maybe it may get denied and sent back to the office until then it comes to me or the doctor.

Ryan Taketomo: I can answer. And just to clarify, the form is, again, just to help facilitate the PA processor prior authorization process. We don't [indistinct] just look at the form. And if they didn't fill out one of the questions correctly, we would deny it. We would definitely look at the clinical documentation or the chart notes provided and really take the package as a whole. Just filling out that form helps our process run more smoothly. I'm not sure if any of our operations staff are online but they made use that information to help them with their processes, their nonclinical processes as well.

Susan Flatebo: Okay, thank you.

Alex Park: This is Alex Park. I'm sorry to be such a pest. Can you scroll down just a little? I just want to see what number C says. Okay, thank you. Okay, thanks.

Ginni Buccola: Alright, this is Ginni. So I'm going to propose that we look at the motion.

Alex Park This is Alex Park and I move the Apple Health Medicaid program implement the clinical criteria listed on policy 21.10.40-1 as recommended.

Susan Flatebo: Susan Flatebo. I second.

Ginni Buccola: This is Ginni Buccola. All those in favor say aye.

All: Aye.

Ginni Buccola: Any opposed? And the motion carries. And that's our last motion for the day. So the DUR board is adjourned. Thanks to everybody for thoughtful comments and consideration. And I'm sorry we couldn't see each other. I look forward to hopefully see everybody in June. Leta, I'll turn it over to you.

Leta Evaskus: Great. Thank you guys so much for staying over. We thought we were going to end at around three. So thank you. And yeah, have a great summer and we'll see you -- or spring, whatever you want to call it. We'll see you in June.

[end of file]