Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board
Meeting Notes
June 17, 2020

Leta Evaskus: Okay. Excellent. So let's kick this off.

Virginia Buccola: Do you want me to kick this off, Leta, or do you want to start with…

Leta Evaskus: I want you to start with the roll call. So introduce yourself as the chair and everybody can say here as Ginni reads off your name.

Virginia Buccola: Well good morning everyone. Thanks for the patience already. Seven minutes into this socially distanced P&T Committee meeting. I'm Virginia Buccola or Ginni. I'm going to read off your names. My apologies if I mispronounce anyone's name. After I say your name, please call "here". Starting with the P&T Committee Members Alex Park?

Alex Park: Here.

Virginia Buccola: Susan Flatebo?

Susan Flatebo: Here.

Virginia Buccola: Diane Schwilke?

Diane Schwilke: Good morning. I'm here.

Virginia Buccola: Jordan Storhaug?

Jordan Storhaug: Here.

Virginia Buccola: Nancy Lee?

Nancy Lee: Here.

Virginia Buccola: Leah Marcotte?

Leah Marcotte: Here.

Virginia Buccola: Catherine Brown?

Catherine Brown: Here.

Virginia Buccola: And Connie Huynh?

Connie Huynh: Here.

Virginia Buccola: Moving to the Health Care Authority members. Leta Evaskus?

Leta Evaskus: Here.

Virginia Buccola: Donna Sullivan?

Donna Sullivan: Here.

Virginia Buccola: Ryan Pistoresi?

Ryan Pistoresi: Here.

Virginia Buccola: Chris Chen?

Donna Sullivan: I don't think Dr. Chen is going to be joining us.

Virginia Buccola: Luke Dearden?

Luke Dearden: Here.

Virginia Buccola: Amy Irwin?

Amy Irwin: Here.

Virginia Buccola: Ryan Taketomo? Pass. I'll move to Marissa Tabile?

Marissa Tabile: Here.

Virginia Buccola: L&I members. Jaymie Mai?

Jaymie Mai: Here.

Virginia Buccola: Magellan Medicaid Administration members Umang Patel?

Umang Patel: Here.

Virginia Buccola: Our DERP presenters are Leila Kahwati?

Leila Kahwati: Here.

Virginia Buccola: And Gerald Gartlehner? Pardon my pronunciation. He might not be on yet. Our Managed Care Organization representatives Jennifer Wang from Molina.

Leta Evaskus: I will have to unmute them.

Virginia Buccola: So it's Jennifer and Catherine.

Leta Evaskus: I see Petra. I have unmuted you.

Petra Eichelsdoerfer: I'm here.

Leta Evaskus: I don't see… oh, Jennifer. I see Jennifer, but she is not on the phone I see.

Virginia Buccola: Okay. And then Catherine Vu of Community Health Plan.

Leta Evaskus: I don't see Catherine.

Virginia Buccola: I want to give a special welcome to Leah Marcotte. Dr. Marcotte, I hope I'm saying your last name correctly. She's our brand new member of our P&T Committee and this is her first meeting. We wish it wasn't socially distanced and we could welcome you. Not to put you on the spot, but if you could share a little bit about yourself with the committee, we'd like to just all say a warm hello.

Leah Marcotte: Yeah. Of course. Thank you, so much. I'm really happy to be here. I am a primary care physician at the University of Washington. I am also the associate medical director of the [inaudible] at UW. I am very excited to be on the committee. I live in South Seattle with my partner and two dogs.

Virginia Buccola: Welcome. And feel free to ask questions as needed. Of course, we're all here. Leta is amazing at supporting us all.

Leah Marcotte: Thank you.

Virginia Buccola: So, I'll move to Leta for you to go over meeting logistics.

Leta Evaskus: So, the committee and presenters have all been added as organizers. You can mute and unmute yourselves. Please mute yourself when you're not speaking to limit the background noise. The presenters will share their webcams while speaking. Then, the P&T Committee will share their webcams during discussion and motions. We did realize this morning that only six webcams are being allowed to be shared at a time. So, I realize not everyone is gonna be able to share their webcam. You can turn off your webcam when you're not presenting. For stakeholder participation, a number of stakeholders did sign up before the meeting. So, during the stakeholder input section on the agenda, the Chair will call the list of names that preregistered. Each person will get three minutes to speak. I will unmute you. After the list of names has been called, then the Chair will ask if anybody else would like to speak. You need to use the raise hand function, which under the attendee list, you'll see a little hand. So just click on that, and I'll see that you want to speak. I'll call your name and unmute you. You could also ask questions in the question tab, and I will address those during the stakeholder input portion. Let's see. The meeting is being recorded. So, please state your name every time that you speak. Now, Donna Sullivan has an announcement.

Donna Sullivan: So, I just wanted to give a slight update to the agenda. We will not be reviewing the Oxpreda clinical policy today. So, we will postpone that to a separate meeting.

Leila Kahwati: Thank you, everybody. I'm happy to be here today to present results from updated systematic reviews on targeted immune modulators. I'm going to be presenting two of the three updated findings. My colleague, Gerald Gartlehner, will present the third one. So, you're gonna hear from me. Then you'll hear from Gerald. Then, I'll be back. These are findings from an updated systematic review that was previously one large review. It was split into three smaller reviews focused on specific clinical conditions. This first one is related to use of TIMs agents in Crohn's disease and ulcerative colitis. I'm going to spend a bit more time taking you through the methods on this. Then, we are going to kind of skip through methods on the subsequent two presentations, because the methods were largely the same, just for the sake of time. These were all originally much longer presentations. We're going to try to condense them for your meeting here today. So, with that, if you'll go to the next slide.

This is just a brief overview of the presentation. Then we'll go right into the background. So, if you'll skip ahead two slides.

So, as you know, Crohn's disease and ulcerative colitis are chronic inflammatory bowel conditions. Whereas Crohn's disease is Crohn's disease involves the full thickness of the bowel wall anywhere from the mouth to anus, ulcerative colitis typically only involves the mucosal surface and is limited to the colon and rectum. Targeted immune modulators, or TIMs for short, are a group of medications that selectively block the mechanisms involved in the immune response. The first TIM for Crohn's disease was infliximab, which was approved by the FDA in 1998. Since then, many additional agents, including biosimilars, have been approved for both conditions.

The TIM agents that are either FDA approved for Crohn's disease or ulcerative colitis, or both, or that are in the pipeline for approval, fall into six categories in terms of their mechanisms of action, as depicted on this slide. So, some agents are approved for both conditions. Those are the ones that are depicted in the light bluish-greyish color. Others are only approved for one or the other condition. Those are depicted in either light green or in yellow on this slide. You'll also notice there are four pipeline agents, which are not yet approved for either Crohn's or ulcerative colitis. Upadacitinib is already approved for rheumatoid arthritis and risankizumab is already approved for psoriasis, while the

other two agents have upadacitinib and PF-04236921, are not yet approved for any indications.

So these are what we call the PICOS, or the study selection criteria that we use for the update. The population for this particular presentation were adults with Crohn's or ulcerative colitis. Gerald will be presenting on populations. That includes persons with rheumatoid arthritis and ankylosing spondylitis. Then, when I come back, I'll be presenting on the populations of persons with psoriasis and psoriatic arthritis. The TIM agents that we considered for across all three were TIMs that are FDA approved or that are in the pipeline for approval. The specific drugs for ulcerative colitis and Crohn's were the ones I just described on the previous slide. For comparators, we selected studies that compared one FDA approved TIM agent to another agent in a head-to-head comparison. For the pipeline agents, we also considered placebo or standard of care comparisons. For outcomes across all three reviews, we selected studies that reported on measures of disease remission, clinical improvement, quality of life, adverse events, serious adverse events, and other health outcomes. Finally, for study designs, we were mainly focused on randomized control trials of at least 12 weeks or longer duration, but for harms, we also selected cohort studies of at least 12 weeks duration that had 1000 or more participants.

This slide describes the three key questions for the update. The first question was about the comparative effectiveness of the TIM agents. The second was about for comparative harms of the TIM agents. The third key question was about variation by subgroups. The full reports also included a question around ongoing studies and I refer you to the full reports for information about that.

This is a brief summary of our methods. Again, that is the same across all three reviews that you're going to hear about today. We searched Ovid MEDLINE, Embase, and the Cochrane library picking up where the prior review had left off, which is January 2017 through last fall with continued active surveillance of the literature through about the end of the year. We used OpenEpi for calculating absolute risk differences and incident rate ratios, risk ratios, and confidence intervals from any newly identified studies where that information was not provided by study authors. Then, we used the GRADE approach for assessing the overall quality of evidence for each comparison for up to six outcomes. Lastly, as I mentioned, we did look at ongoing studies, and those are available in the full report.

As a reminder, in reviews with DERP, we do include an assessment of the methodological quality of each included study using a standardized

assessment that results in a rating of good, fair, or poor methodological quality for each study. The definitions of those are on this slide for your reference.

The next slide is just a reminder of the GRADE approach for evaluating the body of evidence for each comparison. So, in this review, we looked at up to six outcomes, including disease remission, clinical improvement, adverse events, serious adverse events, and withdrawals due to adverse events. The evidence is judged with respect to consistency, precision, study limitations, which is essentially methodological quality, and directness. Bodies of evidence for a comparison and an outcome are then graded as high, moderate, low, or very low quality. Bodies of RCT evidence start by default at a high rating. Then, we downgrade them one or two levels for any concerns in any of those domains I had just mentioned. Bodies of observational evidence, such as cohort studies, start at a low rating. Then, they can be downgraded for those same domains, but they can also be upgraded when other features are present. This slide just shows how each GRADE rating can be interested with respect to confidence in the findings.

So, now, we'll move into the specific findings for ulcerative colitis and Crohn's disease. This is just an overview of our literature flow diagram. Basically, the important part is at the very bottom. We ended up identifying three new studies and carried forward six studies from the previous review for a cumulative total of nine mixed studies that were in this update. Two were conducted among participants with ulcerative colitis. Four were conducted among participants with Crohn's disease. Three were conducted in mixed populations that included participants with both conditions.

This slide is an overview of the nine included studies. As I mentioned three are new to the update. Six were in the previous report. Four were randomized trials, while five were cohort studies. You can see some of the other study characteristics summarized on this graphic. Of note, eight of the nine studies were head-to-head comparisons of TIM agents. One was a pipeline study comparing a TIM agent to placebo.

Before we get into the specific findings, I just wanted to provide you with a key to some of these abbreviations that will be encountered both in this presentation and in the other two you will hear. I won't read them all off the slide, but they are here for your reference, in case you want to refer back to them.

First we'll discuss Crohn's disease, if you'll go to the next slide. For key question one, which is about the comparative effectiveness of TIMs, for

Crohn's disease, we identified one poor methodological quality study and one fair methodological quality study. The poor study was an open label randomized persons who were post-ileocolonic resection and at high risk for recurrence. They were randomized to either adalimumab or infliximab. In this particular study, there was no difference in clinical and endoscopic or histologic recurrence after 12 months. We graded that evidence as very low. The fair quality study was an open label switch trial that randomized persons taking infliximab maintenance therapy to either continue the current regimen or to switch to adalimumab with followup over 54 weeks. The median scores on the inflammatory bowel disease questionnaire, which is a quality of life instrument specific to inflammatory bowel disease were not different between the two groups throughout the study. We also graded the evidence as very low.

For key question two, comparative harms in Crohn's disease, in addition to the one fair methodologic quality I had already mentioned, we also identified three cohort studies. Each used slightly different comparisons. First one compared adalimumab to infliximab, which is from the fair methodological quality RCT. That's listed on the lower panel of this slide. For that trial for adverse events, the relative risk was 1.1 with confidence intervals that included the null effect. So, essentially, no difference between groups in terms of adverse events. We graded that evidence as very low. For serious adverse events, the relative risk was ten, but as you can see, the confidence intervals were very wide, ranging from 0.57 to 174. So, really, you can't make much of that relationship. It's just too imprecise. We also graded that evidence as very low. For withdrawals to adverse events, the relative risk was 6.2, but again, the confidence intervals are way too imprecise to determine the relationship. So, we also graded that evidence as very low. Lastly, for infections, which was an outcome reported in one cohort study, the adjusted hazard ratio was 1.6 with a confidence interval that stands the null effect but was also somewhat imprecise. So, we also graded that outcome as very low.

Moving onto the other comparisons for cohort studies. There was one study that compared adalimumab with certolizumab and infliximab. There were three study arms there. There were no statistically significant differences in serious infections between any of three paralyzed comparisons, as you can see in the top panel of this slide, and all the estimates included the null effect. In the bottom panel of the slide is a comparison of adalimumab with infliximab and etanercept. This particular outcome was reported in two cohort studies that were conducted in mixed populations, meaning the populations included participants with both Crohn's disease, but also included participants with other autoimmune diseases, for which biologics are indicated, for

example, rheumatoid arthritis. The outcome that they reported with tuberculosis incidents, and there was no difference in the incidents of tuberculosis between adalimumab and infliximab, which is the most relevant comparison here, since those were the drugs that are created for Crohn's disease and ulcerative colitis. There was a statistically significant higher incidents of tuberculosis for adalimumab and infliximab when compared to etanercept, but I know etanercept is not FDA approved for ulcerative colitis, or Crohn's. So, it's a less relevant comparison.

For key question three, which is around variation by subgroup, we did not identify any studies reporting any subgroup data. So, that didn't have any evidence there.

We're going to skip pipeline TIMs, just for the sake of time. They all are in the full report, and we are going to move onto the findings in ulcerative colitis. So, this would be slide 22.

For comparative effectiveness in ulcerative colitis, we did identify one new fair methodological quality RCT that compared vedolizumab with adalimumab. This study reported a higher incidents of clinical disease remission and endoscopic remission at 52 weeks for vedolizumab compared to adalimumab. We graded this evidence as moderate quality. Steroid-free remission was numerically lower among participants with vedolizumab, as you can see here. It was 13% versus 22% among adalimumab participants, but this difference was not statistically significant, but it did come close to excluding the null effect, the upper confidence interval was 0.4%. We graded this particular outcome as low quality. Then, lastly, participants that were randomized to vedolizumab experienced significantly larger improvements on two different quality of life measures compared to adalimumab. So, we graded that evidence as moderate quality. So, bottom line, this comparison is that vedolizumab seems to be more effective than adalimumab on most measures.

In terms of comparative harms, we identified three comparisons. The trial that I just mentioned, which compared vedolizumab to adalimumab. Then, there were three cohort studies. I'll discuss each of those in turn. In the trial, which the data is show at the bottom panel of the slide, which compared vedolizumab to adalimumab, there was no difference between groups for adverse events or withdrawals due to adverse events. We assigned a grade of moderate to overall adverse events. Then, low to the other two outcomes, primarily those two outcomes had much rare events. Thus, the estimates were more imprecise. In the next comparison, which is infliximab versus adalimumab, we identified two cohort studies. One reported the risk of serious infection. The other

reported just on the risk of infection. Both reported a lower incidents of infection with infliximab. The hazard ratios were 0.62 and 0.68 respectively, but as you can see, both of these results were imprecise and not statistically significant. So, we graded this evidence as very low quality. The last comparison was between adalimumab on the lower panel of this slide, infliximab and etanercept. These are the same two studies I talked about in the Crohn's disease section. They reported on tuberculosis incidents. As I mentioned, there is no significant difference in tuberculosis incidents between adalimumab and infliximab, which again, are the two drugs approved for these indications.

There were no subgroup findings in studies among persons with ulcerative colitis to report.

We identified several relevant network meta-analysis for use of TIMs among participants with ulcerative colitis. The two most recent and comprehensive are summarized on these next few slides. We don't have time to go through them, but they are here for your reference and information.

We are going to skip over to… I think it's slide 32, the discussion. Just a few limitations to mention, as you think about this evidence. First, there are a limited number of head-to-head studies in these two clinical conditions. No studies were powered for harm outcomes, particularly rare outcomes. Drug manufacturers did sponsor all of the eligible randomized trials. Most of the cohort studies used administrative or claims data, which may not be as valid or reliable as direct measurement, particularly for harms. Finally, we did not include reviews that were shorter than 12 weeks. We didn't include cohort studies with fewer than 1000 participants. We did not include data from conference abstracts, press releases, or studies published in languages other than English.

In conclusion, we found limited evidence for comparative effectiveness or harms of TIMs for Crohn's disease. For ulcerative colitis, we did find that vedolizumab is more effective than adalimumab with no difference in harms, but there is really limited evidence for other comparisons in ulcerative colitis. Thirteen studies are ongoing in this area. Some of them are head-to-head comparisons. Some are studies of pipeline agents against placebo, but the results for all of them, none of them will have results available earlier than March 2021.

I think that's it. I am happy to take any questions at this point on this particular review.

Nancy Lee: Hi, Leila. This is Nancy. Thank you, so much, for your review. I know you didn't spend a lot of time on the network meta-analysis, but I was just

kind of curious looking at that table, in the more thorough evaluation, vedolizumab kind of had more in favor than adalimumab, but in the network meta-analysis table, it said none for a lot of them. What do you... based on your assessment of that network meta-analysis, which I know has a lot of flaws, as well, what are your thoughts about that finding in that network meta-analysis?

Leila Kahwati: That network meta-analysis was published before the trial that came out of the direct comparison of vedolizumab to adalimumab. So, I would say the network meta-analysis is useful information, but as soon as it's published, it's sort of obsolete when new studies come out. So, I would probably favor the direct head-to-head comparison if you're evaluating those two agents side by side, because it's a direct comparison versus this, which did not have the benefit of that study when it was conducted. Does that answer your question?

Nancy Lee: Yes. Thank you, very much.

Leila Kahwati: Mm-hmm.

Virginia Buccola: Thanks again, Leila. That was a great presentation. Committee, are there any other questions for Leila? Alright. So, I believe we're gonna move now to our stakeholders. We have two assigned stakeholders, Piao Ching representing Pfizer, and Dr. Margaret Olmon representing AbbVie. Are there any other stakeholders present that I haven't listed, could you please raise your hand for Leta to be aware. Just as a reminder for the stakeholders, if you could state your name. I'll have a little timer going for three minutes for each stakeholder. So, we'll go now to Piao Ching.

Leta Evaskus: Okay. Just a second. I will. . . okay. Piao, you are unmuted.

Piao Ching: Good morning. My name is Piao Ching. I am a pharmacist with Pfizer Medical Affairs team. I want to thank you for allowing me to provide medical information about tofacitinib, brand name Xeljanz and Xeljanz XR in support of Pfizer's request to add tofacitinib to Apple Health preferred drug list. Tofacitinib is indicated for the treatment of adult patients with moderate to severe ulcerative colitis who have inadequate response or who are intolerant to TNF blockers. Use of tofacitinib in combination with biological therapies for ulcerative colitis [inaudible] potent immunosuppressant, such as azathioprine and cyclosporine is not recommended. We recommend an introduction dose of 10 mg twice daily or 22 mg XR once daily for eight weeks and evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue 10 mg twice daily or 22 mg XR once daily for a maximum of 16 weeks. We recommend a maintenance dose of 5 mg twice daily or 11 mg XR once daily. For patients with loss of response

during maintenance treatment, a dosage of 10 mg twice daily, or 22 mg XR once daily, may be considered and limited to the shortest duration with careful consideration of the benefits and risk for the individual patient. Tofacitinib includes a box warning for serious infection, mortality, malignancy, and thrombosis. While there are a number of available pharmacologic treatments, unmet medical need remains high, and new treatments are needed. A systematic literature reveal conditions for [inaudible] TNF inhibitor primary failures and secondary failures with [inaudible] TNF inhibitors were common for ulcerative colitis patients. In closing, ulcerative colitis continues to have a high unmet medical need in Apple Health population. To further manage this disease, we need alternative agents available after TNF inhibitor. Adding a medication with a novel mechanism of action and with oral administration will offer an additional treatment option for patients with ulcerative colitis in the Apple Health population. Based on the efficacy and safety of tofacitinib, we ask the committee to add Xeljanz and Xeljanz XR to Apple Health preferred drug list. I would be happy to respond to any questions you may have. Thank you.

Virginia Buccola: Thank you, Mr. Ching. Are there any questions from the committee for Mr. Ching? Okay. Thank you, very much. We'll move on to Dr. Margaret Olmon from AbbVie. Dr. Olmon, you have three minutes once we get to you.

Leta Evaskus: Margaret, I see that you are self-muted. So, I've unmuted you, if you can unmute yourself. There you go.

Margaret Olmon: Okay. Great. Thank you. Hello. I'm Dr. Margaret Olmon from medical affairs at AbbVie. Thank you for the opportunity to speak with you. As you know, Humira has ten FDA approved indications. Today, we're examining the data that supported the approval of adalimumab, brand name Humira, for three of those indications, the treatment of adult Crohn's disease, pediatric Crohn's disease, and ulcerative colitis. Since this is only a short summary, please review the full prescribing information at www.rxabbvie.com for comprehensive safety and efficacy data. Humira and TNF antagonist, is indicated to reduce the signs and symptoms and reducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who had inadequate response to conventional therapy or had lost response to or are intolerant to infliximab. The Gain [sounds like] trial evaluated Humira induction therapy in adult Crohn's disease patients initially treated with infliximab and either lost response or discontinued its use as a result of intolerance. At week four, 21% of Humira patients versus 7 of the placebo patients were in clinical remission. The Charm [sounds like] trial evaluated maintenance of clinical remission in adults with moderately to

severely active Crohn's disease. Those who demonstrated a clinical response to Humira during a four-week open label phase were randomized to receive either Humira every week, every other week, or placebo. In the Humira every other week group, 40% of patients achieved clinical remission at week 26 versus 17% in the placebo group. The approved indication for Humira as a treatment of pediatric patients, 6 to 17 years old with moderate to severe Crohn's disease followed the Imagine 1 study that evaluate a safety and efficacy with maintenance dosing regimens following induction. The efficacy and safety of Humira to treat adults with moderate to severe ulcerative colitis was evaluated in two clinical trials with the induction and maintenance of remission. At 52 weeks in the subgroup of patients with prior anti-TNF use, 10% of those in the Humira group were in clinical remission versus 3% in the placebo group. All TNF antagonists carry similar box warnings regarding serious infections, TB, and malignancies. Patients starting any anti-TNF, including Humira, should be screened for TB and carefully monitored for serious events. Humira has sustained efficacy, published long-term safety data, and a durable response in patients with Crohn's disease and ulcerative colitis. I respectfully urge the committee to maintain preferred status for Humira on the PDL for the people of Washington. Thanks, so much, for your time and attention. I would be happy to answer any questions you might have.

Virginia Buccola: Thanks, Dr. Olmon. Opening it up to the committee if there are any questions? Okay. I think we'll move on. I don't believe there are any other stakeholders for this classification.

Leta Evaskus: I don't see any other stakeholders raising their hand.

Virginia Buccola: Again, for the committee, we're just waiting until after all three sections have been reviewed to do a single motion. So, we won't go to motion right now. Is that correct, Leta?

Leta Evaskus: That is correct. I am opening up the next presentation. So, our next presentation will be on rheumatoid arthritis and ankylosing spondylitis. We're welcoming Gerald Gartlehner. Thank you, very much. Welcome, please go ahead.

Gerald Gartlehner: Yeah. Thank you. So, my name is Gerald Gartlehner. I will continue with the TIMs presentation and my presentation is on rheumatoid arthritis.

So, adalimumab versus certolizumab pegol. We found one RCT with 915 participants. This was the Accelerate study. This study reported a similar response in remission rates between adalimumab and certolizumab

pegol. We rated the evidence on the clinical improvement as high quality.

Adalimumab versus etanercept. So, we found two small RCT's with a total of only 167 participants that compared adalimumab with etanercept. These two studies found no differences in clinical improvement. We rated the quality of evidence as very low.

Adalimumab versus sarilumab. So, there was also only one RCT that compared adalimumab to sarilumab. In this study, adalimumab was less effective for clinical improvement, disease remission, and quality of life at 24 weeks. So, for example, the ACR50 response rate was 30% for adalimumab and 46% for sarilumab. We rated the quality of evidence as moderate for clinical improvement and quality of life and as low for remission.

Adalimumab versus tocilizumab. We identified two RCT's with a total of 369 participants. In terms of clinical improvement and remission, adalimumab was less effective than tocilizumab. The ACR50 response, for example, was 28% versus 47%. There is one caveat, however. In the larger one of these two trials, tocilizumab was administered at a higher dose than FDA approved, but quality of life was similar between the groups. We rated all outcomes for this comparison as low.

Adalimumab versus tofacitinib. So, there was no difference between groups in either clinical improvement or disease remission for the three RCT's that compared adalimumab to tofacitinib. The body of evidence includes more than 2000 participants, and we rated this body of evidence as high quality of evidence. We also rated the quality of evidence as high for an RCT that compared adalimumab versus upadacitinib. Clinical improvement was lower with adalimumab than upadacitinib in ACR50, which was 29% versus 45%. Similarly, significantly fewer participants achieved remission with adalimumab than upadacitinib.

For etanercept versus infliximab, we rated the quality of evidence as very low, because this was a very small trial with only 32 participants. It's really not possible to draw any conclusions from this study. Pretty much, the same situation for etanercept versus tocilizumab. Also, very small trial with only 43 participants, and results show similar clinical improvements, but we can't really draw any conclusions from these two studies.

In the report, we also included two RCT's that assessed combination treatments. So, two targeted immunomodulators combined with each

other. One combined etanercept with anakinra. The other one etanercept with abatacept. Overall results showed no or very limited additional benefits of a combination of two targeted immunomodulators, but the serious adverse events were substantially higher in the combination group. So, for example, 11% versus 3%.

So, this were the comparisons on the firstline treatments for rheumatoid arthritis. Now, we're moving onto the second line treatments; so, in patients who did not achieve adequate response with firstline treatment. Here is an evidence map again for second line treatments. We found even fewer studies than for the firstline treatments. As you can see, we do not have any direct head-to-head comparisons for most of the drugs. Many of the available RCT's were of poor methodological quality.

So, in the first comparison for second line treatments, abatacept was compared to TNF alpha inhibitors as a class. The study showed similar treatment effects for clinical improvement or quality of life. We rated the quality of evidence for this outcome as low and very low.

Similarly then, there was no difference between groups for the comparison between abatacept and rituximab. The quality of evidence was low for clinical improvement and quality of life.

One study sets the comparison of abatacept versus secukinumab. The ACR50 response rate was greater in participants treated with abatacept compared with those treated with secukinumab. It was 28% versus 17%. We rated the quality of evidence for this outcome as moderate.

And in the comparison of abatacept versus tocilizumab, one RCT with 132 participants showed similar clinical improvements between the two drugs, but adverse events were lower for abatacept than for tocilizumab. Also, the proportion of serious adverse events was lower for abatacept than for tocilizumab.

We also found one pragmatic RCT that enrolled participants who had an inadequate response to a TNF alpha inhibitor. Then, the study randomized participants to another TNF alpha inhibitor or targeted immunomodulator later with a different mechanism of action. Results showed that switching to a TIM agent with a different mechanism can lead to a greater clinical improvement and to better remission rates than switching to another TNF alpha inhibitor. The remission rates here were 27% for the TIM agent with the different mechanism and 14% for switching to another TNF alpha inhibitor.

Then, finally, one small RCT showed that adding rituximab to a TNF alpha inhibitor is more efficacious than maintaining the same TNF alpha

inhibitor to which [inaudible] did not respond adequately. So, this was a small trial with 54 participants, and the result is not really surprising.

So, now moving onto the pipeline drugs for rheumatoid arthritis. Three placebo controlled trials evaluated filgotinib, which is a new genus pinus inhibitor. The trials included more than 1300 participants, and all outcomes of interest improved significantly on the filgotinib treatment compared with the placebo groups.

Five placebo controlled trials assessed peficitinib compared with placebo. Peficitinib is also another genus pinus inhibitor. Clinical improvement and remission were also significantly greater under the peficitinib treatment than on the placebo treatment.

We also found one head-to-head trial that compared peficitinib with etanercept. This study, etanercept was significantly superior regarding clinical improvement and remission compared with peficitinib.

We found another head-to-head trial that assessed combination therapy of certolizumab pegol and bimekizumab, which is a new interleukin-17 inhibitor. It compared the combination of these two with certolizumab pegol monotherapy. So, the combination of certolizumab pegol plus bimekizumab versus certolizumab pegol monotherapy. Here, the combination therapy led to higher proportions of response and remission than certolizumab pegol monotherapy.

As I mentioned in the beginning, in addition to adverse events from RCT's, we also included data from observational studies. I would like to briefly summarize these findings from the observational studies on the next slide.

Overall, we included 41 cohort studies, which were mostly based on registry data. The majority of studies did not report any differences in serious adverse events, such as mortality, malignancies, or cardiovascular events. There are two notable results, though. Several studies consistently indicated a higher risk for serious infections, opportunistic infections, tuberculosis and herpes zoster for infliximab compared with other TNF alpha inhibitors. Two studies reported higher risk for gastrointestinal perforations for tocilizumab compared with TNF-inhibitors.

So, moving onto findings on ankylosing spondylitis. We found only one head-to-head trial for ankylosing spondylitis, which, unfortunately, also was of poor quality.

So, this head-to-head study included 50 participants and compared etanercept to infliximab. This study reported small improvements for etanercept and infliximab, but we rated the quality as very low and basically, we cannot draw any solid conclusions from this study.

We also found one RCT on the pipeline drug, filgotinib for ankylosing spondylitis, and this study found great improvements for filgotinib than placebo for the treatment of ankylosing spondylitis. So, filgotinib is still a pipeline drug.

We also summarized findings from two network meta-analysis for TIM agents. They are the most recent network meta-analysis, but the searches also go three and four years back. So, they probably have been updated by now, but you can find details on them in the report, and I will not present them here on these slides.

The review of limitations. So, what are the limitations of our update? First, as you saw from the evidence map, for most comparisons, we do not have any direct head-to-head evidence. When we have head-to-head studies, few comparisons actually were evaluated, but more than one or two studies. We also are missing long-term data on the effectiveness and safety. Drug manufacturers sponsored nearly all of the included RCT's. Most observational studies addressing harms were of retrospective design and based on national registries. With these registry studies, the quality and completeness of the databases cannot really be determined. Then there are some inherent potential limitations of the methods. For example, we focused on English language studies only.

We should skip the ongoing studies in the interest of time. So, let's move onto slide 48, which are our conclusions.

So, what are the conclusions? Well, we limit the conclusions here on the evidence of high or moderate quality of evidence. Adalimumab appears to be less effective than baracitinib, sarilumab, and upadacitinib as firstline treatment for rheumatoid arthritis. Abatacept appears to be more effective than secukinumab, as a second line treatment for rheumatoid arthritis. We did not find any differences in the incidence of serious adverse events. The differences that we found in effectiveness and harms that we rated with low or very low quality of evidence, they must be interpreted cautiously.

So, for ankylosing spondylitis, we cannot draw any firm conclusions. This slide also concludes my presentation. Thank you, very much, for your attention. If you have any questions, please go ahead.

Virginia Buccola: I see Alex's camera is on, so just opening to questions.

Alexander Park: If I could just ask, I'm curious why adalimumab is so highly featured in the head-to-head trial. Was there a reason?

Gerald Gartlehner: I think the reason probably is that it was one of the first targeted immunomodulators that came on the market. I think it was one of the first three. Why then adalimumab was not obtained as a, I don't really know, but it is interesting that it has been used often as a comparator.

Alexander Park: Thank you.

Virginia Buccola: Any more questions from the committee for Gerald?

Nancy Lee: Thank you, so much, for your presentation. I know that you've done a lot of work in this drug class. I had more of a question about the study with the 1000 patients, adalimumab with upadacitinib. In terms of that, that one appeared that upadacitinib is leaning more positively. In your further research, I also know that this is a 24-week trial. So, it's also short, as well. Are there any additional things that we should be aware of? I mean, that does kinda seem to be kind of floating to the top. Are there other things that we should be concerned about or conscious about?

Gerald Gartlehner: It is still a single study. It was funded by the maker of upadacitinib, but it was a well-conducted study. And it is a large sample size. So, it had 1629 participants. The methods were done well. So, for us, it looked really, really good. One thing that is really always hard to judge, of course, is publication bias. So, maybe there are other studies that we are not aware of that have never been published, but from what we had this looked like a good well-done study with a large sample size, and that was also the reason why we graded it as high quality of evidence.

Nancy Lee: Thank you, so much. I appreciate your thoughts and comments.

Virginia Buccola: Thank you, Gerald. I appreciate your report. I'm assuming there are no more questions from the committee. Okay. We'll move onto stakeholders. The following three stakeholders are coming up next. We have Anthony Wheeler representing Eli-Lilly. We have Piao Ching with Pfizer, and Dr. Margaret Olman with AbbVie. If there are any other stakeholders, please raise your hand so that Leta Evaskus is aware. Each stakeholder, please state your name for the record, and you'll have three minutes for your words. Thank you.

Leta Evaskus: I do not see Anthony Wheeler on the meeting. So, I'm going to skip to Piao. I'm unmuting you now. Anthony, if you are on under a different name, if you can raise your hand, but Piao, you're up.

Piao Ching: Thank you, Donna. Hello, again, I'm Piao Ching with Pfizer medical affairs team. Thank you, again, 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 DMARDs. The recommended dose of Xeljanz is 5 mg twice daily. The recommended dose of Xeljanz XR is 11 mg once daily. A [inaudible] double blind head-to-head noninferiority randomized controlled trial was conducted to assess the comparative efficacy of tofacitinib 5 mg twice a day monotherapy, tofacitinib 5 mg twice a day plus methotrexate, and adalimumab 40 mg subQ every other week plus methotrexate for the treatment of RA in patients with previous inadequate response to methotrexate. This study was published in [inaudible] in June, 2017. The primary efficacy endpoint was 50% improvement and ACR50 [inaudible]. At this timepoint, ACR is [inaudible] response rate for tofacitinib 5 mg twice a day monotherapy was 38%. Tofacitinib 5 mg twice a day plus methotrexate was 46%. Adalimumab 40 mg every other week plus methotrexate was 44%. Using a noninferiority margin of 13%, noninferiority of the ACR50 response at six months was showing for tofacitinib plus methotrexate versus adalimumab plus methotrexate, but not for tofacitinib monotherapy. The study authors noted no new safety signals with any of the treatments. A 2012 study of the corona registry showed there was only 1% to 85% nonresponder 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 status. Tofacitinib is included in the ACR-RA treatments guideline plus methotrexate in established RA. According to the ACR guideline, if the disease activity remains moderate or high, despite the monotherapy, the recommendation is to use combination traditional DMARD or an anti-TNF, or a non-TNF biologic, or tofacitinib [inaudible] DMARD monotherapy. In closing, adding a medication that is administered orally will offer an additional treatment of implications of RA in Apple Health population. Based on the efficacy and safety of tofacitinib, we ask the committee to ask Xeljanz and Xeljanz XR to Apple Health preferred drug list. Thank you for your attention, and I am happy to take any questions.

Virginia Buccola: Thank you, Piao. Are there any questions from the committee for Piao? Okay. I want to pause for a moment. I see that Anthony Wheeler is here, and I just want to pivot to Leta Evaskus to see how she, if she would like Anthony to go next or move to Dr. Olman?

Leta Evaskus: Okay. I still don't see Anthony on the attendee list.

Virginia Buccola: Leta, under the asker of the question, the name is Jill [inaudible].

Leta Evaskus: There we go. Okay. Alright. Anthony?

Anthony Wheeler: Yep. Here I am. Can you folks hear me okay?

Leta Evaskus: Yes. Thank you.

Anthony Wheeler: Alright. Fantastic. Thanks. Well, again, I am Anthony Wheeler, and I am employee of Eli Lilly and Company, which manufacturers Taltz. This is also known as ixekizumab, and it's an IL17 inhibitor. In this current category reviewing, I wanted to provide an update of a couple new indications that were approved for Taltz, since your last review of this drug. This was originally approved for plaque psoriasis, but again in this category, this drug was approved last summer for ankylosing spondylitis, and then was most recently approved just a couple weeks ago for non-radiographic axial spondyloarthritis. This disease is in the same family of spondyloarthropathies as ankylosing spondylitis but just has some different diagnostic criteria. This latter approval was based on a randomized control trial called the Coast-X Study. This study, patients who received Taltz had a statistically superior to those who received placebo on the primary outcome measure, which was asis-40, or a 40% improvement in spondyloarthritis symptoms. This was a 52-week study. The adverse event profile was similar to what was seen in previous trials of Taltz in psoriasis and other indications, but could certainly see the prescribing information for all of the safety details on Taltz. So, thanks for letting me provide this update, and I am happy to try to answer any questions that you have.

Virginia Buccola: Thanks Anthony. Committee, are there any questions for Anthony? Okay. Thanks, Anthony. We'll move to Dr. Olman.

Margaret Olman: Yes. Hi, this is Dr. Margaret Olman from medical affairs at AbbVie. Thank you for the opportunity to speak with you again. AbbVie now has two targeted immunomodulating medications available to treat patients with rheumatoid arthritis. I'd like to briefly review both RINVOQ and Humira and answer any questions you might have. Please see the full prescribing information at RXAbbVie.com for comprehensive safety and efficacy data. Upadacitinib with the brand name RINVOQ is an oral JAK inhibitor

indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who had inadequate response to methotrexate or other nonbiologic DMARDs. One extended release 15 mg tablet is taken once daily with or without food. The phase 3 clinical program consisted of high studies in over 4300 patients, and it's the medication that Gerald mentioned earlier. The individual trials included RA patients who were methotrexate naïve who [inaudible] DMARD inadequate responders or biologic inadequate responders. RINVOQ met all primary and all secondary endpoints in all five trials, and significantly more patients achieved DAS-28 remission and low disease activity versus controls in each trial. RINVOQ is the only approved JAK inhibitor to demonstrate inhibition of joint damage in its approved population methotrexate IR patients. It is also the only targeted immunomodulatory to show clinical superiority in RA treatment to Humira plus methotrexate. The most common adverse reactions in upadacitinib trials were upper respiratory tract infections, nausea, cough, and fever. All anti-TNFs, including Humira, carried a similar boxed warning regarding serious infections, tuberculosis, and malignancies. JAK inhibitors also include a warning about thrombosis. Patients starting on any of these medications in this class should be screened for TB and carefully monitored for serious events. Humira has ten currently approved indications that include three that we're discussing at this time, in adult patients with moderate link to severely active rheumatoid arthritis, moderately to severely active polyarticular juvenile idiopathic arthritis, and in adult patients with active ankylosing spondylitis. Humira has longstanding safety data, years of on-market experience, and a well-defined, published benefit-risk database with over 1 million patients treated. In summary, I respectfully urge the committee to maintain preferred status on the PDL and to add RINVOQ as a preferred treatment for Washington Medicaid patients. Thank you, so much, for your time. May I answer any questions for you?

Virginia Buccola: Thank you, Dr. Olman. Committee, are there any questions? Okay. And I believe there are no additional stakeholders?

Leta Evaskus: I do not see anybody else raising their hand.

Virginia Buccola: Okay. So, we are scheduled for a break. Why don't we go ahead and do a ten-minute break. It's 10:25. We'll reconvene at 10:35.

Leta Evaskus: Sounds good.

Virginia Buccola: Okay. See everybody then.

Leta Evaskus: Thank you.

Virginia Buccola: We're going to go to Leila Kahwati who is ready to present to us on plaque psoriasis and psoriatic arthritis. Over to you, Leila.

Leila Kahwati: Alright. Thank you, Ginnie. So, I am back again for the last of the three presentations on TIMs. This one is focused on persons with plaque psoriasis and psoriatic arthritis.

We have the same structure for the presentation. So, let me go right into the background. So, two slides forward please.

Plaque psoriasis is a chronic inflammatory disease that effects the skin, scalp, and nails. The hallmark is erythrosquamous scaling skin lesions. Psoriatic arthritis is a chronic inflammatory arthritis associated with psoriasis. As we've already mentioned, we're focused here on targeted immune modulators, TIMs. The first TIM, alefacept, was FDA approved for psoriasis in 2003, and the first TIM, etanercept, was approved for psoriatic arthritis in 2002. Of course, additional agents, including biosimilars, have been approved since then.

This slide provides a snapshot of the difference in agents that we included in the update related to plaque psoriasis and psoriatic arthritis. There are 21 agents overall that cover nine different mechanisms of action that are noted in the green boxes. The agents in the blue boxes are approved for use in both plaque psoriasis and psoriatic arthritis. The agents in the green boxes are approved only for plaque psoriasis, and the agents in the pale yellow boxes are approved for psoriatic arthritis. The agents in the white boxes are not yet approved for either condition, but I will... upadacitinib, again, kinase inhibitor is FDA approved for rheumatoid arthritis, but for this particular report, we considered it a pipeline agent, because it's not yet approved for psoriasis or psoriatic arthritis.

On this slide, again, are the PICO study selection criteria. Again, very similar to what you've already seen before. The difference, obviously, here is that we're focused on adults with plaque psoriasis or psoriatic arthritis. Again, we are focusing on comparative effectiveness. So, mostly interested in head-to-head comparisons of TIM agents.

Key questions: The first key question is around comparative effectiveness. The second key question is around comparative harms. Then, the third key question is around variation in effectiveness or harms by subgroups.

We will skip over the methods, because they are largely the same as what we've already described to you. So, we're going to skip ahead to the findings slide, which should be slide 12, I think.

So, here is an overview of the 38 total studies that we included. Twenty of these studies were new to the update, and 18 were included from the previous report. Thirty-one of the 38 studies are randomized trials while 7 are cohort studies. Thirty-five were fair methodologic quality while 3 were poor methodologic quality. Thirty of the 38 were conducted among participants with plaque psoriasis. Eight were conducted among participants with psoriatic arthritis. Thirty-two of those studies were head-to-head comparisons while the other 6 were comparisons of pipeline TIM agents to placebo controls. Twenty-six of the 38 addressed comparative effectiveness. Then, 32 addressed comparative harms. We had no studies that addressed variation by subgroup.

Before we move into the specific findings, let me just provide you with a key to some of the abbreviations that are going to be encountered, similar to what Gerald mentioned. I want to just cover a few specific ones. Similar to Gerald's presentation, the studies of psoriatic arthritis largely rely on the ACR response, as a measure of clinical improvement or disease remission. We considered ACR20 and 50 as clinical improvement, and ACR70 as disease remission, similar to what Gerald described for the RA review. In terms of other global improvement measures, the physician investigator's global assessment is often reported. That's a score of 0-1, generally reflects disease remission. Then, the other two measures, the DLQI and the PASI are specific to plaque psoriasis studies. The DLQI, a score of 0 or 1, means that the disease is essentially having no impact on their quality of life. The PASI score is a measure of disease response. PASI50 represents a 50% improvement in the score, 75% respectively. So, PASI50 is clinical improvement, and PASI75, 90, or 100 are essentially would be considered disease remission. So, these are the most common outcomes that you'll see in this body of literature.

So, now we're going to move into the findings. We'll start with plaque psoriasis first. This is an evidence map similar to what Gerald showed you for RA that shows all the possible TIM agents and possible [inaudible] comparisons. The first thing you will also notice, similar to RA, is that there are many cells here that are empty, meaning they don't have evidence for those direct comparisons. There were 21 trials total representing 14 different head-to-head comparisons, and the majority of trials, as you can see, are comparing TIM agents to either etanercept or to ustekinumab. There's only three comparisons of other TIM agents. So, there's adalimumab versus guselkumab. There's risankizumab versus ADA, and then secukinumab versus guselkumab. All the other comparisons are either against etanercept or ixekizumab. All studies were sponsored by industry and had expensive industry involved in the study design, execution, and reporting, which is why they were all

downgraded to fair methodological quality. One study was poor quality because of insufficient blinding and switching of treatments that occurred during the study. All these studies enrolled participants with moderate to severe psoriasis based on at least the 10% of body surface area involvement and/or a PASI score meeting a certain threshold, or both. Most studies were at least three to six months duration. In addition, some of the studies required participants to be naïve to biological agents, but this was not universally [inaudible].

We have the same kind of format of presentation, as you've seen before. In the top green box are the TIM agents being compared, the number of studies, the number of participants. So, this first comparison is apremilast against etanercept. One study of 166 participants. The bullets in the boxes below the green boxes are the outcomes that we evaluated with grade. I will note that the full report does include other outcomes that may have been reported by the study, but for the presentation, we focused only on the outcomes that we graded. So, for apremilast versus etanercept, there was no difference in the PASI-75 score at 16 weeks, and we graded that evidence as low quality. In terms of quality of life, there was no differences in quality of life, as measured by the DLQI, and that was also at 16 weeks. That was also graded as low quality. The next comparison in the bottom of the slide is brodalumab versus ustekinumab. There were two RCT's that compared these two agents and together combined analyzed over 3000 participants for disease remission of brodalumb resulted in a higher proportion of participants achieving a PASI-100 response at 12 weeks. We graded this evidence as high quality. So, the consistent findings across the two studies.

The next comparison is etanercept versus infliximab. This was evaluated in one small trial, 50 participants. This was a poor quality study. It had some issues with blinding and switching of treatments. Overall, fewer participants that were treated with etanercept achieved a PASI-75 response compared to infliximab. It was 35% versus 72% achieving no response. We rated this evidence as very low quality. In this case, it was more for imprecision, but also for study limitations. The study also reported quality of life measures. They looked at a relative change in the SF-36 physical health and mental health component scores and reported no differences between the two agents, and we graded that evidence as very low quality. The next comparison was evaluated in two phase-3 multi-[inaudible] trials. These trials compared etanercept with ixekizumab. Etanercept was less effective for achieving disease remission at 12 weeks, as measured by the PASI-75 outcome, and it was also less effective for improving quality of life. That was measured with the DLQI.

The absolute risk differences are provided on the slide. This evidence base, depending on the study, will report things in different ways. Some of them report things as absolute risk differences. Some of them report just the actual absolute incidences. Then we have to go ahead and calculate that risk difference. Some of the outcomes are presented in slightly different ways across the different studies, but we have tried to tell you what is the direction of effectiveness whenever possible.

The next comparison is between etanercept and secukinumab. This was evaluated in one trial of over 1000 participants. In this trial, they evaluated both the 300 mg dosage of secukinumab and 150 mg dose, and etanercept was less effective for achieving a PASI-75 response at 12 weeks, 44% versus 77% for the 300 mg dose, and 44% versus 67% for the 150 mg dose. We rated this evidence as high quality. Similarly, etanercept was less effective for improving quality of life. The change in the mean DLQI score was 7.9 points for etanercept versus 10.4 points in the 300 mg dose group, and 9.7 points in the 150 mg dose group. We rated that evidence as moderate quality. The next comparison at the bottom of the slide is etanercept versus tildrakizumab. This was evaluated in one trial of just over 1000 participants. Two doses of tildrakizumab were evaluated 100 mg or 200 mg dose. Etanercept was less effective for disease remission, as measured by the PASI-75, both at 12 weeks and also at 28 weeks. The 28-week data is not showing on the slide, but it was effective at both timepoints. We rated the data at both those timepoints as high quality. For quality of life, etanercept was also less effective in both doses as tildrakizumab at both 12 weeks, which was rated as moderate quality of evidence, and at 28 weeks, which we rated as high quality evidence.

The next comparison is comparing etanercept to tofacitinib, and this study evaluated either a dose of 5 mg or 10 mg twice daily. This is a good time to just remind you that at the time we did this review, tofacitinib was approved for psoriatic arthritis but was not approved for plaque psoriasis. The FDA had declined to approve it in 2015, and had requested additional efficacy and long-term safety data. We didn't identify any information to suggest the manufacturer has any plans to resubmit it for plaque psoriasis indication, but this study did provide data on that comparison. So, we have included it in the report. In terms of disease remission, etanercept was more effective than 5 mg dosage based on the PASI-75 response, but it was no different compared to the tofacitinib 10 mg dosage. We rated this evidence as moderate quality. Etanercept was also more effective than 5 mg of tofacitinib for achieving clinical improvement, as measured by a PASI-50 response, but again, was no different than the 10 mg dose of tofacitinib. Etanercept was more

effective than 5 mg tofacitinib for improving quality of life. This was based on a DLQI change of 5 points or more. That was moderate quality of evidence, but again, there was no significant difference comparing etanercept to the 10 mg dose of tofacitinib.

The next comparison is etanercept with ustekinumab. This was one study of just under 1000 participants that evaluated a 45 mg dose of ustekinumab and a separate study arm evaluated a 90 mg dose. Significantly fewer patients in the etanercept group achieved a PASI-75 response compared to either of the ustekinumab groups, and those were the only outcomes that we graded for that particular comparison. The next comparison is guselkumab versus adalimumab, and there were three trials, RCT's, for a combined total of 1600 or so patients. One study compared multiple doses and different dosing intervals of guselkumab while the other two RCT's compared doses of 100 mg at weeks 0, 4, and 12 to standard doses of adalimumab. These studies included multiple primary and secondary, including physician's global assessment a 0-1 response, a PASI-75 and 90 response. So, for disease remission, we focused on the PGA 0 or 1 response. In the 100 mg dosage regimen of guselkumab was more effective with absolutely risk differences ranging from as low as 16 to 28 percentage points across the three different trials. For quality of life, two of the trials reported using the DLQI 0 or 1 response, and the absolute risk differences there were 13 and 15 percentage points favoring guselkumab, but they were only statistically significant in one of the two trials. So, same sort of magnitude of difference, but because of precision, significant in one but not the other. All three of the trials reported a mean change in the DLQI from baseline, and the absolute mean differences in change range from reductions of 0.6 points to reduction of 1.7 points.

There was one trial that compared guselkumab to secukinumab just over 1000 participants. This particular study designated its primary endpoint as the PASI-90 response at 48 weeks. Based on this endpoint, guselkumab was more effective than secukinumab. You can see, there was an 84% response rate for guselkumab compared to 70% for secukinumab. However, this study also reported disease remission, as measured by PASI-75, and a combined endpoint of 12 and 48 weeks. For this outcome, guselkumab was noninferior but was not superior to guselkumab. So, they did two different kinds of statistical testing, and guselkumab was also noninferior when only looking at the 12 week outcome. Based on the PASI-90 at 12 weeks, guselkumab had a lower numerical response, 69%, compared to 76% for secukinumab, but the study authors did not conduct any significant testing for that particular outcome at that particular timepoint. That was per the study's analysis

plan, which was somewhat hierarchal in order to control for type 1 error. Overall, we graded the disease remission outcomes as moderate quality. We downgraded it by a level, because of the inconsistency of findings across the measures and the timepoints. Though, one might not view this as an inconsistency, but rather evidence of a better maintenance response, perhaps with guselkumab, but likely probably not difference in an induction response.

The next comparison was ixekizumab versus ustekinumab. There was one trial of just over 300 participants. This study dosed ustekinumab based on weight. So, it's 45 mg for people, I think it was less than 100 kilos and 90 for people over 100 kilos. Ixekizumab was more effective for disease remission, as measured by a PASI-90 at 12 weeks of 73% response versus 42% response, and also at 52 weeks, which data is not on the slide, but the response was 77% compared to 59%. Ixekizumab was also more effective for improving quality of life at 12 weeks with a DLQI of 0 or 1 response, or 61% versus 45%, and we graded both of these outcomes as moderate quality.

There was one trial comparing risankizumab to adalimumab with about 605 people. Risankizumab was more effective than adalimumab for disease remission at 16 weeks. This is based on a PASI-90 response. Risankizumab was also more effective at improving quality of life based on the DLQI 0 to 1 response. We graded both of those outcomes as moderate quality. Then, for the comparison of risankizumab to ustekinumab, we identified three trials with a combined total of over 1000 participants. Risankizumab was more effective than ustekinumab for disease remission at 16 weeks with a timeframe across the three trials. That was measured by a PASI-90 response. Absolute risk differences across the three studies ranged from 28 to 37 percentage points, higher response for risankizumab. Risankizumab was also more effective in improving quality of life, as measured by the DLQI of 0 or 1 response. We graded both of these outcomes as high quality.

The next comparison is secukinumab versus ustekinumab. There were two trials with a combined total of over 1700 participants. Ustekinumab was also a weight based dosing in this study, 45 mg or 90 mg depending on body weight. For disease remission, secukinumab was more effective, as measured by a PASI-90 response. The absolute risk differences were 21 and 22 percentage points in the two studies, and that was at 16 weeks followup. Secukinumab was also more effective for achieving DLQI of 0 or 1 response for quality of life. We rated both of those outcomes as high quality. One of these two studies also reported outcomes at 52 weeks, and secukinumab remained superior to ustekinumab on all the

measures of disease remission, clinical improvement, and quality of life at that further timepoint, as well.

That kind of finishes up the comparative effectiveness. Now, we're going to move into comparative harms for plaque psoriasis. So, all of the 21 trials included for comparative effectiveness also reported on harms of TIM agents. In addition, we identified five cohort studies. Overall, in general across the body of evidence, we observed very few differences in harm in the head-to-head comparison. In the RCT body of evidence, between agent differences were typically in just one of several harm outcomes that may have been reported when differences were present at all. So, in this presentation, I'm only gonna describe findings where a statistically significant difference was observed in at least one of the harm outcomes in one study comparison. I'm going to mention all the harm outcomes for that comparison to put the one isolated finding into some context for you.

The first comparison where there was a statistically significant difference was from a cohort study of over 100,000 participants that compared apremilast to adalimumab. In this particular study, there was a lower incidence of serious infection requiring hospitalization for apremilast compared to adalimumab, and the hazard ratio is 0.31. As you can see, it excludes the null effect. We rated this particular finding as very low quality of evidence. This study did not report any other harm findings. The next comparison is apremilast versus etanercept. This was reported in one trial of 166 participants. This study observed a lower incidence of adverse events for apremilast compared to etanercept. The risk ratio was 0.75, and again excludes the null effect, so statistically significant. We rated this particular evidence as low quality. In this particular study, there was no significant difference in the incidence of serious adverse events, but that particular estimate was really too imprecise to draw a meaningful conclusion.

The next comparison where we had a statistically significant difference in harms was for etanercept versus adalimumab. This was reported in two cohort studies. In the first larger cohort of over 100,000 participants there was a lower incidence of serious infection requiring hospitalization for etanercept compared to adalimumab. The hazard ratio was 0.76. We rated that evidence as very low quality. In the second cohort, which had over 7000 participants, there was a lower incidence of serious adverse events for etanercept compared to adalimumab. The incidence rate ratio there was 0.75. We also rated that one as very low quality of evidence. In the comparison of etanercept versus tildrakizumab, which is in the bottom of the slide, this was from one trial of over 1000 participants, this study reported harms over two different time periods. They reported

things over 0 to 12 weeks and then over 13 to 38 weeks. So, there was a lower incidence of adverse events for the 100 mg dose of tildrakizumab compared to etanercept across both time periods, but there was also a lower incidence for the 200 mg dosage, but only during the second time period, the 13 to 28 weeks. There was no significant differences in serious adverse events for either dosage of tildrakizumab compared to etanercept in any of the time periods.

For the comparison of etanercept to ustekinumab, which was reported in one RCT and one cohort, there is no significant differences in overall adverse events or serious adverse events in the trial, which we rated as low quality of evidence. In the cohort study of over 7000 participants, there was a higher incidence of serious adverse events for ustekinumab compared to etanercept. Incidence rate ratio is 2.4 in this observational study. Participants were enrolled from a national dermatology registry in the U.K. Participants were classified as to whether or not they had a clinical status that would make them eligible to participate in the clinical trial. The incidence rate ratio of 2.4 that I just mentioned is the estimate for participants with a clinical status that would make them not eligible to participate in clinical trials. So, the thinking there is that those patients represent a more real world sort of population than people who are eligible for clinical trials. There was a slightly higher incidence of adverse events in the participants who would have been eligible for clinical trials, but the magnitude was lower. So, it was 1.3 incidence ratio among that more selected population.

Next is a comparison of infliximab versus adalimumab. It was reported in one cohort of over 100,000 participants in this study, a higher incidence of serious infection requiring hospitalization was observed for infliximab compared to adalimumab. Hazard ratio was 1.9, and we assess that evidence as low quality. The next compared risankizumab versus ustekinumab, and that was reported in three trials of over 1000 participants. One of those trials reported no significant difference in any harms. The other two reported harms over two different time periods. There were some slight differences in harms between the two periods, but there was no sort of consistent patterns for any single time period or harm.

Finally, for the comparison of ustekinumab versus adalimumab, there were two cohort studies. In one study of over 100,000 participants, there was no significant differences in serious infection requiring hospitalization, and that evidence was rated as very low quality. In the other cohort of over 7000 participants, there was a higher incidence of serious adverse events for ustekinumab. The incidence rate ratio was 1.2, and we rated that evidence as very low quality. Again, this last

finding is from the study comparing estimates from populations that either would be eligible or ineligible to participate in clinical trials.

We did summarize some findings from three recent network meta-analysis for TIM agents for plaque psoriasis. There are some summary slides in the back of the deck for your reference and the details of that are in the full report if you're interested in that. We are going to, for the sake of time, not go through the slides on pipeline agents, but there were three pipeline agents. The results for those are all summarized in the slide deck and in the full report. So, we are going to skip to slide 3.

So, we're going to move now into psoriatic arthritis. This first slide is the evidence map for comparative effectiveness. You can see we only identified a total of five trials. Two were poor methodologic quality, and three were fair. All but one of the comparisons are comparing it to adalimumab. The sixth study compared ustekinumab to [inaudible] alpha inhibitors generally, like, the class. The specific one was selected by participants and their providers. So, this was not a blinded study and is one of the reasons we assessed it as poor quality.

We'll quickly go through the psoriatic arthritis comparison. The first comparison was the trial of about 100 participants comparing adalimumab to etanercept. This study reported similar ACR20 responses at one year for all the agents. So, adalimumab, etanercept, and infliximab all had similar responses at one year. However, they did not really conduct statistical significance testing, because this is not an aim of the study. Then, at the bottom of the slide is the comparison of adalimumab to ixekizumab. This is a trial of over 400 participants. This study also reported similar ACR responses among participants. Again, also did not conduct any statistical significance testing, as this study also had a placebo arm, and the main point of the study was to compare ixekizumab to placebo. So, they did not do testing for the active comparator arm. This study also reported a numerically lower skin disease remission response for adalimumab compared to ixekizumab and also reported on ixekizumab dosing every two weeks and every four weeks. So, there were multiple study arms in this particular study.

We compared one study looking at 422 participants compared adalimumab to two doses of tofacitinib 10 mg twice daily or 5 mg twice daily. The ACR20 response was 60% for adalimumab compared to 70% for the 10 mg dosage, and 68% for the 5 mg dosage. This study also did not conduct statistical significance testing. We graded that evidence as low quality. They also reported skin disease reemission using the PASI-75, and it was 56% for adalimumab compared to 67% for the 10 mg dose, and 56% for the 5 mg dose. Again, no statistical significant testing was

conducted by the authors. We also graded that evidence as low quality. Then, finally, for quality of life, the study authors reported a change in PCS scores. They are all the same neighborhood across the doses, but there was no statistical significance testing reported. So, we graded all of this evidence as low quality.

Alright, I think the next slide, this is comparing adalimumab to remtolumab, which is a pipeline agent. So, I think we'll go ahead and skip that.

Let's move to slide 38, which is the final comparison of ustekinumab vehicles a class, TNF alpha inhibitor. This is only 47 persons, and these were all participants with active enthesitis, which is inflammation where the tendons and ligaments insert into the bone. So, it's sort of a subset of people with psoriatic arthritis. Participants were randomized to the TNF alpha selected their preferred agent, based on the root and the frequency of administration that they preferred. In terms of both enthesitis and skin disease remission, ustekinumab was more effective at 24 weeks, but there was no difference in arthritis remission. We graded the remission outcomes as very low quality evidence. In terms of quality of life, ustekinumab was more effective, as measured by the SF-36 physical health component score, but there was no difference in the mental health component score.

In terms of comparative harms, four of the five trials also reported comparative harms for psoriatic arthritis. We did not identify any cohort studies, and there was only one significant difference in harms between agents, and that is described on the next slide. This was the trial comparing, if we go to the next slide, adalimumab to etanercept and infliximab, 100 participants. There was a lower incidence of adverse events with adalimumab compared to etanercept. The risk ratio was 0.38. There was also a lower incidence with adalimumab compared to infliximab. That risk ratio was 0.23. The incidence of adverse events is higher for infliximab compared to etanercept, and that risk ratio is 1.6. We rated all these outcomes as very low evidence.

Alright, the next part of the slide deck is again on pipeline agents. So, we're going to skip those and go to slide 43, which is just a summary of the limitations. Many of these are similar to what Gerald and I have presented earlier. There is quite a bit of direct evidence that we're lacking for many of the potential TIM comparisons, head-to-head comparisons. There's limited long-term efficacy and safety data. Most studies aren't powered for those harm outcomes. Some of the cohort studies use claim data, which we've talked about those limitations. Again, manufacturers sponsored nearly all of the trials. Same kind of

methodological limits to the review, including mostly rely on English language studies, and no data from conference abstracts or press releases.

We are going to skip over ongoing studies and go to conclusions, which should be slide 47. So, the largest body of comparative direct evidence in terms of plaque psoriasis is for etanercept and ustekinumab compared to the other TIM agents. This is for disease remission outcomes. So, high quality evidence suggests that etanercept is less effective than ustekinumab, secukinumab, and tildrakizumab. High quality evidence also suggests that ustekinumab is less effective than brodalumab, risankizumab, and then moderate quality suggests it may also be less effective than ixekizumab.

For the other TIM comparisons, in terms of disease remission outcomes, high quality evidence suggests that adalimumab is less effective than guselkumab, and moderate quality evidence suggests that it's also less effective than risankizumab. Moderate quality evidence suggests that guselkumab is more effective than secukinumab for maintenance therapy. A few differences in harms among the TIM agents were observed based on very low to moderate quality evidence.

Lastly, in conclusion for psoriatic arthritis, there is limited head-to-head comparisons available, but based on low quality evidence, ixekizumab, tofacitinib, and remtolumab may be more effective than adalimumab for disease remission with no difference in harms. That's all in terms of the slide deck. I'm happy to entertain any questions at this point.

Virginia Buccola: Just making sure that there aren't any questions from the committee for Leila.

Female: Hi, Leila. Thank you, again, for this great work. I know it's a lot of information and trying to pare it down for us. Thank you. Just a little bit of background. We received a letter from provider in the eastern State of Washington. One of the comments or points that he made was by the time they get to the preferred drug, they no longer see the potential efficacy that the patient could have obtained. For me, this kind of triggered a question about disease severity and applicability of the patient populations. I know that you really looked at a huge amount of information and data. Could you give us a little bit of insight into, like, maybe approximately what percent of patients were naïve to these therapies? Or had they already tried one or two agents before, especially with some of these head-to-head studies.

Leila Kahwati: That's a great question. So, what I can tell you is that the patient populations that were enrolled in these trials, the criteria for enrollment was remarkably similar across the studies. So, most of them required moderate to severe psoriasis, and I'm really focusing on the plaque psoriasis, moderate to severe psoriasis at least 10% body surface area involvement, and a duration of disease, usually a minimum of four to six months. So, the patient enrollment criteria was fairly standard. Where the studies differed was in terms of whether they required patients to be biologically naïve. I would say I don't have all that data right at my fingertips, but I would say most of them probably did not... some of them did require participants to be biologically naïve, but most... I would say over half did not require people to be biologically naïve. I need to go back and dive in if you wanted more specific numbers, but I just don't recall them off the top of my head, but that was where studies varied was whether they required people to be naïve or not.

Female: Thank you, so much. I appreciate it.

Virginia Buccola: Just checking in, any more questions? Leila, thank you, very much. Alright. We have four stakeholders. We have Anthony Wheeler with Eli Lilly. We have Piao Ching with Pfizer. Carrie Johnson with Amgen. Dr. Margaret Olman with AbbVie. If there are any other stakeholders present that I haven't listed, please raise your hand and let Leta know.

Leta Evaskus: Okay. Anthony, I've unmuted you.

Anthony Wheeler: Okay. Great. Thanks, so much. Again, I'm Anthony Wheeler, and I am an employee of Eli Lilly and Company, which manufacturers ixekizumab. This is also known as Taltz. It is an IL-17 inhibitor. I will provide just a short research update on a couple of the indications that are being reviewed in this report the original indication that Taltz received was plaque psoriasis. It was approved a couple years ago also for psoriatic arthritis. The first research update is the completion of the study called Xsora-R. [SP] This was a randomized control trial that compared Taltz with Tremfya, which is also known as guselkumab in participants with plaque psoriasis. This study, Taltz showed superiority to Tremfya on the primary outcome measure, which was PASI-100 or complete clearance of skin lesions. Then, the other study was known as Spirit head-to-head. This was also a randomized control trial, and it compared Taltz with Humira, or 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 ACR50, or a 50% reduction in disease activity and PASI-100, or complete skin clearance. So, thanks again for letting me provide these updates, and do see the

package insert for all the safety details on Taltz. I'm happy to try to answer any questions that you may have.

Virginia Buccola: Thanks, Anthony. Any questions for Anthony from the committee? Okay. Thanks very much. We'll move to Piao Ching.

Piao Ching: Hello again. This is Piao Ching with Pfizer medical affairs team. Thank you, again, for allowing me to provide these comments pertaining to Inflectra, a biosimilar to Remicade. The introduction of biosimilars provide patients and prescriber treatment options, which may extend excess by offering potentially less costly alternatives for biology medicine. The FDA approved Inflectra in April, 2016. Inflectra is a [inaudible] factor, a TNF blocker, indicated for active psoriatic arthritis and chronic severe plaque psoriasis in patients who are a candidate for systemic therapy, and when other systemic therapies are medically less appropriate. Inflectra is also indicated for moderately to severely active RA in conjunction with methotrexate, active ankylosing spondylitis, and patients who have had an inadequate response to conventional therapy for moderately to severely active Crohn's disease and ulcerative colitis. Extensive comparison of the functional [inaudible] chemical routine and higher order structural attributes match the prespecified criteria for analytical similarity of Inflectra, U.S. licensed Remicade, and E.U. approved Remicade. In a three-way pharmacokinetic or PK study in healthy subjects, the [inaudible] comparisons of the Inflectra, U.S. licensed Remicade and E.U. approved Remicade met the prespecified acceptance criteria for similarity. The 90% confidence intervals for the geometric mixed ratio, or GMR, of AUC and CMAX [inaudible] 80% to 125% similarity range comprise of 803 subjects. The safety database identified known [inaudible]. Inflectra and the comparator products had similar incidences of treatment emergence adverse events, serious adverse events, and adverse events leading to discontinuation, infection, infusion related reactions, and anaphylaxis. The FDA was provided with extensive data to address the scientific consideration for extrapolation to conditions of use not clinically studied in the Inflectra development program. Thereby, printing licensure for [inaudible] indication described previously. Inflectra is labeled with the same warnings and precautions of Remicade, including the black box warning for serious infections and malignancy. In closing, I would like to thank the committee for allowing me to present this testimonial, and I would be happy to address any questions. Thank you.

Virginia Buccola: Thank you, Piao. Any questions for Piao? Okay. Before we move to the next speaker, I just want to add that it looks like there is a fifth stakeholder, Shirley Quatch, representing Novartis. We will add them to

the end of the list. Up next, we'll go to Carrie Johnson representing Amgen.

Carrie Johnson: Hi. This is Carrie Johnson. I'm a pharmacist with medical affairs at Amgen. Thank you for the opportunity to speak in support of Otezla or apremilast. Apremilast is FDA approved in 2014 for the treatment of adult patients with active psoriatic arthritis, adult patients with moderate to severe psoriasis who are candidates for phototherapy or systemic therapy, and now in July, 2019, for the treatment of adult patients with oral ulcers associated with Behcet's disease. Warnings and precautions include diarrhea, nausea and vomiting, depression, weight increase, and drug interactions. Please see the full prescribing information at Amgen.com for further information. Important reminders, apremilast is not a biologic, and recent published guidelines place it in a separate category. It's an oral small molecule that works intercellularly to inhibit [inaudible]. This reduces the cell's production of pro-inflammatory cytokines and increases production of anti-inflammatory cytokines. Importantly, apremilast has no black box warning and no requirement for screening or laboratory monitoring. As an oral small molecule, it does not induce [inaudible] antibodies. [inaudible] four updates, two label updates in this past year, and two other updates. In July, 2019, apremilast became the first FDA approved therapy for the treatment or oral ulcers in adult patients with Behcet's disease. This is a rare, chronic, multisystem inflammatory disease that affects approximately 5 in 100,000 people in the U.S. Oral ulcers occur in more than 98% of these patients and can be painful and significantly affect quality of life. In the phase-3 relief study, apremilast demonstrated significant improvement versus placebo at week 12, and the number and pain of oral ulcers associated with Behcet's disease. Most commonly reported adverse events in this trial included diarrhea, nausea, headache, and upper respiratory tract infection. Second label update in the past year, scalp psoriasis occurs in over 90% of patients with psoriasis and is considered a difficult to treat aspect of psoriasis. In the phase-3 style study, apremilast demonstrated significantly greater improvement in scalp psoriasis, scalp and whole body itch, and quality of life versus placebo at week 16 with improvements continuing out 32 weeks. The most common adverse events were diarrhea, nausea, headache, and vomiting. [inaudible] are fully published and were added to the label in April of this year. Long-term data, now published out to five years in psoriatic arthritis and over three years in psoriasis shows no increase in incidence or severity of adverse events, and no new safety signals over time. Recently published claims analyses demonstrates the biologic naïve patient with psoriatic arthritis who initiated apremilast had similar switch rate to biologic users and significantly lower healthcare costs regardless of treatment

switching. In summary, apremilast is not a biologic, and it's placed in a separate category in recent guidelines. Apremilast does not have a black box warning. It has no requirement for screening or laboratory monitoring, as an oral small molecule. It does not induce production of antidrug antibodies. Apremilast represents an important oral nonbiologic option for your adult patients with moderate to severe psoriasis with active psoriatic arthritis, and now for treatment of oral ulcers associated with Behcet's disease. Thank you for your time, and I'll take any questions.

Virginia Buccola: Thank you, Carrie. Any questions from the committee for Carrie? Okay. Moving to Dr. Margaret Olmon with AbbVie.

Margaret Olmon: Hi. This is Dr. Margaret Olmon again. Thank you, very much, for today's opportunity to speak with you. AbbVie now has two targeted immunomodulating medications available to treat patients with psoriasis. I would like to briefly review Skyrizi and Humira and answer any questions you might have. Please see the full prescribing information at rxabbvie.com for comprehensive safety and efficacy data. Risankizumab with brand name Skyrizi is an IL-23 inhibitor indicated for the treatment of moderate to severe plaque psoriasis in adults and is given as a subcutaneous injection at week zero, four, and then every 12 weeks, which means four doses per year for maintenance treatment. The phase-3 clinical program was conducted in four trials with over 2000 patients and had met all primary and all ranked secondary end points in all trials. Skyrizi showed superior efficacy to Stelara, ustekinumab, in both PASI-90 and PASI-100 responses at week 16 and at week 52. After two doses, 75% of Skyrizi patients had at least a 90% reduction in their PASI 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 week 16, and in the long-term. There were no unexpected safety findings, and there were no contraindications to Skyrizi treatment. Patients starting Skyrizi or Humira should be screened for tuberculosis and carefully monitored for serious infections or other adverse events. Humira has ten currently approved indications that include both reducing the signs and symptoms inhibiting the progression of structural damage and improving physical function in adult patients with active psoriatic arthritis, and as a treatment for adult patients with moderate to severe plaque psoriasis and patients who are candidates for systemic therapy. With longstanding safety data, 71 global clinical trials, 14 years of on

market experience, and over 1 million patients exposed, Humira has a well-defined published benefit/risk database. In summary, I respectfully urge the committee to maintain preferred status of Humira on the PDL, and to add Skyrizi, as a preferred psoriasis treatment for Washington Medicaid patients. Thank you, so much. I'd be happy to answer any of your questions.

Virginia Buccola: Thanks, Dr. Olman. Any questions from the committee? Okay. We have one final stakeholder, and that is Shirley Quatch with Novartis. Shirley, you have three minutes to speak.

Shirley Quatch: Great. Thank you. Hi. My name is Shirley Quatch, and I am a regional account MSL for the Northwest at Novartis. I just wanted to first thank you for all your work and effort in your review of the drug class, and thank you for this time for me to provide comment and adding me at the last minute. I wanted to provide some comments and some updates on Cosentyx. So, Cosentyx is a fully human monoclonal antibody, which selectively targets IL-17a, which is a key inflammatory cytokine that effects both the adaptive and the immune system. I want to provide an update to one of the slides, or clarify, because Cosentyx is FDA approved for plaque psoriasis, and also psoriatic arthritis, and ankylosing spondylitis. On Tuesday, we did have an additional approval for Cosentyx, and that was in nonradiographic axial spondyloarthritis, which is a part of the axial spondyloarthritis disease spectrum, and this is based on the phase-3 prevent trial. Cosentyx has also demonstrated consistent long-term efficacy and safety with five year data in patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis demonstrating Cosentyx's consistent efficacy and durability. It also improves all [inaudible] domains of psoriatic disease, such as axial disease, [inaudible], skin and nails, which some of these are considered hard to treat domains. Cosentyx has demonstrated superior efficacy in plaque psoriasis. We also have additional head-to-head trials that are ongoing in psoriatic arthritis and ankylosing spondylitis. There has been no additional safety concerns that have popped up in our long-term studies. I also wanted to address one of the questions that was asked regarding the patients that were treatment naïve in some of these studies. For Cosentyx, [inaudible] trial, they vary across trials, but there are treatment naïve patients up to 50% in each of our trials. I can provide that information if you're interested. Thank you for your time. If there are any questions, I'd be happy to answer it. Thank you.

Virginia Buccola: Thank you, Shirley. Any questions from the committee? Alright. So, I think we need to move to this motion and get ready for some big word pronunciations.

Leta Evaskus: This is Leta. I am opening it up. I'll scroll down for you to view the last motion.

Virginia Buccola: I'm going to go ahead and turn my camera off again, just open it up to the committee knowing I can't see any of you. So, if I'm... if there's more time needed, or we're moving too quickly, please let me know.

Alexander Park: Can I ask a question? Can you hear me?

Group: Yes.

Alexander Park: It's been a couple months, since we've had one of these meetings. So, I just wanted to confirm something. The language here seems a little different than what we have had before. I seem to recall we usually say something like it's safe and efficacious, but this prior motion only seems to say efficacious. I can't remember if there was a reasoning for that, or if I'm mixing up our procedures here between the P&T and the DUR motions.

Leta Evaskus: You're right. The motions do usually say safe and efficacious. Donna do you recall why safe was left out of this one?

Ryan Pistoresi: I'm going to look at some previous motions and just see if it was omitted, or if we've left it off for a little while.

Donna Sullivan: I think one of the reasons why you have left the safe out of the motion for other drug classes that I recall is whether there, there might be a side effect or an adverse reaction that is potentially an unsafe adverse reaction. So, instead of saying that they are unsafe, which would go against an FDA approval that has said it's safe and effective, you have just omitted the word safe. I don't recall the reason for this particular drug class, but I recall that in general, as an option that you have chosen to do as a committee.

Ryan Pistoresi: Thanks for reminding us about that. I think that makes sense, given the number of black box warnings in this particular class.

Donna Sullivan: Okay.

Nancy Lee: Thank you. I think that's resonating with me, as well. Somebody had a question. I know the presentations were done in different chunks from ulcerative colitis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis. Some of the results, obviously, differed depending on the different disease states. Did we want to... this is a question for the... I don't know for HCA committee members to follow along with how it was presented with, like, ulcerative colitis, rheumatoid arthritis, plaque

psoriasis, psoriatic arthritis? Just a question I had. There's a lot of differences within the way the evidence was presented.

Ryan Pistoresi: So, this is the first time that we've had DURP split it out by the different indication. That's primarily because, as this class has so many different drugs and so many different disease states, that it was very burdensome to do the whole report at once. Actually, when we commissioned this report from DURP, they actually split it out and delivered it to the states across several months, which is why it was presented as the separate presentations, which then allowed us, as states, to review just this focused area at a time. So, on the Washington PDL, it is arranged as one big drug class. This is really the first time that we've actually reviewed it by each kind of individual subsection.

Virginia Buccola: I do recall that Leta had it been offered that if this motion felt too broad, we could break it into three smaller motions. I don't know if that addresses any of your questions or wondering, Nancy.

Nancy Lee: I guess that would be a question that I have for other committee members, as well. Do you feel... And also, I don't know, how that impacts the Health Care Authority, because it's gotten so large. My guess is, it will continue to get larger, especially with pipeline medicines. I'm not sure we can clump them together anymore, but I'd like some input from other committee members and Health Care Authority staff, as well.

Donna Sullivan: This is a class that's going to be extremely difficult to lump or split by disease state. The reason being is that there are some that are indicated for multiple disease states and then others that are indicated for only one. I think with the pipeline that indication was to grow. So, I think it is challenging to split them out other than to... if you did it would be by potentially their mechanism of action, which is also challenging, because there's multiple indications that they treat. So, I think it's best to leave them lumped together. Then, make recommendations to the committee based on making sure that there's one preferred product for each FDA indication.

Ryan Pistoresi: Just a followup to Donna's point, when we do look at the cost analysis that follows this step in selecting the preferred drugs, we do look at it for the different indications to make sure that we are meeting your motion for the rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and so on and so forth. So, it may make more sense to keep it at one large drug class for the PDL, rather than split it out by indication. Then, we would have repeating drugs across different disease states. I was able to look back at previous motions. The last time that we used safe and efficacious in the motion for the TIMs was in 2008. So, since them, it's

just been efficacious. So, for the last decade we have only used efficacious.

Alexander Park: Nancy, I share your concern. It is kind of an unwieldy group, including their pronunciations. Just thinking about how this... we want... it's about patients in the end. So, would you feel more comfortable if we added some indications in the list, if you feel like there's something we missed?

Nancy Lee: Now that I got some additional background from Donna and Ryan, I can see their points. So, if, and there's an echo. If we say that in terms of the FDA indications and in terms of the clinical studies, maybe we can... I don't know how we would add wording to say something of the sort that based on the current literature for these individual disease states that, like Donna was saying, that there would be a preferred agent based on current evidence that DURP has provided. I don't know if that kind of meets both aspects. I'm not sure if I'm articulating myself very well, but I understand Donna and Ryan your point. That makes sense to me to say that they're approved, they're efficacious, they're FDA approved, but then maybe adding something in addition to kind of pull out that there are some differences in the evidence base for different disease states within, I don't know.

Ryan Pistoresi: I think what we may want to do is, we can start by copying the old motion over into where the new motion is, and then split out the list of the drugs and the PDL recommendation in the two sections. So that way, you're able to see how we may want to edit it to kind of accommodate what we saw in the DURP reports today.

Leta Evaskus: So, what I'm doing is there were two drugs that were not continued into this review, and they're in black here, canakinumab. So, I'm just gonna take those out, and I'm gonna put these new drugs in.

Nancy Lee: Donna, I'm trying to remember exactly how you said it, but I liked in terms of phrasing it where we'd have a preferred within the disease state.

Donna Sullivan: Yeah. It's really challenging to have a preferred drug. I think we need a preferred drug that covers each of the indications, not necessarily a preferred drug for psoriasis. It's challenging to say one drug is preferred for this condition, but it's not preferred for that condition. It's either preferred or it's not. Or it's firstline. Or it's second line. So, I guess the question is, with some of the newer drugs, do you feel like they are superior enough to call them out as must be preferred? Or maybe in special populations they should be preferred. That's another avenue to go down. That way, when it's a special population we could put limits on

it or put it on prior authorization to make sure that only that particular special population received access to that drug. So, it would be preferred, but on prior authorization. With Medicaid, we can do that through an expedited authorization process. So, it's not as onerous, as a formal prior authorization, but that allows access to those medications for those individuals that have that need without opening it up broadly to the entire population to be used for other indications where there might be less costly alternatives that are equally effective.

Nancy Lee: I would be in favor of that. I don't know whether other committee members feel similarly.

Susan Flatebo: Within the preferred drug list, are we calling out route at all? Because if you look at this list of drugs, some of them are given subQ, some are oral, some are infusion. How does that work, too? Is one preferred over the other based on route? Or are they all kind of clumped together? Or is it...

Donna Sullivan: Sorry, Susan. They are all clumped together right now. If you look at the bottom of the motion, it says it should include a self-administered agent. You could alter that and say it needs to be a self-administered IV, oral, whichever routes that you think are important for us to have, as preferred options. Then, that will help us guide our PDL selection. I know with the [inaudible] class, you have said all routes of administration must be... there must be a preferred product for each route of administration.

Susan Flatebo: Okay. Well, I had to say, yeah. I would think that we would want to have a preferred... and I know all these indications, there is not always a subQ option or an infusion option, but if some patients aren't able to take oral then it's nice to know that they could have an option. Then, I agree, too, that I feel like... I don't know if we should necessarily break out this class based on indication, just because there is so much overlap.

Nancy Lee: I agree with the input from HCA and wanted to bring back the recommendation of kind of Donna what you just said prior about maybe expedited review just to make sure that patients do have access to some of these. Especially, we know that there is limited information and data, and the strength of the evidence varies, but for rheumatoid arthritis, it looks like one of the medications is leaning towards one over the others, but there are also limitations there, as well. So, I just kind of wanted to bring it to the committee for their thoughts.

Virginia Buccola: I just want to say that I'm in agreement with Nancy on that suggestion, in terms of wordsmithing. I would like to turn it back to our experts.

Donna Sullivan: So, Nancy, did you have actual drugs in mind that you felt should be called out for these special stipulations? I think that the best way to do that is to specifically name those in the motion with... and then identify the special population that you feel that they should be preferred for.

Nancy Lee: I'm going to rely back on what the DURP report... so, for ulcerative colitis, is it the vedolizumab appeared to be more in favor for ulcerative colitis. Please, if I get anything incorrect, feel free to correct me. For rheumatoid arthritis, it appears that is it...

Leta Evaskus: Nancy, sorry to interrupt. Do you want to say that vedolizumab has to be preferred for which type?

Nancy Lee: Ulcerative colitis. I don't know, Donna, I'll also defer to your wording recommendations.

Donna Sullivan: Without having the slides, I'm wondering what was the level of evidence, the strength of the evidence showing that it was superior, as well? And are we confident in that level of evidence that to prefer it over all other drugs for ulcerative colitis. Was it only, and I would have, I don't recall what those slides actually said from earlier. Was that a meta-analysis, a network analysis compared to all other drugs? Or was it to one particular drug?

Ryan Pistoresi: This was a fair methodologic quality RCT comparing vedolizumab to adalimumab. And its findings were at 52 weeks. It had a study size of 769. So, it's just one randomized control trial that looked at four different [inaudible]. So, it doesn't...

Donna Sullivan: Understanding the complexity of this particular class with all of these moving parts and different indications, one we don't normally do this, but we could abstain from making a motion today and bring this back at the next meeting with where we have gone through the evidence and looked at the different indications, and we can put together maybe a table that shows all of the drugs, all of their indications, which would assist you in kind of untangling how to make what preferred.

Nancy Lee: I would be in favor of that.

Constance Huynh: I would be in favor that, as well.

Alexander Park: Could I offer a counterpoint here? The head-to-head trials are usually one drug against another. So, I feel uncomfortable making a

recommendation that a particular drug is going to be preferred in that entire class when the data is primarily one drug against another.

Virginia Buccola: I think I'd like to come back to Alex's point and just think about this from the perspective of giving the HCA the most flexibility, and giving patients the greatest access to what they need. I'm in support of wording something that keeps access open to the patients for whatever they need. Maybe not whatever, but you know what I'm saying.

Donna Sullivan: Everything is always covered. So, all of these drugs are covered. It's just a matter of is it covered... do they need to try another drug before they would have access to the second drug. For Medicaid and for the Uniform Medical Plan the costs are quite different, which is why we not have different PDLs. So, it would make it easier for us with more flexibility, because Medicaid does follow your motions, but when we do the cost analysis, we might end up with selecting different drugs.

Virginia Buccola: I would probably tend to, not probably. I would tend towards working with a broader statement and going ahead and moving towards a motion today. However, I am absolutely open to hearing if people don't feel comfortable with that and would like to take the option that Donna has offered of waiting until our next meeting.

Susan Flatebo: I agree. I feel like we should proceed with the motion today.

Alexander Park: I agree.

Catherine Brown: I agree also.

Alexander Park: I think the list of FDA indications probably gets to some of your concerns there, Nancy, I hope, and also that of the committee. It's a fairly broad list of indication, for which we are recommending that the PDL include a TIM for all of those. I don't see a diagnosis, but I would want to make sure that we include so that patients have an access to a preferred TIM. Of course, there are other diagnoses that could go on there. Kawasaki's disease is treated by anakinra and so forth, but those are fairly unique cases that I don't feel that we need to concern ourselves with in this motion.

Nancy Lee: I appreciate everybody's input, and yeah. I would be okay with moving forward, just kind of hearing everything and all the different points to be made, unless others want to chime in.

Alexander Park: I just have one last question before I would feel comfortable making a motion. The difference between saying must include versus should include. What does that mean for the HCA?

Donna Sullivan: We interpret that as to be the same. If you say should or must, we interpret it as must.

Alexander Park: Okay. I only ask because it says must include a drug in terms of the FDA indications, but then it says should include in terms of the other concern that I think Susan had raised about self-administered. So, those two would be considered equally powerful so to speak in terms of our motion? Okay.

Donna Sullivan: Yes. And we can turn, we could change should to must.

Alexander Park: I'd be okay with that. Okay. After considering the evidence of safety, efficacy, effectiveness, and special populations for the use of targeted immune modulators for their FDA approved indications, I move that [inaudible], baricitinib, guselkumab, risankizumab, tildrakizumab, upadacitinib, abatacept, adalimumab, anakinra, apremilast, brodalumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, natalizumab, rituximab, sarilumab, secukinumab, tocilizumab, tofacitinib, ustekinumab, and vedolizumab are efficacious. The PDL must include a drug approved for the treatment of the following FDA indications: Rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis, and must include a self-administered agent, if indicated. These medications cannot be subject to therapeutic interchange in the Washington preferred drug list.

Jordan Storhaug: I second.

Virginia Buccola: All in favor?

Group: Aye.

Virginia Buccola: And the motion carries. Thanks to the committee for that discussion. Thanks to Alex for tackling all of those drug names. We are scheduled to go to lunch. We were going to do a 30-minute lunch. So, it's 11:56. Shall we meet back here at 12:30 to round up?

Leta Evaskus: That sounds good. Ginnie, before we go, there were two questions about the sickle cell anemia being canceled for today. As far as being informed as to when it will be discussed, you can sign up on our website on the stakeholder list so that you will be emailed the agenda 30 days before the meeting. Donna, do you know if that will be reviewed in the next meeting? Or is that on hold.

Donna Sullivan: I think we're anticipating the December meeting. Ryan, does that sound accurate?

Ryan Pistoresi: Yes. I believe we're getting a DURP report on sickle cell anemia due in December. We are planning on having sickle cell drugs be reviewed around that time. We can defer to Marissa, since she is now planning the DUR reviews.

Donna Sullivan: So, for now, I think December is what we will be targeting towards. If that changes, just watch for the December agenda, and it should come out in early November.

Virginia Buccola: I think I will go ahead and adjourn the meeting, as long as there are no questions. We'll meet back at 12:30.

Leta Evaskus: Sounds good. I'm just going to pause the meeting. So, it will still be on so people don't have to log back in.

Virginia Buccola: Thank you.

Leta Evaskus: Alright. See you at 12:30.

Virginia Buccola: Hello everybody. We're coming back from lunch and gonna go ahead and adjourn the DUR, or convene. We're not going to adjourn. We already did that. We're going to convene the DUR board. I know I'm jumping right in. So, I don't know, Umang, if you feel ready to go yet. So, whenever you're ready.

Umang Patel: Absolutely. Can you hear me okay?

Virginia Buccola: Yes.

Umang Patel: Okay. Great. Alright. So, just to get a little bit of a refresher. The therapeutic classes that we will discuss, if you go to the next slide, there will be an overview of disease state, indications, dosage forms, and guideline updates. We have kind of reformatted this a little bit based on committee feedback. It will be different from the past. We will only be reviewing new information, such as guideline updates, new drugs, and additionally approved indications within the last 12 years. The first topic on the next slide will be hematological oral oncology medications.

To give a little bit of background, there is a lot of information here. One of the feedbacks I did receive was to kind of summarize some of these, if possible. So, what I will do is, I won't read through this one by one, but I'll kind of just go over the main pearls, if you will, for some of these slides. As one can imagine, for hematological oral oncology, there are seven subdisease states that fall into this that will be presented. The first three on this slide are AML, cml, and multiple myeloma. So, for AML, which is acute myeloid leukemia, the most common form of acute leukemia among adults estimates roughly less than 6,000 cases

diagnosed and 1500 deaths in the U.S. in 2019. In patients who obtain a CR, 3-year survival rate is 45%, remission rates are inversely proportional to age. For the next disease state for CML, for chronic myeloid leukemia, it comprises of 15% of all adult leukemia. There are three phases of this disease, which are chronic, accelerated, and blast. A gene mutation called the Philadelphia Chromosome has been identified, which involves a translocation T from the 9 to the 22 chromosome, also known as the BCR-ABL translocation. In the discovery of tyrosine kinases that inhibit the BCR-ABL has revolutionized the treatment of CML making long-term remission a reality. In the final disease state here, we have multiple myeloma, which accounts for about 15% of all hematologic malignancies. They usually respond to initial chemotherapy but responses are often transient.

We have the next three being NHL, non-Hodgkin's lymphoma. This is the lymphoma... lymphomas are a heterogeneous groups of malignancies that originate in the immune cells predominantly beta cells and T-cells of the lymphoid tissue. Leukemia and lymphoma are similar diseases with overlapping characteristics. Most lymphomas involve tumor invasion of the lymph nodes and other tissues while the malignant clone in most leukemias predominate in the bone marrow. The most common presentation is that of a solid tumor. For the next one, we have chronic lymphocytic leukemia, CLL, and small lymphocytic leukemia, which is SLL. This is the most prevalent adult leukemia with a median age of diagnosis at 72 years of age. Treatment is individualized, as some patients may have indolent disease while others require treatment. Cytogenetic abnormalities are of prognostic significance and can help to drive the treatment options. For mantle cell lymphoma, or MCL, it has characteristics of both indolent and aggressive NHL, and the median onset is 3 years, but no evidence of survival plateau. It’s similar to indolent leukemia.

The seventh and the final ‘disease state’ we will discuss is graft versus host disease. Although the exact cause is unknown, graft versus host disease is an autoimmune mediated disease that can result following complications of hematopoietic cell transplantation in which the transplanted cells, which are grafts, recognize the recipient’s body as foreign. Chronic graft versus host disease is generally an extension of acute graft versus host disease that often develops more than 100 days after transplant. Pivoting over to the guidelines for graft versus host disease, the American Society for Bone Marrow Transplantation has a clinical practice guideline around the first and second line treatment of acute graft versus host disease. They state that corticosteroids are the standard of care for the initial treatment of acute graft versus host

disease and note that literature does not support the choice of any specific agent or secondary therapy of acute graft versus host disease. These guidelines were published prior to May 2019, FDA approval of Jakafi for the treatment of corticosteroid refractory acute graft versus host disease in adult and pediatric patients aged 12 years of age and older.

Continuing on with guidelines for AML. Keep in mind that the guidelines for this are short, as one can imagine. There are a huge body of guidelines, but as I mentioned earlier, we're only reviewing the ones in the last year. So, for AML, the NCCN guidelines in 2020 stated for standard induction to include Rydact in combination with cytarabine with or without daunorubicin, as part of standard induction, consolidation, and post-remission therapy for patients with FLP-3 mutated AML. For intensive remission induction therapy, adult patients who are candidates for intensive remission induction therapy with unfavorable risk cytogenetics may receive Venclexta in combination with hypomethylating agents, decitabine and azacitidine, or cytarabine, which are all category 2A, while patients 60 years of age or older who are not candidates for intensive remission induction or who decline intensive remission and are without actionable mutations, may be treated with a Venetoclax and Daurismo, among other options. Venetoclax is also listed as an option with Idhifa or Tibsovo for IDH2 mutated, or IDH1 mutated AML respectively. For postinduction therapy in patients who have a response to lower intensity therapy, the lower intensity regimen should be continued. This includes the following medications listed. Lastly, for relapsed/refractory AML, these patients who have IDH1 and IDH2 mutation, therapy with enasidenib and ivosidenib respectively may be utilized. For patients with FLT3 ITD or FLT3 TKD mutations, Xospata is a category 1 recommendation. The guidelines note that these drugs increase the risk for differentiation syndrome in hyperleukocytosis, which may require treatment with hydroxyurea and corticosteroids to mitigate. These guidelines note that in the event of relapsed or refractory disease after the completion of consolidation, targeted therapies may be retried if the drugs were not administered continuously and stopped due to the development of clinical resistance.

On the next slide here, we do have the subcategories based on Apple Health. Of these, you see there are 14 subclasses, the first being the alkylating agents. We have antimetabolites, antineoplastic miscellaneous, BCL-2 inhibitors. We have histone deacetylase inhibitors, immunomodulators, isocitrate dehydrogenase 1 inhibitors and 2 inhibitors. We have the JAK inhibitors, the PI3K inhibitors, proteasome inhibitors, XPO1 inhibitors, and lastly the immunomodulator specifically

myelodysplastic syndromes. If you notice, some of the drug names here are bolded. The bold does indicate there is new information in the last year that we will be going over.

As I mentioned, there are no updates for the first three subclasses, but we'll move right along to Venclexta. For Venclexta, in August of 2019, the FDA alerted the public of a risk associated with the investigational use of Venclexta in patients with multiple myeloma, and it was an off-label use based on data from the Bellini clinical trial, which reported after a median followup of 17.9 months, an increased risk of death with Venetoclax, roughly 21% compared to placebo, which was 11%. When used in combination with bortezomib and dexamethasone in patients with multiple myeloma. Again, just for the committee, I want to remind, there is a lot of information here. Please note that the bolding will indicate things I am going to go over, but the other information is here just for completeness sake. Please know that the indications, the warning and precautions are still here. The dosing, if you would like to see the full prescribing information, it is in the TCR that is in the web portal, the therapeutic class review and availability, as well. To give a little background, Venetoclax is a small molecule inhibitor with beta cell lymphoma 2, which is an antiapoptotic protein, and it restores apoptosis by binding to this protein, which is a part of the lymphatocytic leukemia cells. There is no pediatric safety and efficacy established here. There are warnings with tumor lysis syndrome, neutropenia, and infections, similar to a lot of the other medications in this class.

Continuing through the subclasses for Apple Health, there were no updates for the histone deacetylase inhibitors and the immunomodulators.

The next subclass we will review are the JAK, the Janus Associated Kinase inhibitors. Going to the next slide here, the first medication we will discuss is Inrebic. So, in August 2019, the FDA approved Inrebic, a kinase inhibitor, for the treatment of adults with intermediate 2 or high risk primary or secondary post polycythemia vera or post essential thrombocytopenia myelofibrosis. In terms of warning and precautions, a lot of these have similar black box warnings. This one here does have serious or fatal encephalopathy, including Wernicke's, which has occurred in patients treated with Inrebic. Anemia and thrombocytopenia, as one can imagine, GI toxicity. So, this is managed by a dose reduction, interruption, or transfusion. Similarly, GI toxicity, hepatic toxicity was mentioned earlier with encephalopathy, amylase and lipase elevation, and as one can imagine, you would avoid this in patients who are compromised in said systems, such as hepatic impairment. Dosing and availability is here for your leisure. To go over the mechanism

of action, this is a kinase inhibitor with activity against a wild type and mutationaly activated Janus associated kinase 2, or JAK-2. Essentially, this is a selective inhibitor with high affinity activity, and it helps reduce... without going into kind of the biochemistry of it, it inhibits cell proliferation, as seen in cancer, and it induces apoptosis.

We do have another JAK inhibitor, the Jakafi. In May 2019, FDA approved and expanded indications for steroid refractor acute graft versus host disease, which I mentioned earlier in the background, in adults and pediatric patients 12 years of age and older. As you can see, it had other indications, as well, such as myelofibrosis, polycythemia. The warnings and precautions, I won't continue going over them, because I will sound like a broken record, but I will try to highlight the ones that may be different from the ones you have heard. There is a risk of nonmelanoma skin cancer. So, it is recommended that healthcare practitioners perform periodic skin examinations. It can elevate lipid levels.

Looking at the Apple Health subclasses here, there are no updates for the PI3K inhibitors or the proteasome inhibitors. So, we'll move right along to the XPO1 inhibitors. We have a medication called Xpovio. Now, in July 2019, FDA approved this medication, which is a nuclear export inhibitor indicating a combination of dexamethasone to treat adults with relapsed or refractory multiple myeloma who have received four or more prior therapies and whose disease is refractory to two or more proteasome inhibitors, two or more immunomodulator agents, and an anti-CD38 monoclonal antibody. Very similar warnings and precautions of thrombocytopenia, neutropenia, GI adverse effects, and dosing and availability is found in the PCR. Take a step back for the mechanism of action, this medication, through a pathway, causes apoptosis of cancer cells by inhibiting the tumor suppressor protein. So, it inhibits the suppressor, and it inhibits growth regulators along with oncogenic proteins, as well.

Continuing on, the last updated medication class we'll talk about is the myelodysplastic syndrome for the immunomodulators, which would be Revlimid. You do see, so Revlimid in October 2019, FDA approved Revlimid in combination with a rituximab product for previously treated follicular lymphoma and previously treated marginal zone lymphoma. As you can see, it has a litany of other indications. For a black box warning, it does have an embryo-fetal toxicity, hematologic toxicity specifically with neutropenia and thrombocytopenia, and venous and arterial thromboembolism. Now, this medication is an analog of thalidomide, and it is a category X. So, that is why it does carry that embryo-fetal toxicity, and pregnancy must be excluded in patients at the start of treatment and two reliable forms of contraception must be used in

patients who are of childbearing age. That concludes the hematologic oral oncology medications. Any questions there?

Virginia Buccola: Just double checking, no questions? Thanks, Umang. We just have one stakeholder. It's Dr. Margaret Olmon with AbbVie. Are there any other stakeholders? Please go ahead and raise your hands, and we'll go ahead and go to Dr. Olman. You have three minutes for your comments.

Leta Evaskus: I don't see Margaret Olmon is still on. Wait. I'm sorry. Here she is. Okay. Sorry. She got moved to the bottom. Sorry, Margaret.

Margaret Olmon: No problem at all. I was trying to wave a hand or something to see if you could see me. I want to thank Dr. Patel for such a good summary of so many very difficult topics to look at all at once here. Again, my name is Dr. Margaret Olmon with U.S. medical affairs at AbbVie. I want to thank you for the opportunity to provide a short summary for information about Venetoclax, brand name Venclexta. Again, this is a short summary, so please see the prescribing information at rxabbvie.com for complete safety and efficacy details. A fixed duration of Venclexta treatment is indicated for patients with chronic lymphocytic leukemia and small lymphocytic leukemia. Venclexta is also FDA approved in combination with [inaudible] or [inaudible] or low dose [inaudible] for the treatment of newly diagnosed acute myeloid leukemia in adults 75 years or older, or in patients who have comorbidities that preclude use of intensive induction chemotherapy. Venclexta is a selective and orally bioavailable small molecule inhibitor of BCL-2. Overexpression of BCL-2 has been associated with resistance to chemotherapy agents. Venclexta helps restore the [inaudible]. It's been shown to improve patient response when used either as monotherapy or in combination with other oncology treatments. In two phase-3 studies in CLL, patients treated with combinations that included a fixed duration of Venclexta treatment showed a significant improvement in progression free survival. In two phase-3 clinical trials in AML, in patients on combinations that included Venclexta, the complete response rates ranged from 21 to 54% and time before partial response were between 1 or 2 months. Safety of these Venclexta combinations is consistent with what has been seen in previous clinical trials. Patients taking Venclexta should be assessed for tumor lysis syndrome risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis measures, including hydration, antihyperucemics, and laboratory monitoring. Venclexta is the only oral chemo free regimen that offers sustained treatment through remission across all lines of CLL therapy and is a preferred regimen for firstline and relapsed refractory therapy in the NCCN guidelines. NCCN also recommends the three Venclexta combination therapies as firstline treatments in patients with newly

diagnosed AML in patients who are 60 years or older who have unfavorable risk cytogenics or who are unable to take intensive chemotherapy. In summary, I am requesting the committee continue to have Venclexta available for oncology patients in Washington. Thank you for your time and your consideration. I'd be happy to answer any questions.

Virginia Buccola: Thanks, Dr. Olmon. Any questions from the committee? Okay. It looks like we can go ahead and move to the motion.

Leta Evaskus: Marissa, do you want to walk them through the motion?

Marissa Tabile: Sure. So, I just lumped everything for the oncology agents for the different subclasses onto one slide. So, it'll be one motion for all of them. So, if you want to go to the next slide, Leta.

All the drug classes are listed on slide 2. So, if you want to see those drug classes again, just let me know. Any questions?

Susan Flatebo: I move that all products in the drug classes listed 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 nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Nancy Lee: I second that motion.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: And the motion carries. We're going to move next back to Umang to discuss cytokine and CAM antagonists.

Umang Patel: Okay. Great. Alright. So, for the cytokine and CAM antagonists, I know the committee in the morning half of this meeting saw that there is an abundance of disease states that kind of fall into this umbrella of cytokine and CAM antagonists. I did my best to kind of do the summary; however, it wasn't always feasible, because there is a lot of information here, especially since there's so many disease states. So, for the first one on the next slide here, we'll just do a quick background. So, cytokine and CAM antagonists are chemical mediators involved in inflammatory processes throughout the body. Cytokines are small proteins to create a response to an immune stimulus for the purpose of mediating and

regulating immunity, inflammation, and hematopoiesis. The actions of the individual cytokines are widely varied, and they contribute to fibrosis and tissue degeneration associated with chronic inflammation primarily by inducting proliferation of fibroblasts and collagenous. The proinflammatory cytokines tumor necrosis factors, or TNF, and interleukin 1, or IL1, are involved in tissue destruction in many chronic inflammatory diseases effecting various organs.

CAMS, or cell adhesion molecules, are cell surface proteins involved in the binding of cells, usually leukocytes, to each other, endothelial cells, or the extracellular matrix. Specific signals produced in response to wounds and infection control the expression and activation of these moles. CAMS fall into three general family of proteins. We have the immunoglobulin super family, the integrin family, and the selectin family. Now keep in mind, different CAMS have been implicated in inflammatory fibrotic and autoimmune diseases respective of said disease.

The first disease we'll look at is ulcerative colitis. It is a chronic inflammatory disease primarily affecting the colon and rectum. It affects approximately 1 million people in the United States, and the incidence continue to increase worldwide. The CDC estimates the current prevalence of ulcerative colitis at 238 per 100,000 adults. The predominant symptoms of ulcerative colitis is diarrhea, which is usually associated with blood in the stool. Additional symptoms may include pain in the lower quadrant or rectum, along with systemic features, like a fever, malaise, and weight loss. The initial attack of ulcerative colitis may be fulminant with bloody diarrhea, but the disease more commonly begins indolently with nonbloody diarrhea progressing to bloody diarrhea. Most commonly, it follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. The primary goal of treating ulcerative colitis is essentially inducing then maintaining remission of the disease.

Normally, I do background and then guidelines, but like I said, there are so many disease states I figured for the committee's sanity, I'm trying to stick with the topic. I'm going to do background and guidelines, if it's relevant in the last year. So, American Gastroenterological Association, or AGA, in 2019 stated that again, agents in this class are not addressed in the recommendation for induction and maintenance of mildly active disease. For moderate or severe active ulcerative colitis, specifically induction of remission, the group recommends oral systemic corticosteroids. TNF antagonists are also recommended, and if infliximab is used, it should be used with thiopurine. Notably, these guidelines state that robust data of combining TNF antagonists and immunomodulatory treatment in moderately to severely acute ulcerative colitis exists only for

infliximab and thiopurine. Vedolizumab or tofacitinib is recommended in patients who had previously failed TNF antagonist therapy and in patients who were previously TNF antagonist responders but are subsequently having inadequate response, they recommend monitoring the serum drug level. In addition, the group states that patients who are primary nonresponders to TNF antagonists should be considered for an alternative mechanism of disease control rather than a switch to another TNF antagonist. However, for secondary failure, initial response to TNF antagonists with later loss of efficacy, another TNF antagonist may be used. To maintain remission in patients with previously moderate to severely active ulcerative colitis, these guidelines recommend the addition of 5-ASA in patients on TNF antagonists in those who had previously failed 5-ASA. Continuing adalimumab, golimumab, or infliximab, if used to achieve remission. Continuing vedolizumab if used to achieve remission. Continuing tofacitinib if used to achieve remission. Several other recommendations were detailed in the guidelines, including the role of medications not within this class or nonpharmacological guidance.

Pivoting over to juvenile idiopathic arthritis. We have the organization recommends NSAIDs conditionally as adjunctive therapy regarding traditional DMARDs for polyarthritis. Methotrexate is conditionally recommended over leflunomide or sulfasalazine. Subcutaneous methotrexate is conditionally recommended over oral methotrexate. Combination therapy with a DMARD is conditionally recommended over biologic monotherapy when initiating treatment with a biologic. A combination therapy with a DMARD is strongly recommended for infliximab. Intraarticular glucocorticoids are conditionally recommended as adjunct therapy and oral corticosteroids as a bridge therapy are conditionally recommended in patients with moderate or high disease activity. However, bridge therapy is not recommended in patients with low disease activity. In addition, the group strongly recommends against adding chronic low dose glucocorticoids regardless of disease activity.

With these guidelines for initial therapy with polyarthritis patients, they state that all patients have initial therapy with DMARD over NSAID monotherapy. In patients without risk factors, which are positive anticyclic citrullinated peptide antibodies, positive rheumatoid factor, or presence of joint damage, they recommend initial therapy with a DMARD conditionally over a biologic. However, in those with risk factors, the group recognizes that there are situations in which a biologic may be preferred. For subsequent therapy in low disease activity patients, defined as clinical juvenile disease activity score based on ten joints, they do recommend escalation of therapy, for example, intraarticular

glucocorticoid injection, DMARD dose optimization, methotrexate trial, and adding a biologic is recommended over no escalation. For subsequent therapy in moderate or high disease activity, and that's based on that said score I mentioned a second ago, patients receiving DMARD monotherapy, it is recommended adding a biologic to the original DMARD over changing to a second DMARD or triple DMARD therapy. For subsequent therapy in moderate or high disease activity, polyarthritis patients receiving a TNF antagonist, with or without a DMARD, the group recommends switching to a non TNF antagonist, such as tocilizumab or abatacept over switching to a second TNF antagonist. However, the group recognized that a second TNF antagonist may be appropriate in patients with good initial response to TNF antagonists who have experienced secondary failure. Lastly, if the patient is receiving their second biologic, use of a TNF antagonist abatacept or tocilizumab is conditionally recommended over rituximab.

Continuing with the said guideline, for patients with juvenile idiopathic arthritis or sacroilitis, guidelines strongly recommend treatment with NSAID over no NSAID treatment. In those already on NSAIDs with continued active disease, the group strongly recommends a TNF antagonist over NSAID monotherapy. They continue to recommend against the use of methotrexate monotherapy, bridging therapy with a limited duration oral corticosteroid in select conditions, and adjunct use of intraarticular glucocorticoid are conditionally recommended. Those with JIA and enthesitis, the group recommends NSAID treatment over no NSAID treatment with a TNF antagonist conditionally recommended over methotrexate or sulfasalazine. Bridging therapy with a limited duration oral corticosteroid in select conditions, and the group provides additional recommendations on such glucocorticoids, as well.

We have pediatric psoriasis. In 2019, the American Academy of Dermatology and National Psoriasis Foundation published guidelines for the management of psoriasis in pediatrics. They recommend ongoing assessment for psoriatic arthritis, uveitis, obesity, CV risk factors, dyslipidemia, insulin resistant diabetes, and mental health conditions. Body surface area plus children's dermatology life quality index should be used to assess the disease severity. In terms of treatment, they recommend topical treatments for psoriasis, and those include topical corticosteroids, which is off label, tacrolimus 0.1% ointment for face and genital regions. We have calcipotriene solution, calcipotriol, calcipotriol/betamethasone combination, tazarotene plus topical corticosteroids, topical anthralin, coal tar, phototherapy, and photochemotherapy. They do recommend systemic treatment, which could be methotrexate, cyclosporine, systemic retinoid, and biologics,

such as etanercept, infliximab, adalimumab, and ustekinumab. Lastly, the guidelines recommend treatment of physical and psychosocial wellness, such as quality of life for these pediatric patients, as well. Moving onto the next subdisease class, we have ankylosing spondylitis, and this is an inflammatory condition generally effecting the spine and can be further subdivided into ankylosing spondylitis and nonradiographic ankylosing spondylitis represented here. Now, the American College of Rheumatology Spondylitis Association of America and spondyloarthritis research and treatment network created a joint guideline update in 2019 on the treatment of both ankylosing spondylitis and nonradiographic axial spondyloarthritis. In general, they recommend for ankylosing spondylitis and nonradiographic axial are similar. TNF antagonist, but not a specific one, are recommended as first biologic over Cosentyx or Tremfya, which are then recommended over a second TNF antagonist if the first one does not produce a response. All the prior mentioned agents are recommended over Xeljanz. Concurrent low dose methotrexate with TNF antagonist is not recommended. They do recommend against a strict treat to target strategy. If a patient's disease is stable, guidelines recommend against discontinuing or tapering of biologics. Sulfasalazine provides a viable option for select patients who cannot take a TNF antagonist.

Continuing onto the next disease state, we have periodic fever syndrome. These are rare, hereditary syndromes that are characterized by short and recurrent severe localized inflammation and fever 'attacks' that are not otherwise explained by routine childhood, or even adult infections. It is defined as three or more episodes of unexplained fever within a six-month period occurring at least seven days apart. These could be periodic, or they could be a regular. Cryopyrin associated periodic syndromes, or CAPS, is a family of syndromes associated with mutations in this cryopyrin now known as nucleotide binding domain and leucine-rich repeat containing family, pyrin domain containing 3, or NLRP2. These include things such as Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and chronic infantile neurologic cutaneous articular syndrome, which is also known as neonatal onset multisystem inflammatory disease. The treatment for this, Kineret, Ilaris, and Arcalyst are approved for the treatment of CAPS in select ages. Kineret is only approved for patients with CAPS associated with NOMID. Arcalyst and Ilaris are approved more generally for patients with CAPS, including FCAS and MWS, the subdiseases I mentioned earlier. Ilaris is also approved for the following other periodic fever syndromes, such as tumor necrosis factor receptor associated periodic syndrome, hyperimmunoglobulin D syndrome, and mevalonate kinase deficiency, along with familial Mediterranean fever.

On the next slide here, the next disease state we have is giant cell arteritis, also known as temporal arteritis. It is a systemic inflammatory vasculitis of unknown etiology that is classified as a large vessel vasculitis that typically also involves small and medium arteries. Most commonly, it effects the occipital and ophthalmic posterior ciliary proximal, vertebral, and vertebral arteries. While the incidence of this ranges from 0.5 to 27 cases per 100,000 people in those 50 years of age or older, the incidence is higher in the northern areas of the U.S. It occurs in older persons and can result in a wide variety of neurologic ophthalmologic and systemic complications. The treatment is just high dose corticosteroids, although clinical studies on various dosing protocols are limited. Steroids are generally continued until the resolution of symptoms and then maybe tapered slowly to the lowest dose that adequately suppresses symptoms, and Actemra is the only non-corticosteroid drug FDA approved for the treatment of giant cell arteritis.

On the next slide here, we have hidradenitis suppurativa. This is a chronic condition that affects the terminal follicular epithelium in the apocrine gland bearing skin, such as armpits and perianal area. It occurs in adolescents generally after puberty, and adults, and about 1 to 2% of the population. Signs and symptoms are things such as erythema, raised bumps or lesions, painful lesions, and a local arthritis or arthralgia. Now, the European Dermatology Forum in 2015 stated that guidelines for this are limited, but guidelines recommend either adalimumab or infliximab in severe or refractory disease stating adalimumab seemed to be much more tolerated. However, only adalimumab is the FDA approved medication for this use. Continuing with uveitis, it is a noninfectious intermediate and posterior uveitis, inflammation of the intermediate and posterior uvea while panuveitis is the inflammation of the anterior chamber, vitreous humor, and choroid or retina simultaneously. Together, these represent the most severe and highly recurrent forms of uveitis. The incidence of all cases of uveitis is approximately 15 cases per 100,000 patients per year, and anterior uveitis is the most common form of uveitis.

Continuing onto the guidelines. In the last year, ACR and Arthritis Foundation released this guideline. They recommend topical glucocorticoids in patients with JA and active chronic anterior uveitis for short-term control, but for those unable to control the symptoms, they recommend adding systemic therapy in order to taper topical glucocorticoids. Regarding specific agents, they recommend subcutaneous methotrexate conditionally over oral methotrexate. However, the use of a TNF antagonist with methotrexate in severe active

disease and sight threatening complications is conditionally recommended. If starting a TNF antagonist, they conditionally recommend a monoclonal antibody over etanercept. Abatacept or tocilizumab as biologics and mycophenolate, leflunomide, cyclosporine as a nonbiologic option are conditionally recommended in patients who have failed methotrexate and two monoclonal antibody TNF antagonist. The disease should be well controlled for two years on a DMARD before considering tapering. For pediatric patients who develop acute anterior uveitis, the group conditionally recommends topical glucocorticoids prior to changing to systemic therapy. Notably, the only agent approved for uveitis in this class is adalimumab.

Continuing onto our last background guideline slide, we have cytokine release syndrome, which is a condition that can occur following select immunotherapies and can result in a large rapid release of cytokines into the blood. This can manifest as fever, nausea, headache, rash, tachycardia, hypotension, and dyspnea. As you can imagine, it can be life-threatening. Actemra is approved for the treatment of CAR T-cell induced severe, or life-threatening CRS in adult and pediatric patients 2 years of age and older. Lastly, for the role of biosimilars, although this ACR document is over a year old, I felt it important to keep it in here, as questions sometimes do arise about biosimilars. The ACR published a white paper regarding the use of biosimilars in the treatment of rheumatic disease, and they provided a comprehensive overview. They note that available real-world studies have demonstrated efficacy and extrapolated indications and state that healthcare providers should incorporate biosimilars where appropriate for patients with rheumatologic diseases. The state treatment is a shared decision between patient and clinician, and patient and provider must be educated on biosimilars. In addition, biosimilars are not considered superior or inferior to the originator product, and biosimilars should be considered safe and effective for all the originator products approved indications. However, they do caution against interchangeability without consultation with a prescriber. Before we move onto the next slide, which has our first new updated indication for medication, I do want to let the committee know that a lot of the other guidelines that we did not review, because they were over a year old, are found in the appendices. I did add it there for the committee's leisure, if they wanted to go through that, and that is located at the end of this slide deck.

Moving onward to the next slide. First we have Cimzia here. So, in March 2019, FDA approved the expanded indication of Cimzia for the treatment of adults with nonradiographic axial spondyloarthritis with objective signs of inflammation for the treatment of adults with active

ankylosing spondylitis. Keep in mind, the limitations for a lot of these cytokine and CAM antagonists will be very similar. There are things, such as live vaccine should not be given with this medication. There are black box warnings, such as serious infection and malignancies. So, if a patient is at an increased risk of serious infections leading to hospitalization or death, including TB, bacterial sepsis, invasive fungal infection such as histoplasmosis, and infections due to other opportunistic pathogen. In terms of malignancy, lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers. In terms of tuberculosis, it is important to evaluate the patient for TB prior to initiating treatment. This medication's dosing is stratified by indication and weight, and that is found in the package insert, or for the committee, it is found in the TCR in the web portal that you have. To give a little bit of background, the mechanism of action of this medication, so TNF also is a [inaudible] inflammatory cytokine. That plays a role in inflammatory process. This medication selectively neutralizes that said protein, and it inhibits the TNF alpha protein. In terms of pediatrics, the safety and efficacy of this medication has not been established in patients less than 18 years of age. In terms of patients who have renal or hepatic impairment, specific clinical studies have not been performed to assess the effect on renal and hepatic impaired patients.

The next one we have here is Skyrizi on the next slide. So, for Skyrizi, we have an April 2019 FDA approved for the moderate to severe treatment of plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The limitations, again, live vaccines should not be given with this medication. Additional specific contraindications, per their PI, have not been determined. The dosing and availability is here for you. I'll give similar information I gave for the previous medication. In terms of pediatrics, safety and efficacy have not been established. No specific studies have been established for hepatic or renal impaired patients. In terms of the mechanism of action, this medication is an immunoglobulin, and it binds to a specific T19 subunit, which then, in turn, goes to the IL23. Essentially, it helps mediate that inflammatory pathway process that you see.

We have Inflectra. So, in June 2019, the FDA expanded the indication of Inflectra to also include reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age or older with moderately to severely active ulcerative colitis who have an inadequate response to conventional therapy. It already had other indications, as you can see. Again, the limitations are very similar. We have increased of infection, lymphoma and other malignancies. This one

does have a postmarketing case of fatal hepatosplenic T-cell lymphoma, and similar to others, serious infection. The dosing, again, is stratified by indication and weight. Specific clinical studies have not been performed for hepatic and renal impaired patients.

Moving onward to the next medication in this class that we'll review is Renflexis. In June 2019, the FDA approved expanded indication to reduce the sign and symptoms of inducing and maintaining clinical remission in pediatric patients 6 years of age or older with moderately to severe active ulcerative colitis who have had an inadequate response to conventional therapy, as well. Again, similar to the prior medications, there are a litany of other indications for this medicine. Almost identical limitations that I won't go over. Dosing, again, is stratified by indication and found in the TCR. There is no available data for this medication and its effect on women who are pregnant or patients who have severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholecystitis. That has been reported in postmarketing data. However, no specific studies have been conducted to determine the effect on renal or hepatic impaired patients prior to this medication.

On the next slide here, we have Otezla. In July 2019, the FDA approved a new indication to treat adults with oral ulcers associated with Behcet's disease, and dosage for this indication is consistent with its other indications, as well. In terms of limitations, there are some that are a little unique from the ones we've mentioned before, diarrhea, nausea, and vomiting, and if this does occur with this medication, consider dose reduction or suspension, depression. Advise patients, their caregivers and families to be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes, and weight decrease. So, it is important the healthcare providers monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate and consider discontinuation.

Moving onto the next new medication here, we have Hadlima. In July 2019, Hadlima was approved, a biosimilar to Humira, for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and ulcerative colitis. Please note that the launch is expected on or after June 30, 2023. The black box warnings are similar of Humira. There are serious infections, malignancies, postmarketing cases of hepatosplenic T-cell lymphoma, and serious infection. Again, dosing stratified by indication and weight. In terms of renal impairment and hepatic impairment, no PK data available to show its effect on patients who had a baseline renal or hepatic impairment.

Moving forward with RINVOQ. So, in August 2019, the FDA approved RINVOQ, a Janus kinase inhibitor. This is for the treatment of adults with moderate to severe active rheumatoid arthritis who have had an inadequate response for intolerance to methotrexate. Now, the limitations of use, the use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressant, such as azathioprine and cyclosporine is not recommended. The limitations, again, are similar. Serious infections may occur. A lymphoma or other malignancies have been observed. A newer one is thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. Similar to the other medications, a TB test is required prior to the start of this treatment. The dosing and available can be found here, as well. I have already mentioned the mechanism of JAK before. I'm not going to go into that. In terms of pediatrics, there is no study to show the safety and efficacy of this medication in patients less than 18 years of age. No dosage adjustment is required in patients with mild, moderate, or severe renal impairment, or in patients with mild or moderate hepatic impairment. However, it is not recommended in patients with severe hepatic impairment.

Continuing to the next one, we have Olumiant. So, in October 2019, FDA approved a new formulation of Olumiant 1 mg tablet for dose adjustment in patients with moderate renal impairment or patients taking strong OAT3 inhibitors. Indication for this is treatment of adult patients with moderate to severe rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. So, the dosing normally is 2 mg. However, this new expanded formulation came out of 1 mg tablet, which is used, like I mentioned earlier, with patients who have moderate renal impairment, which is defined as creatinine clearance of 30 to 60 mL/minute. Or patients who are taking strong OAT3 inhibitors. There is no safety and efficacy for patients who are less than 18 years of age, and as I mentioned earlier, there is a dose adjustment needed for renal impairment. No dose adjustment for mild or moderate hepatic impairment, but it is not recommended in patients with severe hepatic impairment.

Continuing onward, we have Erelzi. So, in October 2019, the FDA approved a new indication for the treatment of psoriasis and psoriatic arthritis in adults, and it was already approved for rheumatoid arthritis, ankylosing spondylitis, and polyarticular juvenile idiopathic arthritis. Identical limitations and black box warnings. The dosing is bolded for the respective new indications it received. Pregnancy, the available studies

do not reliably support an association between this medication and major birth defects. This medication has not been studied in patients less than 2 years of age, since the indication is for people 2 years or older. There are no formal PK studies for this medication in hepatic and renal impairment. So, there are no recommendations there.

Moving onward is Stelara. In October 2019, FDA approved a new indication for the treatment of moderate to severe active ulcerative colitis in adults. Again, it has a litany of other indications, such as plaque psoriasis, psoriatic arthritis, and Crohn's disease. Identical limitations as the previous medications, as well. There is a pregnancy registry that monitors pregnancy outcomes in women exposed to Stelara during pregnancy. There is limited data on this medication in pregnant women to inform a drug associated risk. In terms of pediatrics, it's got pediatric indications for certain disease states. So, the safety and efficacy of Stelara has been established for pediatric patients 12 years of age to 17 years of age with moderate to severe plaque psoriasis. It has not been established for any of its other indications. No hepatic or renal impairment dose adjustments.

We have Abrilada. In November 2019, FDA approved this medication, which is a new biosimilar to Humira. It has identical indications, treatment of RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's, ulcerative colitis, and plaque psoriasis. Identical limitations, as well, with vaccines, serious infections, and malignancies. There is kind of a new limitation here that hasn't been mentioned before, and invasive fungal infection. So, for patients with systemic illness on Abrilada, consider empiric antifungal therapy for those who reside or travel to regions where mycosis are endemic. Dosing is weight and indication based. There is no formal recommendation for hepatic renal impairment. There is no reliable association between this medication and major birth defects, as well.

Marching onward, we have Tremfya. In November 2019, this was FDA approved for a new formulation as a single dose one press patient controlled injector, and it's a single dose prefilled syringe, which was already approved in the past. It is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic or phototherapy. Again, identical limitations. There is not too much information here, but the reason this was included into the slide set is because there is a new formulation, any time a new dosage formulation, black box warning, postmarketing study, anything is found, it will be included when this class is rereviewed.

Moving onward. So, then, we have in December 2019, FDA approved Avsola, which is a biosimilar to Remicade. The indications for this include Crohn's disease in adult and pediatric patients, ulcerative colitis in adult and pediatric patients, rheumatoid arthritis in combination with methotrexate, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Identical limitations and black box warnings, as we've already mentioned before. Please note that hepatotoxicity has been seen with this medication. So, severe hepatic reaction, some fatal or necessitating liver transplantation, and if a patient does appear to have jaundice and/or marked liver enzyme elevation, the healthcare provider should stop this medication. Dosing is stratified by indication and weight base. This can be found in the TCR, as well.

Moving onward to Xeljanz and Xeljanz XR. In December 2019, the FDA issued a safety announcement regarding both Xeljanz and Xeljanz XR. An ongoing clinical trial found an increased risk of blood clots in the lungs and death when a 10 mg twice daily dose was used in patients with RA, which is not an FDA approved dose. Patients should be monitored for pulmonary embolism and advised to seek medical attention if symptoms of a pulmonary embolism occur. At that same month, to save a slide for the committee, that same month, the FDA also approved a new indication for Xeljanz XR for the treatment of adult patients with moderate to severe ulcerative colitis who have an inadequate response or who are intolerant to TNF blockers. There is no other extra information here, but this is for completeness sake for the committee.

Moving onward to Ixifi. In January 2020, FDA approved this medication for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age or older with moderate to severe ulcerative colitis who have had an inadequate response to conventional therapy. This was previously only indicated for adults with ulcerative colitis. It also does have other indications, as you can see. Identical limitations, and the dosing is stratified by weight and indication that can be found on the TCR.

Our last slide for this therapeutic class is Taltz. In August 2019, the FDA approved the expanded indication of Taltz for the treatment of adults with active ankylosing spondylitis and then roughly a few months later, in March 2020, they approved Taltz for use in patients 6 years of age or older with moderate to severe plaque psoriasis where candidates where systemic therapy or phototherapy, and previously this was only found in adults. As you can see, there are other indications found, as well. Identical limitations. One unique limitation here, Crohn's disease and ulcerative colitis including exacerbation did occur during clinical findings. So, patients who were treated with Taltz and have inflammatory bowel

disease should be monitored closely by the healthcare practitioner. Again, dosing is stratified by its indication, which is found in the TCR.

That concludes the cytokine and CAM antagonists updates. Any questions from the committee?

Virginia Buccola: Thanks, Umang. That was detailed. Again, opening it back up to the committee for questions. Okay. If there are no questions, it looks like we have one stakeholder, and it is Dr. Margaret Olman with AbbVie. So, Dr. Olman, if you're ready, you can go ahead and have your three minutes.

Margaret Olman: Thank you for the opportunity to speak with you once again. My name is Dr. Margaret Olmon with medical affairs at AbbVie. AbbVie now has three targeted immunomodulating medications available. I'd like to briefly review only the indications for Skyrizi, RINVOQ, and Humira and answer any questions you might have. Please see the full prescribing information online for comprehensive safety and efficacy data. Skyrizi is an IL23 inhibitor indicated for the treatment of moderate to severe plaque psoriasis in adults and is given as a subcutaneous injection at week 0, 4, and every 12 weeks, which means maintenance treatment four times a year. RINVOQ is an oral JAK inhibitor indicated for the treatment of adults with moderately to severely active rheumatoid arthritis that is given as a 15 mg tablet once daily. All TNF's, including Humira, carry similar boxed warnings regarding serious infections, tuberculosis, and malignancies. JAK inhibitors also include warnings about thrombosis. Patients starting any of these medications should be screened for TB and carefully monitored for serious events. Humira has ten currently approved indications, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, adult and pediatric Crohn's disease, plaque psoriasis, uveitis, and hidradenitis supprativa. In summary, I respectfully urge the committee to maintain preferred status for Humira on the PDL and to add both Skyrizi and RINVOQ as available treatments for the Medicaid patients in Washington. May I answer any questions for you at this time?

Virginia Buccola: We'll go back to Umang, and we're going to hear about erythropoiesis stimulating proteins. No. We're probably going to do a motion. Right? Thank you.

Marissa Tabile: Leta, sorry. For the last class, the oncology agents, we do have one of the products in a class by itself. It's in the immune modulators. So, we will actually need a motion for that product. Let me just double check. I believe it's for the Revlimid. So, we just need a motion for that one. I apologize.

Virginia Buccola: That's okay. Was that Marissa?

Marissa Tabile: Sorry. Yes. This is Marissa.

Virginia Buccola: Okay. I'll just... I guess we'll just wait then for Leta to give us some words to look at.

Leta Evaskus: Hang on. I am sharing my screen. Let me check.

Donna Sullivan: I can see your screen, Leta.

Leta Evaskus: Okay. Ginni, can you see my screen?

Virginia Buccola: Yes. I can. Sorry.

Leta Evaskus: Okay.

Susan Flatebo: I just have a question. So, Revlimid is in this class, but it's not... it has other indications, though. I guess, so I'm confused as to why it's in immune modulators, myelodysplastic syndromes when it's also used in other disease states.

Marissa Tabile: So, that's just how we have it classified on the AH PDL. So, of course, if there are other indications, then of course it can be used. Right now, it does have PA for medical necessity. So, if we do get any requests for them, if there is any FDA indications, it can still be used for the other ones. That's just how we divide it on the PDL.

Susan Flatebo: Okay. It also... I think it's used far more often in multiple myeloma and even for mantle cell lymphoma than for myelodysplastic syndrome. So, I just found that interesting.

Donna Sullivan: I'm trying to figure out, and I'm trying to log in. It's possible that this is how MediSpan classifies it. So, I'm not 100 percent sure. Or it is how Magellan classifies it, but I do think this is our drug class name. So, we'll double check that.

Susan Flatebo: Okay. Thanks.

Donna Sullivan: Again, it's just one of those challenges when you have multiple indications that span across different disease states.

Susan Flatebo: Right. I just wanted to make sure that it's still being approved for other reasons besides myelodysplastic syndrome.

Donna Sullivan: Yeah. It would be approved for anything that it's indicated for.

Constance Huynh: So, do we need to get verification that this is the correct class before we go through the motion? Or if we go through this motion, the default is

that it will already be approved for the classes it's indicated for. I mean, is this something that we need to finalize?

Donna Sullivan: Which class it's in, I don't think matters as much. It's in a class all by itself. So, there's no preferred, nonpreferred, try and fail within this class if it's the only drug in it, but we do cover everything for their FDA approved indications. So, it will, regardless of what the drug class name says, if it has an indication that would put it into a different drug class, it would still be reviewed for that and approved when appropriate.

Constance Huynh: So, this motion currently is just specifically for the myelodysplastic syndrome is what we're reviewing. Is that correct?

Donna Sullivan: I'm not 100 percent sure. I think that it will be Revlimid in general. Going back to Umang's presentation, what was included in his presentation for Revlimid? Do we recall?

Umang Patel: Let me pull that up. It is slide 18.

Susan Flatebo: So, [inaudible] or [inaudible] is essentially the same drug class as Revlimid, yet it's... what was [inaudible]? What drug class was that in? I'm just surprised they're not in the same drug class.

Amy Irwin: I just wanted to confirm, this is the drug class based on MediSpan's classification, and they do not have the other product that was just mentioned classified in the same drug class.

Donna Sullivan: So, Susan, can you spell [inaudible] for me?

Susan Flatebo: Yeah. It's P-O-M-A-L-Y-S-T. That's the brand name. The generic name is pomalidamide. [SP]

Donna Sullivan: Okay. I'm looking at it right now. So, hang on, and I'll let you know.

Amy Irwin: I see it, Donna, in the oncology agents' immunomodulators oral class on the PDL. That's in a class by itself.

Donna Sullivan: Yeah. I confirm that. So, it's just a matter of how MediSpan is classifying the drugs. If you think that it's better that they be in the same drug class, we could move Revlimid into that antineoplastic immunomodulators class, but then it begs the myelodysplastic issue.

Susan Flatebo: I suppose it doesn't matter, just so long as... both [inaudible] and [inaudible] can be prescribed for multiple myeloma. I don't want to feel like [inaudible] is necessarily preferred, because they're in that immunomodulatory class and lenalidomide is not. So, does that make a difference if the doctor writes for lenalidomide, it's not going to matter, right? As far as preferred status over [inaudible]? They are, they're

essentially used in some of the same indications, lenalidomide more firstline, [inaudible] more second line. Yet, the [inaudible] is listed in that immunomodulating class and lenalidomide is not. I don't know. I guess I'm find with it, as long as it's not raising questions about what they're being prescribed for.

Donna Sullivan: They're both on prior authorization, so we would require the diagnosis. We're not preferring one over the other at this point. If they were in the same drug class, they could potentially both be equally preferred. Or, we could prefer one to be used. If you think that one should be used prior to another, we can do that through a prior authorization policy, but we can go back and just revisit what we call these classes, as well. We have been trying to follow the MediSpan, because it's based on what's called a generic product identification number, which identifies the drug. MediSpan has put them in two completely different categories, but we can go back and look at the most appropriate place to put it. This isn't the first drug class this has come up with.

Susan Flatebo: I suppose I'm fine with following whatever MediSpan has them classified, since they both require prior authorization. The oncologist would have all that information, able to submit to get it approved. So, I guess I'm fine with it. It just was kind of interesting to me that they classified them separately, but anyway, sorry. One other thing about this slide, requires trial of two preferred products, there may not be two preferred products, but I guess it says right in there, unless... or only one product is preferred. Never mind.

Virginia Buccola: Thanks, Susan. I just want to be sure, with the HCA, Donna and Leta, are we okay then to go ahead and consider this motion as it is?

Donna Sullivan: Yes. That would be fine.

Virginia Buccola: Okay.

Constance Huynh: I move that all products in the immune modulators myelodysplastic syndrome drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of the HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Catherine Brown: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: The motion carries. Now, we will proceed, back to Umang, for erythropoiesis stimulating proteins.

Marissa Tabile: I think we actually need to do the cytokine and CAM motion.

Virginia Buccola: I'm sorry. I heard you say that the first time, and I got caught up in our discussion.

Marissa Tabile: No. It's fine.

Susan Flatebo: I just wonder if Umang could go back to the slide with the periodic fever syndrome. I don't recall what slide number it was.

Umang Patel: Yes. Let me find that for you. It is slide 29, please, Leta.

Susan Flatebo: My question is, the Ilaris, I just wanted to make sure that that was on there. Now, I see it. Never mind. Okay. I didn't, I, yeah. I guess I didn't notice that before. That answers my question. As far as the biosimilars are concerned, where there's multiple biosimilars for some of these agents, does the HCA have a preferred biosimilar? Or is that even something that we need to discuss today?

Donna Sullivan: The biosimilars provide a profound challenge for Medicaid, as they are approved as a brand name drug. Oftentimes, they are more expensive for Medicaid than the original biological product that they are similar to, because of federal rebates and CPI penalties. For Uniform Medical Plan, the biosimilars are cheaper, and I think that cost is considered when Ryan is doing his analysis. So, they might have... they might call out one biosimilar preferred over all other biologics that are of that same drug. So, one etanercept biosimilar might be preferred and then all other etanercept products be nonpreferred, but that's done on a case by case basis.

Susan Flatebo: Okay. Thank you.

Donna Sullivan: They're not treated like generics where if it's a generic, they're all preferred. They are approved as their own brands. And they do have significant cost differences.

Susan Flatebo: I move that all products in the cytokine and CAM antagonists' drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization for medical necessity. All nonpreferred products require a trial of two

preferred products with the same indication before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only product is preferred.

Diane Schwilke: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: And the motion carries. I want to pause for a minute. I'm assuming that the motion is carrying when I hear everyone say aye. So, I just wanted to pause and acknowledge that if I need to formally ask if there are any in disagreement, I can change how I'm doing that.

Leta Evaskus: Afterwards, you can say all of those opposed.

Virginia Buccola: Okay. Thank you. If there's anybody that needs to go back in time to this morning, we can send the message offline, and we can do that. Thank you. Alright. I think we are caught up then on motions. I keep trying to move us ahead too early, but I think we're ready to go back to Umang.

Umang Patel: Okay. So, the next class that we will be reviewing is erythropoiesis stimulating proteins. In this class, I will be doing much better about summarizing the information, since I started out with the oncology, and it was tough to kind of summarize cytokine and CAM. So, with erythropoiesis stimulating protein, to give a little background, anemia is a frequent complication effecting over 3 million Americans. This is associated with a number of serious diseases, such as CKD, diabetes, heart disease, cancer. These conditions can cause anemia by interfering with the production of oxygen carrying red blood cells. Sometimes, as in the case of cancer chemotherapy, anemia is caused by the treatment itself. So, erythropoietin is a glycoprotein produced in the kidneys that stimulates the red blood cell production from bone marrow. Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation and hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis. In normal subjects, the erythropoietin plasma levels range between 0.01 to 0.03 units/mL and may increase 100 to 1000-fold during hypoxia or anemia. In contrast, patients with CKD have impaired production of erythropoietin, which is a primary case of the anemia.

Just to give a little bit of background, there is a new subdisease class that falls into this now and is beta thalassemia. This is the first time, since the last time we reviewed this class. So, I will be a little more in depth with beta thalassemia. It's a rare inherited blood disorder marked by the

reduction of functional hemoglobin levels, has an incidence of approximately 1 in 100000 individuals in the general population. There are three subtypes of beta thalassemia, which are characterized by the severity of symptoms, minor, intermediate, and major. Individuals with beta thalassemia major require regular blood transfusions, as often as once every two to four weeks and are dependent on medical care for survival. Treatment of beta thalassemia is highly dependent on the type of thalassemia progression, severity, and the presence or absence of certain symptoms. Treatment options may include regular blood transfusion, chelation therapy, folic acid treatment, removal of the spleen and/or gallbladder bone marrow transplantation. Reblozyl, which we will go over in a second, is the first FDA approved erythroid maturation agent, which reduces patient's transfusion burden by regulating late stage red blood cell maturation. It is approved for the treatment of anemia patients with beta thalassemia who require regular red blood cell transfusions.

Just to give you updates on guidelines in the last year. We have the National Comprehensive Cancer Network in 2020. Basically, they reinforced that physicians are advised to use the lower ESA dose possible to maintain hemoglobin levels sufficient to avoid blood transfusion. They should be discontinued once the course of chemotherapy has been completed and anemia resolved in patients with cancer. There is not enough evidence to support the use of ESA for the treatment of anemia related to myelosuppressive chemotherapy with curative intent. Patients receiving non-myelosuppressive therapy or patients with cancer not receiving therapy. The ASCO and the ASH updated their 2010 recommendations for use of ESA in patients with cancer. They emphasize the intent of treatment be considered when weighing the benefits and risk of these agents, including thromboembolism. These ESA's may be offered to patients with chemotherapy associated anemia whose cancer treatment is not curative in intent and whose hemoglobin level is less than 10 grams/dL. They can also be used for low risk myelodysplastic syndrome, as well. Essentially, these guidelines reiterate that the goal of hemoglobin should be the lowest value that prevents the patient's need for transfusion. Once that goal is achieved, ESA should be discontinued if there is a lack of hemoglobin increase by 1 to 2 grams/dL every six to eight weeks.

The new medication or updates in medication last year, we have Reblozyl. It's an erythroid maturation agent indicated for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusion, and anemia failing an erythropoiesis stimulating agent and requiring two or more red blood cell units over eight weeks in

adult patients with very low to intermediate risk, myelodysplastic syndrome with ring sideroblasts, or with myelodysplastic myeloproliferative neoplasm with ring sideroblast and thrombocytosis. The limitation for this is it is not indicated for use as a substitute for red blood cell transfusions in patients who require immediate correction of anemia. In terms of contraindications and warnings, it's similar to many other ESA's. Thrombosis, or thromboembolism has been found. There is an increased risk in patients with beta thalassemia, and it is important for healthcare providers to monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly. Hypertension, monitor blood pressure during treatment, and initiate antihypertensive treatment, if needed. Lastly, embryo fetal toxicity. It may cause fetal harm. Therefore, healthcare practitioners are recommended to advise females of reproductive potential of the potential risk to fetus and use effective contraception. The dose is weight based, as well. To give a little bit of background here, the mechanism of action is essentially it induces the erythroid maturation at the binding site, which increases the production of red blood cells here. In terms of pediatric patients, safety and efficacy have not been established. For hepatic and renal impairment, there is no significant difference in mild or moderate hepatic or renal impairment. There has been no evaluation for severe. That is the end of this therapeutic class. Any questions from the committee?

Virginia Buccola: I don't hear any questions. Is everybody ready to move on? It doesn't look like we have any stakeholders, unless anybody is listening and has not put their hand up. I just want to give a moment for anyone to do that. Okay. I'll presume that we can move to the motion.

Alexander Park: Just to clarify, when we talk about all the drugs in the class, we're not referring to the drugs that were in the slides. Is that right? We're talking about the list that was in the Magellan document?

Umang Patel: So, when I do my slides, I have been informed when we revisit a class, I'm just reviewing the changes in the last year. So, my slides would not be reflective of the entire class that the motion is discussing.

Alexander Park: Thanks, Umang. That's helpful. So, for the committee members to know what comprises the class, am I correct in assuming we are to refer to the other PDF that's the Magellan document that has the whole list?

Donna Sullivan: It would be referring to the Apple Health PDL. So, let me look to see what is in this class.

Marissa Tabile: So, in this class, we have the Aranesp, Epogen, Procrit, [inaudible], and [inaudible] in this particular class.

Alexander Park: Great. Thanks. It looks like that's what's on page 2 of the other PDF that came with the documents for the meeting. Okay. I know where I'm looking for my information now. Thank you.

I move that all products in the hematopoietic agents, erythropoiesis stimulating agent's drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization for medical necessity. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Constance Huynh: I second.

Virginia Buccola: All this in favor?

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries. We will move back to Umang for colony stimulating factors.

Umang Patel: Okay. Thank you. So, the next class that we have here is colony stimulating factors. To go back to background. We have... so myelosuppressive chemotherapy can induce neutropenia. The definition is here, and febrile neutropenia, which is a dose-limiting toxicity of chemotherapy. The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported. Colony stimulating factors, or CSF, are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and to improve relative chemotherapy dose intensity. Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection and hospitalization. Medications, such as neupogen, Nivestym, Zarxio, Neulasta, Udenyca, Fulphila, Ziextenzo, Granix are granulocyte colony stimulating factors, or G-CSFs. Leukine is a granulocyte macrophage colony stimulating factor, or GM-CSF.

On the next slide here, we have the NCCN 2020 practice guidelines for myeloid growth factors. In terms of these guidelines, safety data appears similar between Neupogen, Neulasta, and their biosimilars, and subcutaneous route was preferred for all agents. Subcutaneous filgrastim and its biosimilar, Granix, and pegfilgrastim, have a category 1 recommendation stating there is a high level evidence from randomized controlled clinical trials, and there is uniform NCCN consensus that they

prophylactically reduce the risk of febrile neutropenia. I apologize. I thought there was a question, but I think there may be an echo. Fulphila and Udenyca have been designated a category 2A due to recent approval of recommendation of the Ziextenzo is not currently provided by NCCN. To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSF and GM-CSF. Filgrastim, filgrastim biosimilars, and tbo-filgrastim can be administered the day after chemotherapy up to three or four days after chemotherapy and through postnadir recovery. Based on data from clinical trials, pegfilgrastim and its biosimilar should be administered the day after chemotherapy. However, administration up to three or four days after chemotherapy is also reasonable, according to the NCCN guidelines. For patients unable to return to the clinic the next day for medication administration, a delivery device, such as Neulasta Onpro, is available that allows for the device to be applied to patients the same day as chemotherapy administration, but the device does not release the medication until approximately 27 hours after the application. There is evidence to support the use of chemotherapy regimens every three weeks with pegfilgrastim and its biosimilars. Efficacy data exists for pegfilgrastim products in chemotherapy regimens given every two weeks. There is insufficient data to support dose and schedule of weekly chemotherapy regimens. Therefore, pegfilgrastim products should not be used. Leukine is no longer recommended for prophylactic use in patients with solid tumors receiving myelosuppressive chemotherapy.

Continuing with the updated NCCN guidelines, the guidelines note that a biosimilar is a biological product that is highly similar to the FDA approved originator product with very small clinically inactive differences, but no difference in efficacy, safety, or purity. The first biosimilar, Zarxio, was approved in March 2015 with a second filgrastim biosimilar, Nivestym, being approved in 2018. However, Granix was approved in 2012 as a biologic rather than a biosimilar in the United States. In Europe, Granix is available as a biosimilar in a pegfilgrastim. The first pegfilgrastim biosimilar, Fulphila and Udenyca, were approved in 2018. Studies have shown these products have similar safety and efficacy profiles, as the originator product. The guidelines state if overall safety and efficacy are equivalent, biosimilars may be substituted for the originator product. However, the guidelines note that current biosimilars are not interchangeable. Therefore, alternating between a biosimilar and its originator is not recommended. The guidelines also note that the use of biosimilars may provide opportunities for cost containment. The guidelines endorsed the use of Zarxio, Nivestym, Granix, Fulphila, and Udenyca for a myelosuppressive doses of radiation. For mobilization of hematopoietic progenitor cells in the autologous setting, the use of

concurrent filgrastim or one of its biosimilars with sargramostim or single agent filgrastim, Zarxio, Nivestym, or Granix is recommended. Filgrastim, Granix, or filgrastim biosimilars are all NCCN category 1 G-CSF options for prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery. According to the guidelines, the World Marrow Donor Association recommends pegfilgrastim or filgrastim biosimilars for the mobilization of peripheral blood progenitor cells in healthy donors in allogenic settings. The guideline does not recommend Neulasta or its biosimilars for mobilization at this time.

Here on the next slide, you'll see a new medication, Ziextenzo. In November 2019, FDA approved this medication. The indication that it is approved for is, it is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incident of febrile neutropenia. There is a limitation. It is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. In terms of contraindications and warnings, patients with a history of serious allergic reaction to human granulocyte colony-stimulating factors, such as pegfilgrastim products or filgrastim products, fatal splenic rupture has occurred, evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. Acute respiratory distress syndrome has occurred. So, evaluate patients who develop fever, lung infiltrates, or respiratory distress, and discontinue in patients with ARDS. The dosage is here. Again, it is also semi weight-based. In terms of mechanism of action, this medication is a colony stimulating factor that binds to specific cell surface receptors and stimulates proliferation, differentiation, commitment, and end cell functional activation. In terms of patients who are pregnant, there is limited data in pregnant women, and there is no identified drug associated risk for miscarriage or major birth defects. In terms of pediatrics, it is approved for pediatric patients with specific dosing instructions for patients less than 45 kg. Any questions from the committee?

Virginia Buccola: It doesn't sound like there's any questions. Thanks, Umang. We have one stakeholder, Jennifer Shear from Teva Pharmaceuticals. If there are any others [RD]. Jennifer, you'll have three minutes to share your comments.

Jennifer Shear: Thank you. Can everyone hear me?

Virginia Buccola: Yes.

Jennifer Shear: Great. Good afternoon. My name is Jennifer Shear. I am a medical outcomes liaison with Teva Pharmaceutical. Today, I want to provide you with a short update on Granix and its pediatric data. First of all, Granix, tbo-filgrastim, is indicated to reduce situations of severe neutropenia in adults and pediatric patients 1 month and older with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. In terms of pediatric use, the safety and effectiveness of Granix has been established for pediatric patients 1 month to under 17 years old. Use of Granix in these age groups is supported by evidence from adequate and well-controlled studies of Granix in adults. Additional safety and pharmacokinetic data was obtained from a phase-2 multicenter open-label trial that investigated the safety and tolerability of Granix in pediatric patients receiving myelosuppressive chemotherapy. In total, 50 patients aged 1 month to below 16 years of age with solid tumors without bone marrow involvement, were prophylactically administered tbo-filgrastim 5 mg/kg body weight once daily subcutaneously. Granix administered to pediatric patients demonstrated a safety profile consistent with the safety profile in that of adult patients. The incidence of febrile neutropenia was on the lower end of the range reported in literature. And the incidence and duration of severe neutropenia provided supportive data on the efficacy of Granix in pediatric patients that are in line with previous research. This concludes my comment today. I am happy to answer any questions.

Virginia Buccola: Thank you, Jennifer. Any questions from the committee for Jennifer? Okay. Leta, I see that it looks like there is another stakeholder?

Govin Shah: I am a medical science liaison on [inaudible]. Thank you for the opportunity for providing this comment pertaining to Udenyca, pegfilgrastim, [inaudible], and biosimilar to Neulasta pegfilgrastim. Udenyca is a leukocyte growth factor indicated to decrease the incidents of infection, as manifested by febrile neutropenia in patients with nonmyeloid malignancies [inaudible] myelosuppressive anticancer drugs associated with the clinically significant incidents of febrile neutropenia. Udenyca was approved by the FDA as a biosimilar to Neulasta on November 2, 2018. The clinical development program for Udenyca included the following: 1. Extensive analytical data. 2. Preclinical data. 3. Key confirmatory Udenyca clinical studies. The first of those clinical studies was CHS 1701-05. The confirmatory PKPD bioequivalent study with a three-sequence three treated crossover study design in 122 healthy subjects that demonstrated PK and PD bioequivalents between Udenyca and Neulasta. Healthy subjects are the FDA preferred population, due to the lack of confounding variables for PK and PD

evaluation. The second study was CHS 1701-04, which is a two-period parallel arm immunogenicity study in 300 healthy subjects that demonstrated similar immunogenicity between Udenyca and Neulasta. There was also a pooled safety analysis, in which no new important safety signals were observed in the clinical studies conducted for the Udenyca program. The most frequently reported treatment emergent adverse events in both treatment groups included bone pain, back pain, headache, pain in the extremity, and arthralgia. In conclusion, the FDA did not require [inaudible] to perform clinical trials in cancer patients due to the strength and bioanalytical data, and the results of the two clinical trials in healthy subjects. Udenyca was FDA approved. Of note, we had delivered over 150,000 doses, and over 55,000 patients have received Udenyca, and the safety profile is consistent with [inaudible] particle products. In addition, with the healthcare market entry of [inaudible] biosimilar pegfilgrastim, as a clinical option at a lower price, as well as a deterrent to originate a price increase. Udenyca has contributed to nearly one billion dollars in cost savings. In conclusion, I would like to thank the committee for the opportunity to present this testimonial. I would be happy to take any questions.

Virginia Buccola: Thank you, Mr. Shah. Are there any questions from the committee? Okay. We are scheduled to move to a break, but I think because of some timing issues, we need to jump ahead right now and go to Apple Health policy androgenic agents, testosterone, I believe. I keep forgetting to do the motion. My apologies. Let's back up. Let's do that. Thank you.

Nancy Lee: I move that all products in the hematopoietic agent's granulocyte colony stimulating factors drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred products need a trial of one preferred product with the same indication before nonpreferred drugs will be authorized, unless contraindicated or not clinically appropriate.

Alexander Park: I second.

Virginia Buccola: All in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries.

Leta Evaskus: I just wanted to say, we can take a ten-minute break. Sickle cell anemia is cancelled. Then, when we come back from break, we're going to move androgenic agent's testosterone above the oncology

radiopharmaceuticals. Just change the order of those two. So, we're doing okay on time.

Virginia Buccola: Okay. Good. So, let's go ahead then and take a ten minute break. It's 2:15. So, I'll see you all back at 2:25.

Leta Evaskus: Great. Thank you.

Virginia Buccola: Welcome back from break. We're going to go to report with HCA to talk about androgenic agents.

Ryan Pistoresi: We will start with the first of the clinical policies that we'll be presenting today. So, we're at the homestretch for this meeting. So, let's see. So, this is a policy that has been previously reviewed by the DUR board. This is up for rereview today. I wanted to just walk through some of the changes with this policy to kind of help guide your eyes, as you look through it. It's several pages long, but I will point out some of the key areas where it's changed. If we are able to scroll down to that medical necessity section, you will see that we have updated the list of drugs to the left to reflect what's on the market. We have also better reformatted the medical necessity table to the right. So, you will see that it's better listed for kind of what section that you would find that criteria in. So, if you're looking for how testosterone would be approved for use in HIV associated weight loss, you can see there, it would be in the testosterone replacement therapy section. I do want to draw your attention to the criteria for gender dysphoria. Down at the bottom of that table, as you see, there is a note there that says that the use for testosterone is actually moving to a transgender health policy that will be scheduled for an upcoming DUR board meeting. So, we do not have new criteria to share with you today, but we will be bringing that to you at a future meeting. This move allows us better flexibility in updating the medications for gender dysphoria together, and to align with some of the other programs at HCA. So, rather than updating several clinical policies at once. We will have that all together in one policy. So, we'll be bringing that for a future meeting.

If we continue to scroll down, we'll actually be getting into the clinical criteria that we'll use to review a medical determination. So, the criteria for each of these policies is mostly the same as from the previous policy that you reviewed and approved, but we are making clarification about what documentation we will be required for us to do a prior authorization review. So, in this first section, you can see we have the testosterone replacement therapy for adult males. This was formatted to better describe what criteria would be used for the different indications. That can be found in criteria number four. If we can scroll down, you'll

see that each of the diagnoses here have the different criteria in them. So, if you're looking for the criteria that we would use for primary hypogonadism, you'd be looking at 4A, and you would not be need to look at 4B or C or any of the other sub-bullets to criteria 4. So, the criteria is largely the same, just updating the language to make it clear what documentation would be required by Apple Health to make a medical determination for appropriate use.

We can scroll down to the reauthorization criteria section. I guess it's kind of split between these two pages. So, let's kind of scroll down to the next one actually. 'Cuz, that's where most of the, great. Thanks. So, for this reauthorization section, verify response to treatment and including specific criteria now for chronic high-dose glucocorticoid therapy and on the HIV associated weight loss. So, better describing what we're looking for here to ensure that these patients are responding to therapy and that reauthorization is necessary for the correct treatment of their condition. So, for the chronic high dose glucocorticoid therapy, just letting us know that they are still continuing the therapy and that the testosterone is necessary for that patient.

If we scroll down, the next section will be on delayed puberty. So, this was updated to clarify when authorization would be approved, because previously it would only look at the initial authorization criteria. So, most of the updates for delayed puberty were in the reauthorization section. The formatting had been updated to make it clearer, exactly what labs and what criteria would be necessary for that initial determination. That reauthorization section at the bottom had been updated.

Below this is the metastatic breast cancer section. So, this one, we removed the recommended therapy section and instead just focused it on the clinical criteria like we have for our other clinical policies that we've presented. Otherwise, there wasn't really any changes besides general formatting. Okay. If we continue to scroll down, you'll notice that we don't have the transgender health criteria anymore, as that is being moved. So, now it's going to be reviewed at an upcoming DUR board meeting. So, this ends the clinical criteria for the proposed testosterone policy. Everything that you see from here on out is more general information about the drugs that are covered by this policy. So, here is the updated list of drugs and their quantity level limits, which you can find in the right column. Then below that, is our relevant HCPCS codes, the references that we used to develop this policy, and then at the very end is the history of this policy, which we are using to document what changes have been made between the last time this was reviewed in 2018 to what we have here today.

Bringing this back to the Board, do you have any questions, comments, thoughts on the... oh, yes. Thank you. So, this is the penned form that we are proposing for the testosterone PA. So, this is the penned form that would be used that we would send out to gather the information for the prior authorization determination. I forgot we had that at the end. So, this just helps organize the data from the clinical policy that we had just presented and shows you kind of how we would be asking for it from the provider's office. Now, back to the Board. Any questions, comments? Any feedback for HCA on this testosterone policy?

Virginia Buccola: This is Virginia. Thanks, Ryan. Anybody have any questions that they needed to ask?

Nancy Lee: I just have a quick question. So, when you say that the February 2020 update for transgender health is included, it means that it's going to be included in a separate policy. Is that correct? I thought that's what I heard.

Ryan Pistoresi: Yes. We do have staff that are currently working on the transgender health clinical policy. We are planning on bringing that to an upcoming DUR board meeting, but this is not ready for today.

Nancy Lee: Thank you. All I just wanted to say was thank you. It looks good.

Ryan Pistoresi: Thank you.

Virginia Buccola: It doesn't look as if we have any stakeholders. So, we will move right to the motion.

Nancy Lee: I move that Apple Health Medicaid program implement the clinical criteria listed on policy 23.10.00 as recommended.

Susan Flatebo: I second.

Virginia Buccola: All those in favor, please say aye.

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. Thank you. So, we're going to move next to Luke with the HCA to discuss oncology radiopharmaceuticals, specifically Lutathera, I believe.

Luke Dearden: Thank you. Can you hear me?

Virginia Buccola: Yes. I can hear you.

Luke Dearden: My name is Luke Dearden from HCA. The purpose of this is to discuss Apple Health policy regarding lutetium dotatate, also known as Lutathera, and unlike the testosterone policy, this is a new policy to Apple Health. So, a little bit of background. Lutathera is a radiolabeled somatostatin analog and was approved by the FDA in 2018 for the treatment of somatostatin receptive positive gastroenteropancreatic neuroendocrine tumors. In the Nedder-1 [sounds like] trial, which is summarized at the bottom of this document, Lutathera, in combination with standard of care, was compared to standard of care alone, which happened to be longacting octeotride. Lutathera contributed to a progression free survival at 20 months of 65.2% compared to 10.8% in standard of care group, which was statistically significant, and that was the primary outcome. There was an interim analysis of overall survival that revealed 14 deaths in the Lutathera group versus 26 deaths in the standard of care group. However, final analysis of that is ongoing and will be concluded after either five years or 158 total deaths. The overall population of that trial was 229 patients. Lutathera is administered intravenously once every eight weeks for a total of four doses. The clinical criteria if we scroll down here, they are largely based on the phase-3 trial that I just described. The product labeling and also the National Comprehensive Cancer Network, or NCCN. So, I will provide a very high level review of the criteria that include appropriate diagnosis, tumor must be well-differentiated, must be inoperable or metastatic, must be documentation of disease progression on standard of care, like I said before, which would be a longacting somatostatin analog. The client must have labwork that demonstrates adequate renal and bone marrow function. They must be over 18 years or older, cannot be pregnant or breastfeeding. Somatostatin analogs must be discontinued prior to Lutathera administration. This policy has a maximum lifetime quantity of four doses. At this point, I guess if you scroll down a little bit more, it just kind of goes over what I've summarized. Then, the dose and quantity limits down below, which summarizes the four maximum doses and also gives a summary of how it is supposed to be appropriately administered.

Below that is just a summary and background and clinical trials, and also a brief summary of the safety data with this medication. So, I guess I would direct it back to the committee now if there are any questions.

Virginia Buccola: Thank you, Luke. I want to make sure I'm not talking over anyone who may have had questions. I don't see that there are any stakeholders. So, we will go ahead and move to the motion.

Luke Dearden: Just one other thing. This is the penned format, as Ryan was previously talking about. This is the information we collect from the clinical to make sure this medication prescribing is in compliance with the policy.

Susan Flatebo: I move that the Apple Health Medicaid program implement the clinical criteria listed on policy 21.60.00.45.20, as recommended.

Jordan Storhaug: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries. Thanks a lot, Luke. I believe next, if I'm following things along correctly, we should be with Marissa to discuss endocrine and metabolic agents. I'm just going to use the brand name, Revcovi.

Marissa Tabile: Yep. Thank you, Ginnie. Can you guys hear me okay? Let me actually turn on my webcam.

Virginia Buccola: We hear you. Thanks.

Marissa Tabile: Okay. Great. I was having internet issues earlier. So, hopefully, everything goes smooth. So, today, I'll be presenting our clinical policy, or our proposed clinical policy for Revcovi. Just to give you a little bit of background on Revcovi and the disease state that it treats, it's for adenosine deaminase deficiency specifically severe combined immune deficiency. So, just for simplicity sake, I'll call it ADA SCID. The drug Revcovi is a recombinant adenosine deaminase. Before, there was a product that was made before Revcovi, which is called Adagen. That product is called pegadeaminase, but because Adagen is actually discontinued due to the permanent shortage of pegadeaminase, now Revcovi is replacing Adagen. So, we'll go ahead and scroll down, Leta.

Revcovi has a clinical criteria here that we created based off of the phase-3 open label one-way crossover study. So, the study that was conducted, there was a crossover where patients were first started on Adagen, and then they were given Revcovi, and then continued on Revcovi. So, the criteria was based off of the method for that particular study. The primary endpoint for that particular study was measuring trough VAXP levels. That's having a tough VAXP less than 0.02 mmol/L. It was found that about five out of the six participants in the study were able to reach that particular endpoint. Then also having another endpoint was plasma ADA activity greater than 15 mmol/hour/L, but it was found that when participants were given Revcovi, their plasma ADA levels were actually maintained at an average of greater than 30. So, that's actually included in the criteria here. So, just to get into some of their criteria that we have created, they have to have a diagnosis of ADA SCID, which is confirmed by genetic testing. Or if they have very low ADA catalytic activity, which

is less than 1% of normal in their baseline. Part of the package insert of Revcovi states it is not recommended for patients to use this if they have severe thrombocytopenia. For ADA SCID, there is a consensus statement made by the Journal of Allergy and Clinical Immunology. They do recommend that the treatment for this is specifically stem cell transplant. So, ERT is really used for bridging or if they're not candidates of HSCT at the time or have failed HSCT. So, that is one of the criteria included here.

Then, also if it's prescribed and administered by a specialist or a physician in ADA SCID, then also monitoring the trough plasma ADA activity, the trough DAXP levels, lymphocyte counts, and neutralizing antibodies. Then, the reauthorization criteria is listed below.

This is the dosing for Revcovi specifically. Like I said, Adagen was discontinued, but I did find that it was listed that Adagen had an obsolete date of June 20, 2020. So, there could still be... they did think that Adagen was going to run out in March of 2019, but I did see that there was an obsolete date of June 20, 2020. So, there could still be patients that were on Adagen. On the package insert of Revcovi, they do have dosing specifically for if patients were started on Adagen and transferred over to Revcovi or transitioned over to Revcovi. This is the dosing schedule that they would follow, but there is also dosing for if clients are Adagen naïve, and that is listed here, as well.

Here is the authorization form where we collect the information from the providers that are requesting Revcovi. It is aligned with the criteria for the policy. So, if the Board has any questions we can review it. Please let me know.

Virginia Buccola: Thanks, Marissa. Any questions from the committee for Marissa? We have one stakeholder. I see Tom Arnhart representing Ultragenyx. Tom, if you're ready to go, you'll have three minutes to share your comments.

Leta Evaskus: I do not see Tom on the attendee list. So, Tom, if you are on, please raise your hand. You might have come up under a different name. Okay. I see here under Megan Bell. Unmute yourself.

Tom Arnhart: Good afternoon. Can you hear me okay?

Leta Evaskus: Yes.

Tom Arnhart: I'm speaking on Crysvita under the endocrine and metabolic agents. Is that the category we're speaking on now?

Virginia Buccola: No. That is our next category.

Tom Arnhart: So, I'll be speaking on the next category then. Thank you, very much.

Virginia Buccola: Sure. We'll get back to you then.

Tom Arnhart: Thank you.

Virginia Buccola: Okay. So, let's go ahead then and move to Ryan Taketomo with HCA to talk about endocrine and metabolic agents, specifically Crysvita.

Marissa Tabile: I think we actually have the motion for the Revcovi.

Virginia Buccola: Why can I not remember to? Thank you so much.

Marissa Tabile: No problem.

Virginia Buccola: We'll do the motion. It's right there on the agenda. It's not like it's something different.

Alexander Park: Marissa, can I ask you a quick question?

Marissa Tabile: Yes.

Alexander Park: I definitely won't pretend to be an expert on this condition. So, I've got my little drug database situation opened up here, and I've been following along with you. The criteria appears quite appropriate based on the reading that I've been doing, as you've been presenting. The only question I have is the reauthorization. So, number four it says that prescriber verifies client is still not an eligible candidate. So, what if they have failed definitive therapy with stem cell transplant? Would that be considered being not eligible?

Marissa Tabile: For Revcovi or for, sorry, for stem cell. Right?

Alexander Park: For Revcovi.

Marissa Tabile: Sorry. Hold on. I'm trying to look at the... you said it was number four in the reauthorization?

Alexander Park: Yeah.

Donna Sullivan: Are you asking if they've had a stem cell transplant, and then they relapse, are they then eligible for Revcovi?

Alexander Park: Yes. I just want to make sure the patients can still have access to it if they've had definitive therapy with stem cell, but failed. That's part of the original initial approval criteria, but I don't see it in the reauthorization criteria.

Marissa Tabile: We can add that in.

Alexander Park: Okay. Thank you.

Marissa Tabile: Yeah. That should be included in the reauthorization criteria.

Alexander Park: Okay. Great. Thanks.

Leta Evaskus: Do you want to tell me again, was that... I'm going to copy and paste it in.

Alexander Park: I think you could, let's see. Take from number three under initial approval and make number four under reauthorization match that.

Donna Sullivan: Yeah. I think that's what the intent of number four was, but to explicitly state it is much more clear.

Alexander Park: Thanks, Donna.

Donna Sullivan: I'm gonna open up the Word.

Marissa Tabile: Leta, I am documenting it on a Word document, as well. So, I have it.

Leta Evaskus: Okay. Alright.

Alexander Park: Then, in terms of the motion, is there a difference in the policy that's listed here versus the one that we just reviewed? What am I trying to say? There's a dash-1 on the policy that we are seeing here. So, I guess that must be a more recent version that we're trying to approve.

Donna Sullivan: That's just the version number. So, this policy is the number. Then, the dash-1 would be the version. It's version one.

Alexander Park: Okay.

Marissa Tabile: Leta, can you put the dash-1 after the last 30? Is that better, Alex?

Alexander Park: Thanks for placating my OCD.

Marissa Tabile: No. It's fine. I think we should specify that it's version one, as well. So, that was very helpful.

Alexander Park: On that topic, I think there was a dash-2 on the androgen policy that we might have to update, Leta. We could probably take care of that on the back end. Beautiful. Okay. With that, this is Alex Park. I move that the Apple Health Medicaid program implement the clinical criteria listed on policy 30.90.20.30-1, as recommended.

Diane Schwilke: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. Okay. Moving on. Now, we're ready to go to Ryan Taketomo talking about Crysvita.

Ryan Taketomo: Good afternoon, everyone. Can you hear me?

Virginia Buccola: Yes. I can hear you, Ryan.

Ryan Taketomo: Alright. So, we'll be talking about the Crysvita policy. This was a policy previously approved. So, for this annual review, we will be discussing a few changes, which have been made, which incorporates new evidence and feedback, which we have received. So, a brief overview of the background. Crysvita is used to treat hypophosphatemia, which is an inherited disorder that effects one in approximately 20,000, and it is caused by a mutation in the PHEX gene. This mutation increases fibroblast growth factor 23, which reduces the absorption of phosphate by the kidneys. Symptoms of hypophosphatemia include rickets, bone softening, muscle pain, swelling of legs, short stature, tooth abscesses, and hearing loss. Symptoms for this disease are also highly variable, as some patients show no signs or symptoms. Others may experience complications. Typical treatment for X-linked hypophosphatemia has for a long time been phosphate supplements with calcitriol. So, with burosumab or Crysvita, burosumab works by binding two inhibiting fibroblast growth of factor 23, which restores renal absorption of phosphate. So, now, we can move onto the policy section, or the criteria section, where I will highlight some of the big changes.

So, with criteria one, we expanded the age range to reflect the FDA labeling, which reduces the age limit from a minimum of one year to six months of age and older. With criteria two and three, they are mostly the same. We added some feedback we received that we wanted to add some additional guidance around the laboratory values for criteria 2C. So, if they don't have 2A or 2B, the can use 2C. Pretty much, these [inaudible] are not to be definitive, but are to act as guidance in that patients with this disease, depending on what stage they're at, they may or may not have an abnormal laboratory value. So, the values are really for guidance based on the feedback we had received. Criteria 3 and 4 are the same as the previous version. With criteria 4 and 5, these were split out. They used to be combined into one line. However, we received feedback that it was a little bit complicated to read. So, those have been split out, and 6 and 7 are the same as the previous version.

With the reauthorization criteria, points 1, 2, and 5 are the same as the previous version. The only changes were 3 and 4, which is that the client is not taking oral phosphate or vitamin D, as these are contraindicated.

With that, we have the dosing and quantity limits, HCPCS coding, definitions, and then the review of the clinical trials.

Here we have the penned form, which we use to facilitate the prior authorization process. So, with that, please review the policy. If you have any questions or feedback, please feel free to ask those.

Virginia Buccola: Thanks, Ryan. Any questions from the committee for Ryan? Okay. We do have the one stakeholder that we introduced with the last topic. Tom Arnhart from Ultragenyx. Tom, you'll have three minutes to share your comments.

Tom Arnhart: Good afternoon. I'm Tom Arnhart. I'm a pharmacist with medical affairs at Ultragenyx. I really didn't have a public comment I want to make. I just wanted to point out a clarification with Crysvita or burosumab for XLH in use in adult and pediatric populations. As you mentioned, you updated your policy for the recent changes from the FDA. So, I wanted to clarify that in the policy on the dosage, the range down to 6 months of age, on your policy it shows the dosage as 1 mg/kg rounded to the near 10 mg. That is the adult dose. With that change back in September of last year, there was a difference for the pediatric dosing. For patients who weighed less than 10 kg, the recommended starting dose was 1 mg/kg rounded to the nearest 1 mg. For patients who weighed 10 kg and greater, the recommended dose was 0.8 mg/kg rounded to the nearest 10 mg. So, I just wanted to clarify that. I also wanted to bring up one other thing to your attention. Ultragenyx recently announced that the FDA had accepted our supplemental biologic license application for Crysvita for an ultra-rare disease called tumor-induced osteomalacia. It was assigned a priority review with a target date of tomorrow, June 18th. So, I just wanted you to be aware of that potential new indication. I appreciate your time. I'm happy to address any questions.

Virginia Buccola: Thank you, Tom. Any questions from the committee? We'll move to the motion.

Marissa Tabile: Can you add a dash-2, after the 95?

Alexander Park: I move that the Apple Health Medicaid program implement the clinical criteria listed on policy 30.90.95-2, as recommended.

Catherine Brown: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We will move, again, back to Ryan to discuss agents for ALS, Radicava.

Ryan Taketomo: For the next policy, we have edaravone or Radicava. For review of this drug background, this medication is used to treat amyotrophic lateral sclerosis, also known as Lou Gehrig's disease. It's a progressive disease that causes degeneration of motor neurons. Symptoms of this disease initially present as slurred speech and dysphagia, but as the disease progresses, patients may lose their ability to control muscle movement and may eventually develop paralysis. So, with this drug, Radicava's current mechanism of action is not known, but it is thought to be due to its antioxidant properties, which prevent oxidated stress to neurons.

The clinical criteria for this policy was based off of evidence and FDA labeling. I can provide a brief overview of the trials that kind of went into this criteria. There are three trials. The first trial was the initial trial that had 206 subjects with ALS. Their primary outcome was looking at the change in ALS functional rating scale, the revised version. At 24 weeks, they found that there was no significant difference between edaravone compared to placebo. However, they conducted a post-hoc analysis, which showed that a particular subgroup of subjects with definite or probable ALS and other criteria, did seem to have some benefit. So, they conducted this second trial. This second trial enrolled 137 patients with early stage ALS. This criteria was more specific, as it was a subgroup. It targeted patients who had a disease duration of two years or less. They were living independently. They had a score of 2 or more in all items of the ALS revised scale. They also had a vital capacity greater than or equal to 80%. At the 24-week mark, they did find that there was a clinically significant difference with the decreases of -5 and -7.5 for Radicava and placebo respectively. This difference was considered to be clinically significant with the swelling of approximately 33%. That's relative. So, the third trial was sort of a long-term extension to kind of gain some additional data. There was no statistical analysis involved with this trial. So, what kind of happened was, the participants from the second trial I discussed, they continued, and the members who were on placebo were given Radicava. At the end of the study, they found that both groups continued to have decreases in ALS revised scores with the ultimate conclusion that long-term treatment for efficacy and safety remain a future issue.

Those are the summaries of the clinical trials that went into the development of this criteria. With that, you then go into some of the other general information with the dosing and quantity limits, the HCPCS coding references, and at the end, there should be the penned form with the criteria that helped facilitate the prior authorization process.

Virginia Buccola: Are you ready for us to move to questions? Or did you need more?

Ryan Taketomo: I was wondering if there were blanks. I wasn't seeing the documents scroll up. Sorry. I should have maybe specifically stated to scroll down. Is there a penned form for this one, Leta? So, with that, now we can open up for questions and feedback.

Virginia Buccola: Thanks for that Ryan. Committee members, any questions? Okay. I see that we have one stakeholder listed. I do see a hand raised. So, the first stakeholder is Bill Gittinger with Mitsubishi Tanabe Pharma America.

Bill Gittinger: Yes. Can you hear me okay?

Virginia Buccola: Yes. Bill, you have three minutes.

Bill Gittinger: Great. Thank you. Ryan, thanks for the summary. My name is Bill Gittinger. I'm the director of government accounts, which is Medicare and Medicaid for Mitsubishi Tanabe Pharmaceuticals. We have one comment on the policy, as it's drafted here. If it's possible to go back up to the criteria for reauthorization, please. Thank you. We see this reauthorization, number one, frequently with payers. It's common, just a level set here, though. These patients do not get better. They're ALS. Radicava simply slows the loss of function, but ALS patients are... Radicava is the last product for them, more than likely. Using the ALSFRS scale to determine that they should be on it is great, but these patients will all still slide, as they go on. It's requiring a score of 2 or better on each of 12 boxes on the scale. As it's written here, if any patient drops to a 1, even though they're out walking to get the paper or walking to get the mail, if they drop to a 1, they're no longer eligible to receive Radicava. What we recommend the payers are two recommendations or two options. Instead of having this language, use the language for medical necessity. We recommend that the decision to continue or discontinue be between the doctor and the patient. Does the patient want to continue to fight the good fight? Or do they not feel it's worth it anymore, and they're going to accept their position. Then, we have some payers that will say, Bill, we really like the idea of a score, but we don't want to penalize the patient for dropping on one area from a 2 to a 1. The recommendation is theirs to give the patient a cumulative score, and then to set a drop percentage on that score. What payers are doing is, they're looking at it and saying, okay. As long as the patient doesn't drop more than 4 points, then they can stay on if they choose to, but to have them thrive, or to do well on 11 and then have just one area knock them out, again, we think that maybe they go from a 25 to a 20, Radicava is probably not working well for them, but if they go from a 25 to a 23, they're probably still doing well and can continue to do well on the

product. So, we would like to have you just consider modifying this language and making it between the physician and their patient, or do a cumulative. I think that's my time. So, I would be glad to answer any questions or provide followup material. So, thank you.

Virginia Buccola: Thank you, Bill. Are there any questions from the committee for Bill? Okay. We will go ahead and move to the motion.

Constance Huynh: I have a quick question. Are we missing any dashes before we... since we had dashes before for the policy?

Ryan Taketomo: So, if we were to add a dash, it would be a dash-1 for this one.

Marissa Tabile: We can add that to the policy, as well. I don't believe it has a dash-1, but we'll add that.

Alexander Park: Can I ask you a question, Ryan?

Ryan Taketomo: Sure. Go ahead.

Alexander Park: So, you characterized quite thoughtfully. I think the data for this seems to be best in early ALS. I'm guessing that's why the policy says onset of ALS less than or equal to two years, but this is a pretty devastating disease. So, what happens if the patient is at four years, and they want to try this?

Ryan Taketomo: So, that's sort of the struggle where we had to balance access with evidence that is currently available, because as we talked about... or as I talked about the first trial where the onset of the disease for that one was up to three years, they found no significant difference between Radicava and placebo.

Donna Sullivan: Based on the FDA indication, it would be reviewed on a case-by-case basis for anything outside of the policy. If it were approved, I think that's where relying on the scores for the reauthorization would be extremely important to make sure that the patient is actually improving on the medication rather than just staying the same or continuing to get worse. So, there is a way to get to the medication for patients that have had ALS for more than two years.

Alexander Park: That's reassuring. I just want to make sure the policy jives with that, because when I read this, it says number one and number two and number three and etcetera, etcetera. It kind of reads like you have to have that time limit on the two years or less. Was that not how you intended the policy to read?

Donna Sullivan: I think that is intended. I think what I was talking about was more an exception or reconsideration of, is there a reason why they really think the medication would work in this particular patient that was above and beyond the two year mark of ALS.

Alexander Park: Okay. Thank you.

Leah Marcotte: I had a quick clarification, as well. Related to the stakeholder comment, are there policy exceptions that can be made for patients in the example that there is a single point score difference, but in some of the other dimensions, there is either improvement or evidence that there is effectiveness of the medication? Or is that the way the policy worded going to restrict people, potentially, in those situations?

Donna Sullivan: I think we could take into consideration the point from the stakeholder regarding not falling below 2 in all 12 areas of the testing. If you want to make some recommendations on what... is there a number that you feel comfortable putting in there? Or maybe if they don't fall below 2 on more than 2 of the 12, or 3 of the 12 areas?

Leah Marcotte: I would want some specialist input from people who are actually representing this to answer that question, but I think that would be helpful to make sure that the policy isn't so restrictive that we're reducing access to people who need it.

Donna Sullivan: We can take that back and get some further review from providers that treat people with ALS and see if we can come up with a recommendation for the reauthorization criteria.

Leah Marcotte: Thank you.

Donna Sullivan: So, with that being said, why don't we table the motion on this one, and we'll bring it back for October for a final review and approval.

Virginia Buccola: Thanks, Donna. That sounds like a great plan.

Nancy Lee: I second that motion to revisit and rereview in October.

Donna Sullivan: Alright. We'll leave it and make the motion in October.

Virginia Buccola: Okay. So, we'll move onto the final topic.

Alexander Park: I'm sorry to be a pest here, but if we are going to revisit the policy, I would appreciate if we would also ask the experts about the two years or less stipulation.

Donna Sullivan: Absolutely. That was what I was thinking, as well. We'll do that.

Alexander Park: Thank you, very much. Yeah. It's, I mean, it's a drug that we don't really know how it works. A 130-something patients is not necessarily definitive. I totally understand we have to kind of go by the letter of the trials. I thought the policy was well made to reflect that, but yeah. If we're going to talk to some experts, we should include that. Thank you.

Virginia Buccola: We'll move on to our final topic with Marissa, ophthalmic agents' gene therapy, Luxturna.

Marissa Tabile: So, the policy that I'll be presenting today is on Luxturna, which is a gene therapy. So, just to give you kind of some background on the disease state. So, retinitis pigmentosa is a type of inherited retinal dystrophy, which is characterized by progressive dysfunction and degeneration of the retina, which ultimately causes blindness. So, Luxturna is a gene therapy, which is used to treat children and adults with an inherited form of vision loss that could result in blindness. Luxturna is the first directly administered gene therapy approved by the FDA that treats patients with [inaudible] like RPE65 mutation associated with retinal dystrophy. What Luxturna does, the mechanism of action, is that it delivers a normal copy of the RPE65 protein to retinal cells, which augments reduced or absent levels of biologically active RPE65, which leads to normal production of the protein, which ultimately helps restore patient's vision loss.

This is the clinical criteria that was created for Luxturna. It is based off of the phase-3 trial that was conducted for Luxturna. So, just to go through the criteria quickly. The patient is 1 to 65 years of age with a confirmed diagnosis of biallelic RPE65 mutations. That would be confirmed via genetic testing. The patient has a visual acuity worse than 20/60 in both eyes, or visual field less than 20 degrees in any [inaudible]. The patient should have viable retinal cells and verification must be documented. So, in the phase-3 study, they did have... this was part of the inclusion criteria and also number two that I just mentioned was part of the inclusion criteria, as well. So, that can be verified by an area of the retina within the posterior pole greater than 100 micron thickness, which can be shown on optical coherent tomography. Or it can be a clinical examination, which would show three or more areas of retina without atrophy, or the remaining visual field within 30 degrees of fixation, as measured by that isopoter. We are putting in criteria that they have not previously received RPE65 gene therapy, but Luxturna is the first product of its kind. So, they can't have been previously treated with Luxturna. The patient has not had intraocular surgery within six months in the intended eyes. It's recommended that it be prescribed and administered by an ophthalmologist or retinal surgeon who specializes in performing intraocular surgery. In the clinical trials, these are still ongoing clinical trials that are expected to be completed between 2024 and 2029. So, for

the reauthorization criteria, since it hasn't been studied, there is no reauthorization criteria.

We would only allow for this particular product one dose per eye per lifetime. This is the HCPCS Code and the dosing for Luxturna for your reference.

Here is the authorization form that we would be asking providers for information. If anyone has any questions, I'd be happy to answer them.

Virginia Buccola: Thanks, Marissa. Any questions from the committee? I don't want to move too fast. It doesn't look as if we have any stakeholders. So, if there are, and I am missing you, make sure you raise your hand. Otherwise, if there are no questions and no stakeholders, we'll move to the final motion.

Laurie Mischley: Can you add a dash-1. Sorry. Thank you.

Alexander Park: Just looking at the FDA reference for this, Marissa, it looks like there is some sort of a steroid requirement that you have to be on that at the same time you take this. Did you see that in your run-through?

Marissa Tabile: I did. Yes. I did have that. Initially, when I was drafting the criteria, I did have that included, but I did get feedback that maybe it should be taken out. So, did you want... are you recommending to add that back in?

Alexander Park: I'm just thinking we should be consistent. We have been fairly proscriptive in some of the other criteria about phosphate or vitamin D, this or that being stopped one week before, etc. I'm curious to know what you were thinking, what the thought process was behind taking it out. Since, it already seems like you thought about that requirement.

Nancy Lee: I had the same question. I guess what was the reasoning for... because you had it in before. Then we [inaudible] or what your thought process was for taking it out.

Marissa Tabile: I think I just took it out just because it was already on the FDA labeling. Then I got recommendations to take it out. So, it might have been redundant, but I can definitely add it back in.

Alexander Park: I think that'd be fine, just to be consistent with how we've been on some of the other policies that we've reviewed today. Thank you, Marissa.

Marissa Tabile: No problem. Thank you for the recommendation. I will definitely add that back in.

Alexander Park: I move that the Apple Health Medicaid program implement the clinical criteria listed on policy 86.37.00-1, as recommended, adding back simultaneous steroid use.

Constance Huynh: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? Okay. The motion carries. With that, we are ready to adjourn the Drug Utilization Review Board for today. Thanks to everybody for helping me keep on track. Thank you, Leta, and the HCA, for helping us do this virtually. I look forward to seeing everybody again in August. We'll turn it over to Leta if there are any last minute comments.

Leta Evaskus: Ginnie, thank you. You did a great job.

Virginia Buccola: You're welcome. Once we figured out how to make sure I was doing the motions correctly.

Marissa Tabile: Thank you, Ginnie.

Virginia Buccola: You're welcome, guys. It's good to see you all a little bit.

Leta Evaskus: Bye everyone.