

Washington State Pharmacy and Therapeutics Committee
P&T Meeting Notes
August 17, 2016

Shelley Selph: Listed are the included harms outcomes.

We used a best evidence approach for determining included study designs, prioritizing RCTs, but we did not include observational studies for longterm clinical outcomes to determine how well SVR-12 (inaudible) SVR-24. We also included single arm studies for harms in special populations, such as HIV coinfection, liver transplant, drug abuse, and chronic renal disease.

Here are the included interventions. As you recall, this review is unique in that we included drugs, which have not yet been approved but have accepted NDA. Since the last update, three new drug combinations have been approved, and one NDA accepted. Trials of daclatasvir alone have been removed from the report and trials of daclatasvir with sofosbuvir were already previously included, and since this review is completed, um, the combination of sofosbuvir and velpatasvir has been approved. That was on June 28th of 2016, and the last two drug combinations also have trade names now, Zepatier and Epclusa.

Our searches ran through the end of last year. We identified 25 new randomized control trials and received dossiers from five drug companies.

We identified, for this update, two trials comparing one DAA oral regimen with a different oral regimen, and that was new for this update. There was no DAA evidence on SVR on long-term health outcomes. Generally, we consider strength of evidence for SVR to be low, and we consider strength of evidence for relapse to be insufficient, as very few patients relapse during the followup period. So, you don't have a lot of data to work with, and on the remaining slides, we note when the strength of evidence is otherwise.

So, strengths of this review are the fact that we do look at DAA's prior to approval. Most studies were well conducted. Trial protocols occasionally let us . . . enabled us to upgrade the quality ratings from, say fair to good, and the supplemental data that's often available online helps us get more information on results that have been stratified by say age, gender, race, etc.

So, for this update, we did modify the key questions from the previous version. Key question one now includes all genotypes. In the report and on these slides, results are broken down by genotype, and as before, results are further divided by prior treatment history. That is, whether the patients are treatment naïve or experienced, or whether the trial includes both types of patients but does not report outcomes by treatment history. We refer to it, in that case, as a mixed treatment history.

There were 24 total trials, including old and new, providing evidence from all oral regimen comparisons. For key question one, these trials were almost exclusively the drug regimen with or without ribavirin. Trials comparing only different doses or different durations of treatment are reported under other key questions. Several trials have many treatment arms, as many as 16 different arms and compared treatment with or without ribavirin, different doses at different treatment durations. Currently, we are including these complex trials in each applicable section of the report.

For each key question, we start with the hepatitis C population that had received no prior treatment. Oh, and I should also mention that information that is new to this report is underlined. New to this report is adding ribavirin to the 3D regimen that improved SVR by 9% but only in genotype 1A. In the last update, we reported increased risk of harms with the use of ribavirin.

We found no differences between several treatment regimens in treatment naïve genotype 1 patients, including three newly-approved regimens.

There is still much less information on genotypes other than 1, but at least now there is some for most of the genotypes. There was no differences in SVR relapse with the addition of ribavirin to sofosbuvir and velpatasvir in patients with genotype 2. In genotype 3, patients' SVR was increased by 55% by including ribavirin to treatment with velpatasvir and sofosbuvir.

In patients with genotype 4, there were no differences attributable to the addition of ribavirin when added to the 2D regimen or when ribavirin was added to treatment with grazoprevir and elbasvir.

The previous trial with grazoprevir and elbasvir also enrolled small numbers of patients with genotype 5 and 6 and found no statistically significant differences between treatments, but there was a suggestion in patients with genotype 5 that the addition of ribavirin may be needed, as only 25% of four patients achieved SVR without ribavirin compared with 100 percent of four patients who received ribavirin, and those are very small numbers, but that still is a suggestion.

In a trial of treatment naïve patients who were either genotype 2 or 3, the addition of ribavirin did not improve SVR rates.

Moving on now to a treatment experienced population on genotype 1, rash was less likely when ribavirin was not included with 3D regimen, and a trial of patients with genotypes 1 or 3 who were treated with sofosbuvir and velpatasvir, rash and anemia were less likely when ribavirin was omitted from the treatment regimen.

As noted, in the prior report, there is moderate strength of evidence with the addition of ribavirin did not improve SVR rates with ledipasvir and sofosbuvir. However, without ribavirin, the risk of rash and anemia were lower. Anemia risk was also decreased when ribavirin was excluded from treatment with simeprevir and sofosbuvir.

In a study where only some of the genotype 2 patients had prior treatment, treatment with a new regimen of sofosbuvir and velpatasvir was associated with increased rates of SVR and lower relapse than with sofosbuvir and ribavirin.

Still, in treatment experienced patients, now genotype 3. There were no differences in relapse or SVR rates when ribavirin was added to sofosbuvir and velpatasvir.

In patients with genotype 3 in a mixed treatment history, the addition of ribavirin improved rates with SVR and relapse. In this case, the risk of anemia was increased with the addition of ribavirin or conversely reduced without ribavirin.

That concludes the direct evidence for key question one. For indirect evidence, we used CADTH, which stands for Canadian Agency for Drugs and Technologies and Health. They had a good quality updated network meta-analysis. We used that to provide you with comparisons made using indirect methods. This is when two drug regimens are compared based on their performance against other drug regimens, which could be placebo. We report here all statistically significant comparisons and SVR in patients with genotype 1 for all included drug regimens. While grazoprevir and elbasvir that combination, and daclatasvir and sofosbuvir combination were included in CADTH analysis, sofosbuvir and velpatasvir was not. CADTH also included evidence for regimens not included in the U.S., such as those containing simeprevir. We considered all indirect methods as providing low strength of evidence. In treatment naïve patients treated with ledipasvir and sofosbuvir for 12 weeks with or without ribavirin resulted in improved rates of SVR when compared with 24 weeks treatment of sofosbuvir and ribavirin using indirect method. The lower two bullets on the other regimens with higher rates of SVR when compared indirectly with treatment of 24 weeks of sofosbuvir and ribavirin.

CADTH results for treatment experienced genotype 1 patients suggests that when compared with 12 weeks of treatment with sofosbuvir and ribavirin, SVR. Rates were improved with 12 or 24 weeks of ledipasvir and sofosbuvir with or without ribavirin. The lower three bullets provide the other treatment regimens showing a significant improvement in SVR, including grazoprevir and elbasvir.

Moving on now to key question two, which looks at the effects of different doses and durations of DAA treatment.

21 trials provided evidence for all oral regimens. Again, the lion's share of the evidence is in patients with genotype 1.

Starting with treatment naïve patient, genotype 1 and pooling results from treatment arms containing velpatasvir 25 mg and velpatasvir 100 mg, treatment with sofosbuvir and velpatasvir for eight weeks resulted in lower SVR rates and treatment for 12 weeks, while there was no difference in relapse rates.

Similar to sofosbuvir and velpatasvir, treatment with simeprevir and sofosbuvir for only eight weeks resulted in decreased SVR rates compared with 12 weeks treatment. Relapse rates were also higher with shorter treatment, whereas shorter treatment with ledipasvir and sofosbuvir resulted in similar rates of SVR but increased rates of viral relapse.

Still in a treatment naïve genotype 1 population, there were no differences attributable to duration of treatment with the listed regimen.

Or with these listed regimens. There was moderate strength of evidence of no difference in SVR with different treatment lengths of treatment with ledipasvir and sofosbuvir.

Dose of velpatasvir in combination with sofosbuvir and velpatasvir did not affect SVR or relapse rates in treatment naïve patients with either genotype 2 or genotype 3.

In patients with genotype 4, treatment length did not affect benefits or harms with sofosbuvir and either simeprevir or ribavirin. In a variety of genotypes that did not include genotype 1, a dose of velpatasvir given with sofosbuvir did not affect SVR or relapse.

Now, looking at dose and duration studies of patients with prior treatment for hepatitis C, there was low strength of evidence that shorter treatment length did affect rates of relapse and moderate strength of

evidence of no effect on SVR with ledipasvir and sofosbuvir where half of the patients also received ribavirin. Longer treatment also resulted in more serious adverse events.

There was less anemia with shorter treatments with simeprevir and sofosbuvir.

There were no differences between treatment doses or durations with the listed regimens.

Different doses of paritaprevir as part of the 2D regimen in treatment experienced patients with genotype 2 resulted in similar rates of SVR and harms.

The rates of SVR and harms were similar, regardless of velpatasvir dose when given with sofosbuvir, but there was a nonsignificant increase in risk of relapse in patients with genotype 3 with the lower dose. Also in genotype 3 patients, treatment length with daclatasvir and sofosbuvir did not affect the rates of benefits or harms.

In treatment experienced patients with genotype 4, shorter treatment with simeprevir and sofosbuvir resulted in lower rates of SVR but similar rates of harms. In patients of Egyptian descent, SVR rates were lower with 12 weeks treatment with sofosbuvir and ribavirin than with 24 weeks treatment.

Also, relapse rates were more likely with shorter treatment with sofosbuvir and ribavirin in patients of Egyptian ancestry; however, rash was less likely with shorter treatment in these patients.

In patients with genotype 2 to genotype 3 analyzed together. Shorter treatment with sofosbuvir and ribavirin was associated with lower SVR rates with higher relapse rate. Strength of evidence for relapse in this case was low rather than insufficient.

Going on now to key question three, which looks at subgroups or subpopulations.

We evaluated subgroups based on initial viral load, IL28 genotype, gender, race, age, comorbidities, and Q80K mutation. Almost all subgroup analyses by trial authors were exploratory in nature. Unfortunately, when patients were stratified into different subgroups, many of the subgroups had relatively few patients, such as subgroups of racial minorities, IL28 genotype P, T, or subgroups of patients with lower initial viral load. While there may be true differences in bio-response to various DAAs in whites versus blacks, for example, we were not able to determine this with the limited evidence available. In the evidence that was available from trials that reported SVR by subgroup, there were no statistically significant differences in the effects of DAA regimen changes between any of the subgroups.

In the hepatitis C population with genotypes 1 through 4 who were also coinfecting with HIV, shorter treatment with daclatasvir and sofosbuvir resulted in lower rates of SVR and higher rates of relapse, whereas the addition of ribavirin to grazoprevir and elbasvir did not significantly effect SVR or harms in a treatment naive population with genotype 1, this is also with HIV.

There were no differences based on treatment length when treated with the 3D regimen, and there was no other comparative evidence in this population.

In the case of liver transplant, there was one RCT indicating fewer adverse events with shorter treatment with ledipasvir and sofosbuvir in patients with a mixed treatment history and who were genotypes 1 and 4, and that did not affect SVR or relapse. There was no other comparative evidence in liver transplant patients. We did include the special populations of injection drug users and also patients with chronic renal disease, but there was no true comparisons in these populations. Trial information in immediate versus delayed treatment in these populations is in the report.

Key question four looks at comparative effects based on stage of disease.

In patients who were treatment naive and genotype 1, stage of disease had no effect with the listed treatment regimens.

In treatment experienced patients with cirrhosis, benefit outcomes were improved with the addition of ribavirin to sofosbuvir and velpatasvir. The risk of anemia was increased. There was low strength of evidence that relapse was increased with shorter treatment with the 3D regimen.

Also in patients with cirrhosis, longer treatment duration with velpatasvir and sofosbuvir improved SVR relapse rate with a risk of anemia was increased with longer treatment when ribavirin was part of the treatment regimen.

There were no differences based on stage of disease with the list of treatment regimens in genotype 1 patients who were treatment experienced.

In treatment experienced patients with genotype 3 and cirrhosis, the addition of ribavirin improved SVR and relapse rates when added to sofosbuvir and velpatasvir. Treatment with 100 mg of velpatasvir was similarly more effective than treatment with 25 mg in this population.

In a group of genotype 3 patients with a mixed treatment history, shorter duration treatment with sofosbuvir and velpatasvir was better than the longer treatment with sofosbuvir and ribavirin, regardless of cirrhosis status. In patients with 3 or 4 disease, treatment length did not affect SVR with daclatasvir plus sofosbuvir and ribavirin.

The results for key question five did not change from the last update.

SVR-12 and 24 seemed to correlate well on trials and are leaning toward only reporting SVR-12. There was moderate strength of evidence on the association from the SVR and mortality in that of cellular carcinoma. That's with interferon regimens, but no other evidence for other associations.

So, to summarize, we identified 25 new trials of DAA that's new to this update that included all oral regimens. The only comparative evidence that was not due to the inclusion of ribavirin, different doses or different durations of DAA treatment were two trials comparing sofosbuvir and

velpatasvir with sofosbuvir and ribavirin in treatment experienced genotype 2 patients. We used CADTH for indirect comparisons of DAA regimens.

New to this review, there was low to moderate strength of evidence that treatment with sofosbuvir and velpatasvir improved rates of SVR compared with longer treatment with sofosbuvir and ribavirin in genotype 2 and genotype 3, and for genotype 3, we considered that moderate strength of evidence. There was longer treatment with sofosbuvir and velpatasvir that was associated with higher SVR rates.

Rates of viral relapse were improved with longer treatment with simeprevir and sofosbuvir, and indirect analysis, the use of 2 DAAs improved SVR compared with sofosbuvir and ribavirin in treatment experienced patients. In treatment naive patients, indirect comparisons with sofosbuvir and ribavirin indicated that both treatment with ledipasvir and sofosbuvir and treatment with the 3D regimen improved SVR rates.

Adding ribavirin to the 3D regimen in treatment naive patients improved SVR in patients with genotype 1A but not 1B. Longer treatment in genotype 4 patients with simeprevir and sofosbuvir increased SVR rates, but the trial is small.

Adding ribavirin may or may not improve benefit outcomes, depending on the population and DAA regimen, but it often increases risk of anemia and rash. Certain populations may benefit from longer treatment regimens, depending on the DAA regimen chosen. SVR-12 seems to correlate well with SVR-24, and there were few comparative trials of the newest of the drug combinations, sofosbuvir and velpatasvir, or grazoprevir and elbasvir, or daclatasvir and sofosbuvir, or the 2D regimen.

Michael Johnson: OK. Thank you, Shelley. Are there any questions from the committee for Shelley?

Amber Figueroa: Shelley, this is Amber Figueroa. Can you clarify the definition of relapse?

Shelley Selph: Well, we are limited to what the trials consider relapse to be, but oftentimes it is an increased viral load.

Amber Figueroa: Is that of a certain time period out? I mean, how far out are they looking?

Shelley Selph: Usually, it's the length of the trial. So, if it's something . . . if it's a trial that's measuring SVR-24, then it's generally 24 weeks. If it's a trial that's only reporting SVR-12, then it would be 12 weeks. Occasionally, they will report relapse information say four weeks out or SVR four weeks out, but we are not including those as outcomes at this point.

Amber Figueroa: Thank you.

Michael Johnson: Any other questions? OK. This is Michael Johnson. At this point, we're going to call the stakeholders. There is a three-minute limit, and the first person will be Bridget Hernandez. So, I'll ask her to come up to the front, and she'll introduce herself. Then, the next one up after that will be Stuart, is it Brochta? O'Brochta. Oh, sorry.

Bridget Hernandez: Good morning. I'm Bridget Hernandez, medical science liaison with Bristol-Myers Squibb. Just to add onto the question that was just asked about relapse, in our studies the . . . once the patient was undetectable while receiving therapy, if the patient then became detectable with their viral load again, even after the end of the regimen in our studies, they were 12 weeks. So, if they became detectable again after that, then it was considered a relapse. OK.

So, I wanted to thank you for the opportunity to discuss briefly Daklinza this morning which is approved for the use with sofosbuvir plus or minus ribavirin for the treatment of hepatitis C, genotype 1 and genotype 3. The safety and efficacy of this regimen was established in three registrational open label phase-3 trials, which included patients with compensated, decompensated cirrhosis, hepatitis C post liver transplant, as well as HIV coinfection. In speaking with many of the healthcare providers within Washington State, it seems that the primary utilization of Daklinza-containing regimens is for genotype 3 infection. Incurred estimates are that genotype 3 prevalence is less than 12% of those

infected with hepatitis C within the U.S. However, this is significant because genotype 3 infection has emerged as the most challenging to treat and is associated with an accelerated progression of fibrosis and cirrhosis when compared to genotype 1. The combination of Daklinza plus sofosbuvir with or without ribavirin provides a 12-week regimen that offers SVR-12 for the majority of genotype 3 patients and is well tolerated with the most common adverse events being headache, fatigue, nausea, and diarrhea. The typical dose of Daklinza is 60 mg; however, a benefit of this regimen is that it is administered separately from sofosbuvir. It is not a fixed-dose tablet, which allows for dose modification of Daklinza to 30 or 90 mg when needed, if it's being Carson Odegard-administered with an interacting medication, as described in the label.

Another benefit is that this regimen does not have a drug-drug interaction with acid-suppressing agents, such as antacids, H2 receptor antagonists, or proton pump inhibitors, and there is no recommendation with regard to dose separation when Daklinza is administered with these agents.

Finally, I wanted to mention that the ASLD guidelines were updated in July, and Daklinza with sofosbuvir plus or minus ribavirin remains a recommended regimen for patients with genotype 3, including those with decompensated cirrhosis, as well as recurrence after liver transplantation. The guidelines also state that patients who are HIV coinfecting should be treated the same as patients without coinfection after recognizing and managing for the drug-drug interactions with their antiretroviral medications, and that daily Daklinza with sofosbuvir with or with or without ribavirin is a recommended regimen when their antiretroviral regimen cannot be changed.

To close, I ask that the committee allow Daklinza to remain on the PDL and be an option for appropriate patients, and I'm happy to address any questions that you may have. Thank you.

Michael Johnson: Alright. Thank you. So, the next step, Stuart O'Brochta, and then to follow is Dr. Raulo Frear will be next.

Stuart O'Brochta: This is a handout just of the . . . a clinical summary that may be helpful. You'll note that it . . . I think it's slightly off the page on my printer and I didn't have time to fix that this morning. So, I apologize, but all the data is there for you to review. So, again, thank you and it's good to see you again, as we've been here before. My name is Stuart O'Brochta with Gilead Sciences and I will be mainly talking about Epclusa today, which is our newest approved hepatitis C therapy. I think key points is that Epclusa is the combination of, as you've already seen, velpatasvir and sofosbuvir, and it is the third regimen now that we have with sofosbuvir, and the only regimen that continues to contain sofosbuvir, which is an NS5A nucleoside, which has been shown to have a significant high barrier to resistance and it's no requirement for baseline NS5A RAV testing and no impact, or almost no impact, no significant impact, on the treatment when you use the sofosbuvir based regimen, as included in Epclusa. Epclusa is the first single table pangenotypic HCV therapy. So, it can treat all six genotypes at high levels of SVR. You will see on the summary there that in genotype 2, 4, 5, and 6, there were no virologic relapses. So, to clarify, I think her name was Bridget from BMS, did a good job. So, there . . . to add a little bit of clarity. So, relapse is generally considered after you get to the end of treatment. So, if you get to the end of treatment if it's a 12-week course or an 8-week course or whatever that is, and you relapse before you measure SVR and most are measuring SVR at 12 weeks after treatment, that's what we could consider relapse. To this point in our clinical trials, sofosbuvir based regimens have only had relapse as a failure if people have had drug levels on board. So, there have been no on treatment sofosbuvir based failures. So, I think that's an important distinction, as well, as you consider the effectiveness of these regimens. So, velpatasvir with sofosbuvir being a pangenotypic regimen, as you can see there by the SVR rates, really where it's meeting its unmet medical need is in genotype 3, as mentioned. Genotype 3 has become a very difficult genotype to treat, and with a 95% SVR with a 12-week regimen without ribavirin. Now, because you've already talked about other studies that have been done, we did not study ribavirin with our Astral trials with sofosbuvir and velpatasvir, but there is evidence to show that you do increase the SVR in specific, very difficult treatment experience (inaudible) when you add ribavirin, but that's out of our label. So, this is the first 12-week regimen to treat all genotypes without

ribavirin with the exception of the decompensated patients, and I'd like to point out that this is a regimen . . .

Michael Johnson: Excuse me. Your three minutes is up.

Stuart O'Brochta: OK. I will end with that this is the only regimen that is 12 weeks with ribavirin with a 94% effectiveness rate in a decompensated patient without a PI. So, it's safe to use in decompensated patients. So, I'd like you to consider to add Epclusa to the PDL, specifically for the treatment of genotype 2 and 3, as you can see that unmet medical need, but it can be used in all other genotypes, as well. So, it does fill that need.

Michael Johnson: Great. Thank you.

Stuart O'Brochta: Thank you.

Raulo Frear: Good morning. I am Raulo Frear. I'm a medical affairs director for Merck and Company in the Pacific Northwest region. Thanks for the opportunity to speak today. Today, I will be commenting on unique attributes of Merck direct-acting antiviral drug, Zepatier, the combination of grazoprevir and elbasvir. I have had the opportunity to discuss this drug with the Health Care Authority pharmacy staff in the past, and based on that presentation and the question and answer period, I believe that the Authority has a thorough understanding of situations where Zepatier is a critical addition to the armamentarium for many hepatitis C patients with genotype 1 or 4 disease who are newly presented for initiation of therapy. You've all had the opportunity to hear Shelley do a thorough review of DURP's review of hepatitis C therapies. Merck has, as noted, had the opportunity to comment on the initial draft, and we certainly thank you for that. Based on that review, I'm going to confine my points to the following five ideas for the committee's consideration.

Number one, Zepatier can be used as a single daily dose 12-week regimen without ribavirin for approximately 90% of those genotypes 1 and 4 patients who present for treatment. Zepatier can be used confidently in those patients who require concomitant acid suppression therapy. Zepatier has efficacy in both cirrhotic and non-cirrhotics without treatment regimen changes. Zepatier can be used in a

population of chronic kidney disease patients, stages 4 and 5, including those patients that are on dialysis, and last but not least, RAVs or RAFs if you prefer, the recommendation for testing in genotypes 1A patients gives healthcare practitioners the ability to select a longer regimen with the addition of ribavirin that in our study population shows 100% SVR at the end of therapy. This significantly reduces the potential for treatment failures in that population of patients with baseline RAV and certainly any incumbent retreatment needs. Thank you, very much. I'd be happy to answer questions.

Michael Johnson: Questions from the committee? Alright. Thank you.

Donna Sullivan: Michael, we can let Shelley go.

Michael Johnson: OK.

Shelley Selph: Bye.

Michael Johnson: Alright. So, I think the first thing we need to do is look at accepting the report? No?

Donna Sullivan: No. It's an update.

Michael Johnson: It's just an update. OK. So, we'll go ahead and start looking at the motions here up on the screen.

Christine Klingel: This is Christine Klingel. I guess looking at this, we had separated them out last time, separating genotype 1 from 2 through 6. I'm wondering if we can combine them but yet use the wording that they can be used for their FDA-approved genotype instead of separating them out.

Donna Sullivan: This is Donna. That's what we intended. Now that they all have a genotype 1 indication, we didn't feel that there was a need to separate them.

Christine Klingel: I think if we, let's see. Oh, good. You have some of it started. Yeah, I don't want to pronounce them all. Yeah. So, if we add the new agents that we've just reviewed, let's see. So, if we use the wording, Christine

Klingel again, there . . . so we have all of them are approved for their . . . according to . . . are safe and efficacious according to their FDA approved indications or the AASLD or IDSA guidelines. I know we had indicated some in particular, but I would say that the whole class, none of the class should be subject to therapeutic interchange on the preferred drug list.

Amber Figueroa: Amber Figueroa. I don't see the daclatasvir with sofosbuvir combo listed anywhere.

Donna Sullivan: They are two different drugs. So, you have to take two different products. So, you have to take sofosbuvir and Daklinza. There is not a combination single pill. So, Daklinza is indicated for genotype 1 and 3 when taken with sofosbuvir. And this is Donna. I'm just going to, with Medicaid, the AASLD guidelines are not part of the compendia, and oftentimes recommend drug combinations or regimens that are off label. So, it puts us in a really tight position to have reference to the AASLD guideline in safe and efficacious compared to that, because it's not the official compendia that Medicaid has to follow. So, we have to cover things that are according to their FDA indications and the indications that are supported in the compendia and AASLD guidelines are not part of the compendia.

Susan Rowe: This is Susan Rowe. Donna, so, the fact that part of our referral criteria, though, does indicate that hepatologists or gastroenterologists or ID specialists are involved. Does that help with that walking tightrope or not?

Donna Sullivan: It still puts us in a, I think, a sticky situation when providers are requesting something off label that, you know, we would not necessarily cover it off label if there is something that is on label as an alternative.

Lisa Chew: This is Lisa Chew. So, in that case, can we say, safe and efficacious for their FDA approved indications and leave out the AASLD.

Donna Sullivan: That's what I would prefer.

Lisa Chew: I think that's reasonable.

Michael Johnson: Any other discussion on this, or do we want to tackle this? Do we need to read the . . . read this? Let's see if I can pronounce these. So, after considering the evidence of safety and efficacy in special populations for the treatment of hepatitis C, I move that . . . let's see. I'll look down here. I can't see that far. Daclatasvir, should I say Zepatier? Shout out the brand names here? Ledipasvir, sofosbuvir combination; paritaprevir, ritonavir, ombitasvir combination; paritaprevir, ritonavir, ombitasvir, disabuvir combination; simeprevir; sofosbuvir; velpatasvir and sofosbuvir combination are safe and efficacious for their FDA approved indications. These drugs cannot be subject to therapeutic interchange in the Washington Preferred Drug List.

Susan Rowe: This is Susan Rowe. I'll second.

Michael Johnson: Ready to move on to the, yeah. So, all in favor say aye.

Group: Aye.

Michael Johnson: So, all opposed same sign. OK. This passes. OK. Next topic are TIMS, I believe. So, we have someone on the phone potentially?

Donna Sullivan: We're about ten minutes ahead of schedule. So, we'll give them a call.

Michael Johnson: OK.

Donna Sullivan: Actually, I won't, because this caller is calling in from Austria.

Michael Johnson: We'll take a few minute break here. We'll take a five-minute break.

Donna Sullivan: Gerald? The caller is having trouble getting into the caller's line.

Michael Johnson: OK.

Donna Sullivan: Hello, Gerald?

Gerald Gartlehner: Hi. This is Gerald.

Donna Sullivan: Oh, great. Sorry for the difficulty.

Gerald Gartlehner: Oh, no. That's OK. With a couple more times, I got a busy signal, but it works now. That's great.

Michael Johnson: This is Michael Johnson. Welcome. I think we're ready for you to get started.

Gerald Gartlehner: OK. So, I assume someone will advance the slides. Do you have them up already?

Michael Johnson: Yes. We have the first slide up, the title.

Gerald Gartlehner: OK. Alright. So, again, sorry for the delay. For my presentation, I will summarize the fifth update of the report on targeted immune modulators and, like the other presentations, I will summarize the entire evidence, not just the new evidence. In the slides, the new evidence is always indicated with bold writing and in the beginning, I will briefly talk about scoping methods and then the main part will be a presentation of the results, and I will end with conclusions.

So, we address three key questions that basically follow standard format. So, key question one addresses the comparative efficacy and effectiveness, and it reads how do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. Question two addresses the comparative risk of harms and reads what are the comparative incidents and severity of harms associated with the use of these drugs, and key question three is on subgroups and it reads do the included drugs differ in effectiveness or harms in the following subgroups, different genders or different racial age, socioeconomic groups, patients with comorbidities, patients taking other commonly prescribed drugs, and patients with early aggressive compared with persistent rheumatoid arthritis.

So, on slide three, you see the 18 different medications that the TIMS report now includes, and for this update, we added for new drugs

apremilast, which is a phosphodiesterase inhibitor. It is currently approved only for psoriatic arthritis. Then, canakinumab that's an interleukin-1 beta inhibitor. It is currently approved for systemic juvenile idiopathic arthritis. Secukinumab is an interleukin-17A inhibitor and is approved for plaque psoriasis. The fourth one is vedolizumab. It's an integrin inhibitor, and it is approved for Crohn's disease and ulcerative colitis.

So, as for all the other streamlined DURP reports, we focused on head-to-head evidence and compared with the last report, the last update, we made a small change to our eligibility criteria. We raised the bar for the sample size. We included observational studies only if they included more than 1000 patients.

To grade and summarize the strength of the evidence, we used the approach of HRQ, the HRQ evidence based practice centers. It incorporates four domains to grade the overall strength of a body of evidence. So, the four key domains are risk of bias, consistency of results across studies, directness of results, and precision of the estimate.

The EPC approach uses four categories to grade the strength of evidence, high, moderate, low, and insufficient. High means we are very confident that the estimate is close to the true effect, and we think that future studies will not change much anymore, and on the other end, insufficient means either we have no evidence or the evidence is so uncertain and flawed with methodological limitations that we really can't say anything about the effect.

Literature search, so for this update, we used standard DURP search methods. You can see the electronic databases that we searched on this slide. Our search dates for this report were through January of 2016. We also received dossiers from ten pharmaceutical companies, which are listed at the bottom of this slide.

Results of our searches, so our update searches detected more than 3800 new citations, 132 full text articles, and we included 23 new studies. So, overall, the report now includes 60 studies, 18 head to head randomized trials and 42 head to head observational studies.

So, slide nine here really just provides an overview of the evidence that we have now for different conditions. For rheumatoid arthritis, we now have 11 head to head trials. We included one new study. For Crohn's disease, we have two studies, one new one. For plaque psoriasis, we have three new studies altogether now four. For harms, we included 19 new observational studies and also data from the head to head trials.

So, key question one, how do targeted immune modulators compare in their efficacy and longterm effectiveness, and I would like to go through the individual indications now summarizing the evidence and pointing out what is new.

Rheumatoid arthritis, so since the last update in 2014, no new drugs were approved for the treatment of rheumatoid arthritis. We now have evidence for nine comparisons and all of them, unfortunately, are still of low or insufficient strength of evidence. So, during our update for this report, we found one new poor quality RCT that compared abatacept with rituximab. This was a small back open label effectiveness trial, and we rated the study as poor because of high dropout rates, lack of blinding of outcomes, and the results reported similar effectiveness between the two treatments.

So, most of the other comparisons that we have for rheumatoid arthritis were limited to single trials and also showed similar efficacy. One exception is the comparison of adalimumab with tocilizumab. This is a study from the last update, still. We have two trials for this comparison, a double-blinded RCT, the ADACTA study, and a small open label study. The ADACTA study was funded by the producer of tocilizumab, and it also showed a greater efficacy of tocilizumab. So, we rated this comparison as low, because our confidence in this trial was somehow limited because tocilizumab was used at a higher dose than actual FDA approved. The smaller study, which was open label, did not show . . . was not consistent with these results.

We did not find any other new studies on the combination of targeted immune modulators for the treatment of rheumatoid arthritis based on three RCTs still from the previous updates. We still have moderate

confidence that a combination therapy does actually not lead to better efficacy.

Juvenile idiopathic arthritis, we still have no evidence, no head to head evidence for juvenile idiopathic arthritis.

Ankylosing spondylitis, the same situation for ankylosing spondylitis. We still do not have any head to head evidence.

Psoriatic arthritis, we did not find any new evidence. We still have one poor quality RCT that compared etanercept with infliximab, and this study showed no difference in efficacy, but the strength of evidence is insufficient.

For Crohn's disease, we included one new study. This was an open label RCT that we rated as poor quality. It was a very small study with 20 participants that compared adalimumab with infliximab for postoperative treatment in patients with Crohn's disease. This study did not find any statistically significant differences in endoscopic or clinical recurrence of the surgery, but the strength of evidence overall is still insufficient.

Ulcerative colitis, we still do not have any head to head evidence for ulcerative colitis.

Plaque psoriasis, so for plaque psoriasis, we actually included three new RCTs. One trial compared etanercept with secukinumab. Secukinumab is a new drug approved for the treatment of plaque psoriasis, and this study was funded by the producer of secukinumab and results showed that secukinumab is more efficacious than etanercept. The second trial compared etanercept with tofacitinib. This was a study with more than 1000 patients. It was a noninferiority trial and compared two doses of tofacitinib with a standard dose of 50 mg of etanercept twice weekly. Tofacitinib, as you know, can be administered orally, but it is currently not approved for the treatment of plaque psoriasis. So, it's only approved for rheumatoid arthritis, and the recommended dose for rheumatoid arthritis is 10 mg. So, in this trial, in this noninferiority trial for plaque psoriasis, 10 mg had similar efficacy compared with etanercept, while 5 mg per day did not.

The study comparing etanercept with ustekinumab was already part of the last update. It showed that ustekinumab is more efficacious than etanercept, and the third new trial for plaque psoriasis compared secukinumab with ustekinumab, and in general, this is a well conducted study, but what reduced our confidence in these findings was that the publication that we had only presented preliminary data. So, the study is still ongoing, and we know from method studies that interim analysis often overestimate differences in efficacy. So, we are still waiting for the final results of this study.

For all these indications, we do not have any head to head evidence about the efficacy and effectiveness in children.

Key question two, so what are the comparative incidence and severity of harms associated with the use of targeted immune modulators. For key question two, we included data from 17 head to head trials and 42 head to head observational studies.

As always for harms, we focused on general tolerability, such as overall rates of adverse events, withdrawal because of adverse events, serious adverse events, and then also specific harms, such as serious infections, malignancies, cardiovascular events, and so on.

So, for overall adverse events, we included 12 randomized control trials and they reported that these drugs basically all had similar risks; however, most of the comparisons were limited to single RCTs and they often had wide confidence intervals that basically rendered inconclusive results very often. So, we really cannot rule out differences with certainty. Therefore, we rated the strength of evidence for overall adverse events as low.

Discontinuation, because of adverse events, we included seven large observational studies and here these studies that infliximab consistently had higher risks of discontinuation because of adverse events than adalimumab and etanercept. We rated the strength of evidence here as moderate. All the other comparisons that we found showed no differences, but then again, often these results were based on single

studies with few events and sometimes if there were more than a single study, results were contradicting. So, for all the other comparisons except adalimumab and etanercept versus infliximab, so all the other comparisons we rated as insufficient.

Serious adverse events, the situation is similar for serious adverse events. The evidence is insufficient to draw conclusions with any certainty. One RCT detected higher serious adverse events, higher rates of serious adverse events with infliximab than adalimumab. All the other comparisons did not find any statistically significant differences, but overall, we have little confidence in these results, and we rated them as insufficient.

Specific adverse events, injection site reactions and infusion reactions, so we found several differences in injection site reactions or infusion reactions. Abatacept had lower risk of injection site reactions than adalimumab and a lower risk of infusion reactions than infliximab. Adalimumab and ustekinumab had lower risks than etanercept but again, all of these comparisons have low certainty and we rated them as low strength of evidence.

Mortality for all-cause mortality, we found no differences in risks among adalimumab, etanercept, and infliximab based on three observational studies. Strength of evidence is low.

For serious infections, infliximab, again, consistently had higher risks than comparator drugs, such as abatacept, adalimumab, etanercept, and rituximab. This is based on five large observational studies with more than 50,000 patients. They all showed consistent findings. So, we rated the strength of evidence for serious infections as moderate.

For tuberculosis, some observational studies indicated high risk for adalimumab and infliximab than etanercept, but the strength of evidence here, again, is low, and all the other comparisons that showed similar risks were rated as insufficient.

Malignancies, for the comparative risk of malignancies, we found no significant differences among adalimumab, anakinra, etanercept, and

infliximab based on six observational studies with more than 29,000 patients. The strength of evidence here also is low.

Then, we included several other harms that we just list here on this slide without going into any further detail. All these studies reported no differences for these outcomes, but there is a lot of uncertainty around these results, and we rated the strength of evidence for all of these outcomes as insufficient.

Where we actually do have strong evidence is on the risk of harms of combination therapies. We have evidence from three randomized control trials and all three trials that compared combination therapies with monotherapies of targeted immune modulators reported no additional benefits but substantially higher risk of serious adverse events and withdrawals because of adverse events. So, because of the large effect and the consistency, we graded the strength of evidence here as high.

For children, unfortunately, we still do not have a single study on the comparative risks of harms in children.

Key question three subgroups, we did not find any new evidence on differences in subgroups.

The evidence that we have is still limited to the results of one RCT that compared adalimumab versus tocilizumab, and this study found no differences in efficacy for age, gender, or early versus established rheumatoid arthritis.

So, summary and conclusions, so in summary, data for the comparative efficacy for most comparisons are limited to single highly-selected randomized control trials that show similar efficacy of targeted immune modulators for rheumatoid arthritis, psoriatic arthritis, and Crohn's disease. There appear to be some differences in efficacy for plaque psoriasis, although they are still rated low strength of evidence. So, we are still waiting for more trials. Combination strategies do not provide additional benefits, and funding bias could play a role in these studies regarding efficacy.

Summary of harms, so for harms the data is based on RCTs and large observational studies. Infliximab is associated with a greater risk of serious adverse events and serious infections, and combination strategies really seem to higher risk of harms and here we really have high strength of evidence. We still do not have any comparative evidence on children, and the insufficient evidence and differences in benefits and harms also carry through to subgroups.

So, this slide concludes my presentation. Thank you, very much, for your attention, and if you have any questions, please go ahead.

Michael Johnson: Alright, thank you. This is Michael Johnson. Any questions from the committee?

Susan Rowe: This is Susan Rowe. I have a question, Gerald. When you looked at cardiovascular events, did that include heart failure?

Gerald Gartlehner: That would have included heart failure, yeah. I don't think we found much on cardiovascular events. I don't think we have anything on heart failure, since we have evidence on heart failure when we still compared the drugs with placebo.

Susan Rowe: OK.

Gerald Gartlehner: Now, with the head to head studies, I think this is not included anymore.

Susan Rowe: OK. Thank you.

Mason Bowman: Just a brief, minor clarification, Gerald. On slide 12, there is parenthesis on . . . it says mixed. I just wasn't sure what that meant.

Gerald Gartlehner: Oh, mixed means that the two RCTs show different findings. So, we have to . . . the ADACTA study showed that tocilizumab is more efficacious and then adalimumab, the smaller study did not show that. That's what we mean with mixed . . . mixed results, mixed findings.

Mason Bowman: OK. That's what I thought. Thank you, very much.

Michael Johnson: Any other questions? Alright, thank you, Gerald. This will bring us to the stakeholder input.

Donna Sullivan: Excuse me, Michael. We can let Gerald go.

Michael Johnson: Oh, yeah. Thank you, Gerald, you can, yeah.

Gerald Gartlehner: Alright. Thank you, very much.

Michael Johnson: Alright. Thank you.

Gerald Gartlehner: Bye.

Michael Johnson: Alright. So, we'll go to stakeholder input at this point, and when you get up to the podium, please introduce yourself and who you represent. We have three minutes. First person will be Anthony Hager and following him will be David Gross.

Anthony Hager: Hello. Thank you for this opportunity. My name is Anthony Hager, and I am here representing Bristol Myer Squibb immunoscience. I am here to provide testimony in support of Orencia/abatacept on behalf of BMS. In adults, Orencia/abatacept subQ or I.V. is indicated for the reduction of the signs and symptoms of moderate to severe rheumatoid arthritis, as mono or combination therapy. In children six and over, I.V. Orencia is indicated for the reduction of the signs and symptoms of moderate to severe polyarticular JIA. I am required to draw your attention to an important limitation of use. Orencia should not be administered concomitantly with TNF antagonist, and its use is not recommended concurrently with other biologic RA treatment, such as anakinra. In clinical trials, the most commonly reported adverse events included headache, URTI, nasopharyngitis, and nausea. The most serious adverse events in clinical trials with Orencia were serious infections. As the only T-cell co-stimulation modulator among biologic therapies for RA, Orencia has a unique mechanism of action. Since it works upstream at the level of the T-cell, Orencia has been shown in clinical trials to reduce serum levels of TNF alpha, IL-6, soluble IL-2 receptor, rheumatoid factor, and acute phase reactant, such as CRP. I'd like to draw the committee's

attention to some recent changes in the ACR, American College of Rheumatology's recommendations for the treatment of patients for both early and established RA. This is an update, as of November, 2015. Specifically, for patients with moderate or high disease activity, despite conventional DMARD therapy, combination conventional DMARDs, TNF antagonists, with or without methotrexate, and non-TNF biologics with or without methotrexate are strongly recommended in no particular order of preference. Also, for patients with established RA and patients with moderate or high disease activity despite initial TNF inhibitor therapy, the 2015 ACR guidelines initially recommend using a non-TNF biologic. In a noninferiority randomized control trial comparing subQ abatacept with subQ adalimumab in biologic naïve adults with RA who had active disease despite methotrexate therapy. While abatacept was noninferior to adalimumab in terms of efficacy end points, injection site reactions occurred at a rate of 3.8% with abatacept versus 9.1% with adalimumab, T-value of 0.06 for the comparison, and discontinuation was due to serious adverse events were over three times as common in the adalimumab versus the abatacept group, 4.9% versus 1.6%. In closing, I ask that you evaluate coverage policy in this class to allow for a non-TNF biologic treatment option by adding Orencia/abatacept to the Washington Medicaid preferred drug list. Thank you.

Michael Johnson: Thank you. Next up will be Dr. David Gross and to follow him will be Mary Kemhus.

David Gross: Good morning. I'm Dave Gross, medical affairs division with Pfizer, and I am here today to provide a brief update on Xeljanz and Xeljanz XR or tofacitinib, and to request that you consider it for addition to the Washington Medicaid PDL. Xeljanz and recently approved Xeljanz XR or tofacitinib are indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. They may be used as monotherapy or in combination with methotrexate or other nonbiologic disease modifying antirheumatic drugs. The recommended dose for Xeljanz is 5 mg twice daily, Xeljanz XR 11 mg once daily given orally with or without food. Because they are tablets, they require no special storage requirements. Xeljanz does include a boxed warning for serious infections and malignancies. Patients treated with Xeljanz and

Xeljanz XR are at increased risk for developing serious infections that may lead to hospitalization or death. Lymphoma and other malignancies have been observed in patients being treated with Xeljanz. Most common serious adverse events are serious infections. Xeljanz is an oral small molecule. It's a Janus kinase or JAK inhibitor, and by inhibiting the JAK pathway intercellularly, Xeljanz modulates the signalling of multiple different cytokines involved in the pathogenesis of rheumatoid arthritis. Across the six randomized controlled phase-3 trials, Xeljanz showed significant reduction in RA signs and symptoms and improvement in physical functioning, as assessed by the ACR response rates and the validated health assessment questionnaire or HAQ-DI. The patients that were studied in the extensive phase-3 program included those that were either intolerant to or had not adequately responded to methotrexate, those that were either intolerant to or had not adequately responded to TNF inhibitors, and those that had not previously been exposed to methotrexate, although this is not currently in the indication. Additionally, two of the phase-3 studies evaluated Xeljanz as monotherapy and one study evaluated Xeljanz in combination with the variety of other oral disease modifying antirheumatic drugs. As my colleague just stated, there is a recent update in November of 2015 ACR rheumatoid arthritis treatment guideline, and one thing that I will add is that it does say that if the disease activity remains moderate or high despite DMARD monotherapy, switch to using a combination of DMARD, adding a TNF inhibitor or a nonbiologic TNF or tofacitinib in any order of preference rather than continuing with monotherapy, and the guideline committee classified this as a strong recommendation. With regard to the safety profile of Xeljanz . . .

Michael Johnson: Excuse me.

David Gross: Yes.

Michael Johnson: Time is up. Sorry.

David Gross: OK. Just wanted to let you know that there have been two recently published longterm extension studies on safety and the safety is the same as we saw in the randomized trials. Any questions? Thank you for your time and attention.

Michael Johnson: Thank you. Questions? Alright. Thank you. Next up will be Dr. Mary Kemhus followed by Dr. Carrie Johnson.

Mary Kemhus: Hi. I feel like the podium got further away today. So, my name is Mary Kemhus, and I'm a pharmacist with Novartis Medical Affairs. Today, I would like to discuss secukinumab, or Cosentyx, which is indicated for the treatment of moderate to severe plaque psoriasis and actually, as of January of this year, which was not included in the DURP report. It's indicated for psoriatic arthritis and ankylosing spondylitis, as well. Cosentyx works by a novel mechanism of action in that it binds the IL-17A cytokine and inhibits its interaction with the IL-17 receptor. The reason this pathway is unique and important is because there are actually high concentrations of IL-17 found in psoriatic plaques and in the joints of patients with psoriatic arthritis and ankylosing spondylitis. So, today, I am actually going to focus my comments on the CLEAR trial, which is the head to head trial versus Stelara that the DURP report briefly mentioned. At the time of the DURP review, the final results weren't available, but I can actually share them with you now, and they've recently been published. So, CLEAR is a 52-week head to head trial, as I said, versus Stelara. It looked at 679 patients with moderate to severe plaque psoriasis. This is the first psoriasis trial they actually looked at PASI 90 as a primary endpoint versus previously used PASI 75. So, what that means is, basically 90% clearance in psoriatic plaques from baseline. PASI 90 responses were obtained by 79% of patients treated with Cosentyx at week 16 versus 58% in the Stelara arm, and this response was maintained out to 52 weeks. Regarding ankylosing spondylitis and psoriatic arthritis, Cosentyx has demonstrated clinical benefits, including improvements in dactylitis, enthesitis, patient reported outcomes, and other measures of disease activity. Cosentyx has demonstrated a consistent and well tolerated safety profile now in over 18,000 patients between postmarketing data and our clinical trials. Higher rates of candida were observed about a 1% difference versus placebo, and that's actually to be expected from drugs that work on the IL-17 pathway. So, in conclusion, I ask that you consider adding Cosentyx to the Washington Medicaid PDL, as it's the only IL-17 inhibitor for the treatment of moderate to severe plaque psoriasis and active forms of ankylosing spondylitis and psoriatic arthritis. It has demonstrated early and sustained skin clearance over 52

weeks, as well as a favorable and consistent safety profile across all three indications. Any questions? Nope? OK. Thank you.

Michael Johnson: Alright. Next up is Dr. Carrie Johnson followed by Dr. Robert Olson.

Carrie Johnson: Hi. Carrie Johnson. I'm a Pharm.D. with Celgene, medical liaison. So, apremilast was not included in the DURP report, because we only have placebo controlled trials at this point. However, apremilast is now recognized, since its approval in 2014 as a valuable oral nonbiologic option for patients with psoriasis and psoriatic arthritis. Apremilast's brand name, Otezla, is an oral small molecule that works intracellularly to inhibit phosphodiesterase-4. It's not a biologic. Inhibition of phosphodiesterase-4 by apremilast results in increased intracellular concentrations, a cyclic adenosine monophosphate. This is thought to indirectly modulate the levels of proinflammatory cytokines, such as TNF for IL-23 and IL-17, which decrease after apremilast administration and antiinflammatory cytokine, such as IL-10, which increase after apremilast administration. So, it modulates multiple cytokines involved in inflammatory pathway, not concentrating on one. Apremilast was approved in 2014 first for the treatment of adults with active psoriatic arthritis and then subsequently received approval for treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Following a five-day titration, the approved dose is 30 mg orally twice daily. Apremilast has no black box warnings and no requirement for medication specific prescreening or ongoing laboratory monitoring. Local trial programs for psoriatic arthritis and psoriasis are going out to five years; however, there is no mandate or (inaudible) program. There is now safety data publicly presented in psoriatic arthritis out to 3 years and psoriasis out to 3.5 years. The prescribing information includes warnings for depression, weight decrease, and drug interactions. There is no other precautions or warnings in terms of serious infection, opportunistic infection, or malignancy. Depression, during clinical trials, 1.3% of patients treated with apremilast and 0.4% of patients treated with placebo reported depression. Prescribers are to carefully weigh the risk and benefit of treatment. Weight decrease was seen, as well, and drug interactions (inaudible) apremilast efficacy may occur with concomitant use with (inaudible) enzyme inducer. So, new for 2016 are psoriatic arthritis data,

longterm data from the clinical trial program evaluating apremilast in moderate to severe psoriatic arthritis were presented at the European rheumatology meeting, ULAR, in June of 2016. Included were three year pool of efficacy and safety data from the phase-3 palace program on psoriatic arthritis. The portions of patients achieving ACR-20, 50, and 70 at week 156 or 3 years in the palace-3 trial were approximately 60, 40, and 20% respectively. Durability of effect was evident across all efficacy parameters through week 52 and extended to week 156 for this program. In psoriasis longterm data from our psoriasis program esteem evaluating apremilast in moderate to severe plaque psoriasis were presented at the American Academy of Dermatology meeting in March, 2016. Durability and effect was evident through week 104. For longterm safety, profile was similar between psoriatic arthritis and psoriasis clinical trial programs. It has remained consistent out to three and three and a half years with no increase in incidence or severity of adverse events with longer exposure to apremilast. For serious adverse events of special interest, cardiac events . . .

Michael Johnson: Excuse me. The three minutes is up.

Carrie Johnson: Time is up? OK. And then just the guidelines recently published were from a group of (inaudible) published indicating, including apremilast for the first time in the U.S. published guidelines. Thank you.

Michael Johnson: Next up is Robert Olson.

Robert Olson: Hi. My name is Robert Olson, and I am here on behalf of Amgen. Thank you for the opportunity to address the committee on behalf of Enbrel. Enbrel is the only fully human soluble TNF receptor inhibitor. The mechanism of action of Enbrel is unique among TNF antagonists. Enbrel is approved in reducing signs and symptoms, including major clinical response inhibiting progression of structural damage, and improving physical function in moderately to severe active rheumatoid arthritis. Enbrel can be initiated in combination with methotrexate or used alone. Additionally, Enbrel is approved in juvenile idiopathic patients, age 2 years and older. Psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Most common adverse events in rheumatoid arthritis clinical trials were injection site reactions, infection, and headache. In clinical

trials of all other adult indications, adverse events were similar to those reported in the RA trials. Enbrel has not been shown to induce neutralizing antibodies. Enbrel's recommended dose in adult patients with RA, psoriatic arthritis and/or ankylosing spondylitis is 50 mg per week subcutaneous injection. For adult plaque psoriasis patients, the dose is 50 mg given twice weekly for three months followed by a reduction in maintenance dose of 50 mg per week. In clinical studies, Enbrel was shown to be effective in approximately two out of three adults with RA. Clinical response to Enbrel generally appeared within one to two weeks and nearly always occurred within three months. Enbrel has 19 years of collective clinical experience and nearly 3 million patient years of exposure. I'm available to answer any questions, and thank you for your consideration.

Michael Johnson: Alright. Thank you. Alright. I think next we will look at the motion. This is Michael Johnson. Just my initial impression was that other than the four new agents, I didn't see anything really that struck out as different in patient population etcetera. So, we'll probably start with that.

Susan Rowe: I would agree that we maybe saw some new indications, but that our motion, as it's written, does cover the selection of agents for the PDL for various indications. I think it still works.

Mason Bowman: I agree. I can tackle this. Don't judge me. Alright. Are we ready? OK. I can wait a minute. After considering the evidence of safety, efficacy, effectiveness and special populations for the use of targeted immune modulators for the treatment of immunologic conditions, for which they have FDA indications. I move that abatacept, adalimumab, alefacept, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, ustekinumab, and vedolizumab are efficacious. The FDA must include a drug approved for treatment of each immunologic condition for which they have FDA indications: Rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis and should include a self-administered agent if indicated. These medications cannot be subject to therapeutic interchange in the Washington preferred drug list.

Eric Harvey: I'll second.

Chuck Agte: I actually, sorry to backtrack, but I have a question for clarification on the P&T Committee's intent on possibly a change in wording. We're currently saying the PDL must include a drug approved for treatment of each immunologic condition for which they have FDA indications and then we list some. Those are the conditions that these drugs must have in common, but several of them have a lot of other random conditions. So, is it the Board's intent for there to be one for each condition that is FDA indicated for these products as a whole, or for that specific list of conditions?

Eric Harvey: I'd like to propose that the list is the minimum set of disease that we want to make sure are covered.

Chuck Agte: Thank you.

Michael Johnson: Any other comment?

Susan Rowe: I agree with Eric. I think we are listing these disease as examples, but we don't not want to treat something that's not included on the list if there is evidence and an FDA indication.

Donna Sullivan: So, if there was a drug that was not preferred, and it's the only drug that has that FDA indication, then we would approve it, but it wouldn't be preferred for the same indications that all of the other drugs that have in common with other drugs. So, there are a couple that have some unique indications, but they would be . . . they are also indicated for rheumatoid arthritis. I think what Chuck was trying to say is, do we need to make it preferred for that one unique indication that it has that none of the others have versus just make sure that it's available when prescribed for that indication.

Susan Rowe: So, to the end user who is trying to prescribe it for maybe that unique indication, is there a difference?

Donna Sullivan: We would just have . . . there would just be a phone call, and then when they call in, we would have, if they tell the staff that they're using it for that indication, then it would be approved.

Susan Rowe: So, if we made it preferred, then would that skip the phone call?

Donna Sullivan: Yes, it would.

Chuck Agte: Not necessarily. As frequently, the bureaucrat in the process, it's a fine distinction that may only matter to mean having to implement these things, but the difference would be whether the product is technically preferred for that indication or whether it is something that is nonpreferred, but we approve for that indication, because the actual status of preferred or not makes a difference. The end result for a prescriber is pretty much the same either way. Somebody's going to have to contact us and tell us this is the diagnosis. It's just, are we approving it because we say it's preferred for the diagnosis or are we approving it because we're saying those unique indications are exceptions to their nonpreferred status, and I think what I heard the Board saying is that for those unique indications, they don't necessarily have to be preferred.

Eric Harvey: That is my intention, yeah.

Chuck Agte: Thank you.

Amber Figueroa: Would it be helpful then if we pulled the list of FDA indications, if we're saying that it may be applying to something else? Is that too restrictive?

Donna Sullivan: I jotted them all down while we were doing the . . . going through. It looks anakinra has a unique indication, and the acronym, I didn't write down the full, it was NOMID, which is I'm not exactly sure what that is. I believe that is the only one that had a significantly unique indication. I can pull up the report again. Hang on.

Chuck Agte: I would suggest the simplest way to clarify that would be, in that sentence I read before, instead of must include a drug approved for treatment of each immunological condition for which they have FDA

indications that that sentence possibly be changed to, the PDL must include a drug approved for treatment of the following indications.

Michael Johnson: I like that proposal. I think we should do that.

Lisa Chew: I agree.

Amber Figueroa: NOMID is neonatal onset of multisystem inflammatory disease.

Michael Johnson: So, do we need to reread this now that we changed this?

Donna Sullivan: I think what you want to do is definitely make sure that you say you're restating the motion with the discussed changes and then second the motion again and then vote on it.

Michael Johnson: So, the previous motion has been amended to say the PDL must include a drug approved for treatment of the following FDA indications. So, that's, really the big change. So, with that change, all in favor say aye.

Group: Aye.

Michael Johnson: All opposed, same sign. Alright, the motion carries. Alright. I think we're on to antiemetics.

Donna Sullivan: Hi, Brittany?

Brittany Holzhammer:Hi. This is Brittany.

Michael Johnson: Welcome. I think we have your title slide up. You can go ahead and get started anytime.

Brittany Holzhammer:Great. Thank you. So, this is the sixth scan, since the last report, on newer antiemetics. This scan was conducted in July of this year.

So, the previous report was update number one, which was completed in January of 2009 with searches through October of 2008. The last scan, again, was last year, and the searches for this scan were June 2015 through June 2016.

So, we included adults or children at risk for or with nausea, vomiting, or both related to chemotherapy, radiation therapy, surgical procedure, or pregnancy.

This slide shows the drugs that were included in the scan, and the shaded drug is the one that we've identified in this current scan.

In this scan, we identified one new drug, which was rolapitant approved in September of 2015 for use with other agents to prevent delayed nausea and vomiting associated with chemotherapy in adults. In previous scans, we identified two new combination products, including netupitant and palonosetron, which was approved in October of 2014. We also identified doxylamine succinate and pyridoxine hydrochloride, which was approved in 2013. We also identified two new formulations, including the ondansetron oral film and the granisetron transdermal patch. We identified no new uses in this or prior scans, and in this scan, we identified no new serious harms, but in the previous scans, we identified three new harms pertaining to dolasetron and ondansetron.

On this current scan, we identified one new comparative effectiveness review. This relates to antiemetic medication used to prevent and to treat chemotherapy induced nausea and vomiting in kids. In previous scans, we identified three comparative effectiveness reviews, one Cochrane review and two CADTH reviews related to interventions for treating nausea and vomiting in early pregnancy, longterm use of three specific antiemetics for prevention of nausea and vomiting, and finally the use of ondansetron to manage chemotherapy induced nausea and vomiting in kids.

In terms of new evidence, we've identified a total of 31 new head to head trials, since the last report, six of which were found in this current scan and two pertaining to new drugs. In terms of add-on trials, specifically the addition of NK1 antagonist to 5-HT3 antagonist with or without steroid therapy, we have found 17 add-on trials, ten in this scan and four of the new drugs. We've also identified two secondary analyses and 23 total placebo-controlled trials, seven of which were found in this scan.

So, slide 8, this slide shows the six new head to head trials that we've identified in this scan of the 31 total. In the two trials at the bottom of the table are of the new drugs that have been identified since the last report.

Slide nine shows the new add-on trials, the ten new add-on trials that we've identified in this scan of the total of 17 since the last report, and the four trials at the bottom of the table are of new drugs.

In summary, since the last update report, we have identified three newly approved drugs, rolapitant in this scan, which had four trials, one head to head trial, and three add-on trials. In addition, doxylamine succinate and pyridoxine hydrochloride, which was approved for use in pregnancy and only has placebo-controlled trials at this point. Finally, netupitant and palonosetron and it had two trials, as identified. We also identified two new formulations of granisetron and ondansetron. We found four new comparative effectiveness reviews. In terms of evidence, we found 31 new head to head trials, six this scan and two of the new drugs, and 17 new add-on trials, ten found in this scan and four of new drugs. Any questions?

Michael Johnson: Questions from the committee here? I don't see any questions from the committee. Thank you. I see no stakeholders. So, we'll move into the business at hand. I think first we need to . . . what's that? We need to approve the scan. I'm just going to propose that we accept this scan, as adequate.

Christine Klingel: I second.

Michael Johnson: All in favor, say aye.

Group: Aye.

Michael Johnson: All opposed, same sign. OK. Motion carries.

Eric Harvey: I'd like to move to reiterate the prior motion.

Susan Rowe: I'll second.

Michael Johnson: All in favor, say aye.

Group: Aye.

Michael Johnson: All opposed same sign. OK. Motion carries. The last topic for the morning will be the ADHD.

Donna Sullivan: We have the slides up.

Brittany Holzhammer: Oh. OK. Great. So, this is the first scan, since the last report, on pharmacological treatment for ADHD. This scan was conducted in June of this year.

The last update was update five, which was completed in July of 2015 with searches through February of 2015. Again, this is the first scan, since that last report, and the searches for this scan were January of 2015 through May of 2016.

We included children and adults with attention deficit disorder or attention deficit hyperactivity disorder. We included outcomes, such as functional capacity, quality of life, symptoms and abuse/misuse or diversion. In terms of study design, we included head to head randomized control trials and recent good quality systematic reviews. We excluded placebo controlled trials based on the limit that was imposed in the last report.

So, this slide shows the drugs included in this scan, and the shading indicates the new drugs that were identified in this scan.

So, we have identified, in this scan, two new amphetamine formulations, including Adzenys XR-ODT, orally disintegrating tablet, and Dyanaval XR oral suspension. We have also identified two new methylphenidate formulations, including QuilliChew ER chewable tablets and Aptension XR oral capsule.

We have identified no new populations, no new serious harms in this scan.

In terms of comparative effectiveness reviews, we have identified one protocol for an ongoing AHRQ Effective Health Care Program report on ADHD and as of yesterday, this report is still in progress.

In terms of evidence, we identified three potentially relevant new head to head trials.

This slide shows the three head to head trials that were identified in this scan, and they are all in children.

In summary, we found four new formulations of existing drugs. We excluded placebo-controlled trials in our searches; therefore, we found three new head to head trials in this scan, none of the new formulations that we've identified though, in this scan. Any questions?

Michael Johnson: I don't see any questions. Thank you, Brittany.

Brittany Holzhammer: Great. Thank you.

Michael Johnson: So, I'll make a motion that we accept this scan as adequate.

Lisa Chew: I second.

Michael Johnson: All in favor, say aye.

Group: Aye.

Michael Johnson: All opposed, same sign. Looking at the previous motion, I don't see anything that we looked at today that would change the . . . I propose we just reiterate that.

Dale Sanderson: I'll second.

Michael Johnson: All approve say aye.

Group: Aye.

Michael Johnson: All opposed same sign. OK. Motion carries. So, I think at this time, we're going to adjourn the Pharmacy and Therapeutics Committee. Do you still want a five minute break? A 15-minute break? OK. We'll do a 15 minute break and reconvene at 11:20.

I think we'll go ahead and get started. At this point, we're going to convene the Drug Utilization Review Board. I think Donna will take it from here.

Donna Sullivan: I'm chief pharmacy officer with the Healthcare Authority. I am going to go through the classes that we just reviewed today, review our . . . the current limitations we have on these classes if there are any, and then recommend changes to those limitations. I do want to provide a point of clarity for either the stakeholders or for the committee. I had put on each . . . for each drug class, I have created a slide that looks like the one that I'm displaying now that shows the current PDL status of these drugs before the meeting today. This is not the recommendation of the PDL status for these drugs after the results of the motion from this meeting, and that's true for each of these. So, I just want to make sure that when you're making your recommendations on these limitations, you are not recommending the PDL status. That goes, now, through our cost analysis where we look at the supplemental rebates and the utilization data from all of the agencies and make our selection that way. So, I just wanted to clarify that. There was some confusion with some of the stakeholders, and I just wanted to make sure that the committee did not think that they were making these specific decisions today either.

So, moving forward. We are going to start with the targeted immune modulators. I'm not going to go through all of these. The drugs that say that they are not reviewed will be considered reviewed as of this morning's presentation, because it was a full updated report. So, the four new drugs will be considered for PDL status when we do our cost analysis. The current limitations on the TIMS class is that there is no therapeutic interchange, and that is based on the previous motion, as well as the motion that you had today. So, that will continue. They currently are limited to their FDA approved and compendia supported indications, including diagnosis, dose, dosing schedule, and use of other first line agents. So, we don't let them use doses outside of their

labeling. Currently, Tysabri require prior authorization. We have an expedited authorization that for each indication for the TIMS, and it is allowed when used according to labeling and prescribed by a specialist appropriate to the patient's diagnosis. So, each drug indication combination has its own expedited authorization code at this time. Then the PDL is applied through a combination of expedited authorization and prior authorization status. The indications for these drugs is growing, and so it is becoming difficult to try to maintain this expedited auth code per indication. So, our recommendation is that we remove all of the expedited authorization and prior authorization criteria on the TIMS products and instead manage this class by requiring patients step through all of the preferred agents before they get a nonpreferred agent. So, that is the current recommendation. Any questions?

Christine Klingel: You mentioned the Tysabri, but that's not on our list.

Donna Sullivan: The Tysabri was not included in the last full update of the TIMS report, but it has been in historical reports. It is indicated for, I believe, rheumatoid arthritis, as well as multiple sclerosis. So, it's in both classes and because it was previously included in the reports historically, we have carried it forward in the class, because it is part of the class. Chuck, were you going to say something?

Chuck Agate: Just for clarity, the indication it shares with the other TIMS is Crohn's.

Donna Sullivan: Oh, thank you.

Susan Rowe: So, Donna, end-user impact of this is not seeing . . . what we anticipate for the physician who is now prescribing it as a result of if we accept these changes.

Donna Sullivan: So, I think that the effect of this change is one, currently they only have to only try and fail, I believe, one PDL product instead of two, or instead of all PDL products. Pharmacies will no longer have to chase down the diagnosis and the specialty of the prescriber to insert the right expedited authorization code on the prescription. So, I think it'll be easier for the entire process to happen, other than doctors, if they want to prescribe off-label, they will have to try and fail, try and fail the two preferred

drugs. I guess, amend the recommendation to say that we would grandfather people into their current regimen. So, if they are already on a nonpreferred drug, we're not going to go back and make them try Enbrel or Humira, or whichever drugs become preferred after the results of today's meeting.

Susan Rowe: Grandfathering in, I think, sounds very reasonable.

Christine Klingel: So, I guess one other thought is, I know that some of them are infusion versus self-administered subcutaneous injections versus oral tablets. So, say you have someone who has, like, some access issues and can't get in for an infusion, I'm trying to think of a case, not knowing which one is indicated, but could it be a possibility where that patient would have to step through an infusion medication before getting say a preferred subQ or oral medication?

Donna Sullivan: If there was a . . . by nature of that policy, yes. If there was a preferred infused product, then yes. They would have to step through it. At this time, there is not a preferred infused product, or at least that's not its only dosage form.

Chuck Agte: In the situation you described in terms of access, although those things can develop, I just want to state that Medicaid does have a transportation program for clients, as well. So, clients who do have travel issues can contact the agency, and we have a program for providing transportation to doctor's visits and things like that.

Donna Sullivan: I just want to reiterate that for every request that comes in, if the doctor supplies medical justification for the medical necessity for a nonpreferred drug and not stepping through both or all preferreds, we do look at those on a case by case basis. So, it's not, you know, just a slam, you have to try and fail. If you have . . . if you can justify why not stepping through all of the preferred agents is not appropriate for the client, then we do take that into consideration.

Michael Johnson: Do we want to make this motion, then?

Susan Rowe: I'm willing to make this motion. I move the Medicaid Fee for Service Program implement the limitations for targeted immune modulator drug class as listed on slide three, which Donna did add the grandfathering in to the other criteria.

Mason Bowman: I second.

Michael Johnson: All in favor, say aye.

Group: Aye.

Michael Johnson: All opposed, same sign.

Donna Sullivan: Just for the record, I want to state that there were no stakeholders to speak on that. So, for the antiemetic drug products, this drug class was a scan this time around. So, if the drug says it's not been reviewed, it has not been reviewed. Again, these are the PDL status as of today, prior to your motion earlier this morning. So, the current preferred drugs are the generic forms of granisetron and the generic forms of ondansetron.

Mason Bowman: Is that all forms of these generics?

Donna Sullivan: I'd have to check the PDL that's listed. I believe so. At this time, I don't think ODTs are not preferred, but I believe they might require authorization.

Chuck Agte: I believe Sancuso, I don't know if it has generics yet or not, but Sancuso is still unstudied. So, it's a form of granisetron. So, I think the oral forms is what we would be talking about.

Donna Sullivan: So, like I say here, the Sancuso . . . it says here on the slide the Sancuso is not reviewed. So, looking at the PDL that is posted online, the granisetron solution, tablets, and the ondansetron ODT and ondansetron solution and tablets are all preferred.

Mason Bowman: Thank you.

Donna Sullivan: The current limitations, ondansetron is limited to 24 mg per day. The ondansetron ODT and the solution require an expedited authorization, and they . . . indicating that it's used for 18 years and older. Then, there is also an expedited authorization code for the inability to swallow oral tablets or capsules for clients aged 18 and older, again with a maximum dose of 24 mg per day. Looking at the relative cost of the medications, I'm recommending that we remove the expedited authorization for the ondansetron ODT and maintain the ondansetron solution and add an expedited authorization to the other antiemetic oral solutions to be consistent with the ondansetron. Again, patients must step through all preferred drugs with the same indication before a nonpreferred drug would be authorized.

Chuck Agte: Just to clarify, because I'm not sure it came across, the limitation isn't that they can only be used for 18 and older in that particular one. It's that for 18 and older is when that expedited authorization applies. For children under the age of 18, basically, that's just assumed there is some issue with consuming solid oral forms.

Donna Sullivan: Thank you.

Lisa Chew: As we discussed with the previous drug class, would there be a grandfathering, as well, for patients who are on the nonpreferred?

Donna Sullivan: Yes. I mean, that's typically how, how it works when we make a change is to grandfather the patients and they are already on nonpreferred drugs. We have already reviewed those and approved those nonpreferred products. Or the providers wrote DAW on the prescription. So, we have honored those. At this point in time, I don't know. We have very few patients on the granisetron solution, because it's nonpreferred. So, I don't see there being a big disruption with this change.

Christine Klingel: I move to accept the recommendations listed on slide six for the antiemetic drug class.

Eric Harvey: I'll second.

Michael Johnson: All approve, say aye.

Group: Aye.

Michael Johnson: All opposed, same sign. Great. Motion carries.

Donna Sullivan: Again, for the record, I want to state that there were no stakeholders signed up to testify on the antiemetic topic. So, moving onto the ADHD product, this class was a scan, as well, today. So, drugs that are listed as not reviewed are currently not reviewed. The existing products that are preferred are the generic forms of amphetamine, the generic forms of demethylphenidate, dextroamphetamine, Guanfacine extended release, the generic product, and the methylphenidate immediate release generic products only. Current limitations, we have age dose limits. We have prior authorization for patients that are getting two or more agents from different subclasses. So, that would be a methylphenidate type or an amphetamine combination, using those together, or using a nonstimulant with a stimulant, or two nonstimulants together. We do require generics first, and we have some adult diagnosis limitations. So, I'm going to go review each one of these. So, on the slide here are the age dose limits that have been recommended by our pediatric mental health workgroup and previously approved by the DUR Board. I'm not going to read through them all. You can read them. We just added, if you remember, the nonstimulant drugs at the last update of this particular class. For alpha agonists for ADHD, this slide shows the age-dose limits for those. Essentially, it's an equivalent of 0.1 mg of clonidine, which equals 1 mg of Guanfacine. ADHD duplication, the drugs listed in this slide, if there is an X in the box, then that combination of products would require a second opinion or prior authorization. For ADHD for adults, the diagnosis restrictions are across between the legal uses in Washington State and the uses that can be considered medically accepted indications under the federal Medicaid statutes. We have it limited to ADHD by expedited authorization. Any other use requires a prior authorization, and it requires a full review. We don't allow any off-label uses currently supported . . . or there are no off-label uses supported at this time in the compendia. So, I wanted to let you know this slide, it's a little confusing of what is a legally accepted indication for prescribing stimulants to adults, or prescribing stimulants in general. We have a statute that it is unlawful to prescribe a stimulant for any

indication other than narcolepsy, hyperkinesia, drug-induced brain dysfunction, epilepsy, differential diagnostic psychiatric evaluation of depression, refractory depression, and multiple sclerosis. So, any other indications we would not accept for medical necessity.

Chuck Agte: As of last legislative session, they also threw in, or an FDA approved diagnosis at the end of that, because there is one drug that has received another indication.

Donna Sullivan: That is correct. There is a binge-eating disorder indication. I don't know which one it is, but thanks Chuck for the clarification. So FDA approved indications or the following are those diagnoses and conditions I just mentioned. So, the recommendation is to continue the current limitations, as described in slides 10 through 13, and that members must step through all preferred drugs within the same indication before a nonpreferred drug would be authorized.

Dale Sanderson: There is some evidence in the literature of using stimulants in the geriatric population for, like, depression.

Donna Sullivan: I'm sorry, what?

Dale Sanderson: In the geriatric population for actually severe depression. So, that would be included in this?

Donna Sullivan: Yes. That is one of the acceptable indications.

Amber Figueroa: I move the Medicaid Fee for Service program implement the limitations for the Attention Deficit Hyperactivity drug class listed on slide 14.

Dale Sanderson: I'll second.

Michael Johnson: All in favor, say aye.

Group: Aye.

Michael Johnson: All opposed, same sign. Alright. Motion carries.

Donna Sullivan: Moving onto the multiple sclerosis . . . back up. For the record, there were no stakeholders signed up to testify on the ADHD drugs. Now moving onto multiple sclerosis products. Again, the drugs here that are considered not reviewed are based on the status prior to the last meeting where I believe it was a full updated report. Currently, our preferred products are dimethyl fumarate, fingolimod, which is Gilenya and Tecfidera, copaxone 40 mg, Avonex, Betaseron, and I believe Glatopa the 20 mg product is preferred. So, for the MS drugs, right now, we have continuation of therapy of nonpreferred drugs are allowed with the exception of the following: Rebif, which is interferon beta-1a, and Extavia, which is beta interferon 1b, that if they were taking Extavia and the preferred product is Betaseron, because Betaseron is the same interferon beta-1b, we would require them to switch to Betaseron, the same with Rebif and Avonex. We would make them switch to the preferred interferon type. There is no therapeutic interchange and again we require prior authorization on Tysabri for Crohn's or MS. The recommendation is to continue with the no TIP based on the P&T Committee's motion, and I actually have jotted some amended changes that I was making during the meeting today for this class. Because there are several beta interferons, there are actually several interferons, my thought was whether or not it made sense to step through each of the interferon types or even copaxone 40 mg . . . copaxone and Glatopa are the same drug. They're glatiramer. If they are both preferred, this recommendation would require that they go through Glatopa and copaxone 40. I don't know if that makes sense. So, I was jotting down a change that they must step through a preferred drug of each ingredient. I don't know if that's the cleanest way to say that, that they must step through a preferred drug of each ingredient with the same indication before a nonpreferred drug would be authorized. So, essentially, depending on the results, if there is a glatiramer product where there are multiple products that would be preferred, they would have to try one of those products with the interferons. If there are multiple interferons that are preferred, that they would have to step through one of those interferon products instead of each individual interferon product.

Susan Rowe: I think that's good. We could use each drug entity instead of ingredient if you like that. Otherwise, I think what you're saying is clear, and I think it's a . . . that's nice for the patient not to try multiple interferons, yeah.

- Amber Figueroa: You could also put active ingredient, so it sounds less like a recipe and more like a drug.
- Mason Bowman: I'm glad you clarified that, Donna, because that's kind of what I was going to key in on. So, I think this is a good discussion here to clarify this.
- Donna Sullivan: So, we do have stakeholders and here first, let me go, we do have the Tysabri PA criteria. We didn't have it in the TIMS section, but the Tysabri is limited to prescriber client enrolled in the Touch Program. They must not be immune compromised. There's a dose limit of 300 mg every 4 weeks. For relapsing forms of MS, they must be prescribed by a neurologist. They need to have an MRI. They must have tried and failed other MS treatments and must be used as monotherapy. For Crohn's disease, it must be prescribed by a gastroenterologist. They must have tried and failed the other preferred Crohn's Disease medications. They must not be taking any other immunosuppressants or TNF inhibitors. They must have experienced their therapeutic benefit after three months of starting the treatment, and they must have discontinued corticosteroids within six months of starting the treatment. So, there are stakeholder comments . . . or stakeholders that have signed up.
- Michael Johnson: So, again, we're going to limit each discussion to three minutes. First up would be Dr. Margaret Olmon. To follow would be Dr. Contessa Fincher. Please identify yourself and who you represent. Thanks.
- Margaret Olmon: Good morning. My name is Maggie Olmon and I'm representing the medical affairs team at AbbVie. Posted on the Washington Health Care Authority website for discussion today is the recommendation that patients with relapsing forms of multiple sclerosis must step through all, and I had preferred drugs on my notes, but obviously you've made that change to the different entities, but you are recommending that patients go through all the preferred drugs before a nonpreferred drug is authorized, and the preferred disease-modifying therapies include Tecfidera, Gilenya, either copaxone or Glatopa, and Avonex or Betaseron, so an interferon. We are asking that you reconsider the recommendation of failing all of the preferred agent entities for the following reasons: The American Academy of Neurology, AAN, urges access to all disease

modifying therapy for treatment of MS individuals when they have the potential to provide clinical benefit. The disease activity of MS is different for every patient, and the AAN believes that the highly individualized decisions around the use of DMT should be made by persons living with MS in consultation with their treatment team. Many factors impact the choice of DMT and switching among them and should be considered if implementing step therapy programs. These include relative efficacy of DMT's mechanism of action, patient's disease activity, lifestyle, route of administration, treatment schedule, and the medication side effect profile. If step therapy programs are used, the AAN recommends that these programs should be driven by evidence based clinical and safety data and not just cost. Early diagnosis and treatment of MS has been associated with reduced disease progression and improved disease control. The optimal window for impacting longterm disability with disease modifying therapy is during relapsing phase of the disease with the goal being to decrease the number of relapses, slow the accumulation of lesion volume, and prevent disability from both unresolved relapses and disease progression. Therefore, stepping through multiple DMTs with similar efficacy may not be in the best interest of the patient. Requiring a physician to work through medical exception process to obtain a nonpreferred agent that may be a better treatment option for that patient when taking all the patient's factors into consideration, can cause a delay in therapy. We are respectfully asking that you reconsider the recommendation of failing all the preferred agents for the patients with relapsing multiple sclerosis. Do you have any questions for me at this time? Thank you very much for your attention.

Michael Johnson: Next up will be Dr. Contessa Fincher followed by Mary Fitzpatrick.

Contessa Fincher: Hello. My name is Contessa Fincher. I'm a medical outcomes liaison for Teva Pharmaceuticals. I do appreciate what a colleague at a different manufacturing company just said. From Teva's perspective, we understand that this area is under scrutiny. It's becoming a crowded marketplace, and there are some controls that are being put in place. We would request the committee to consider and agree with the Health Care Authority recommendations for stepping through the preferred

agents. Thank you. If you have any questions about copaxone 40 mg or 20, I'd be happy to answer that.

Michael Johnson: Thank you. Next up is Mary Fitzpatrick.

Mary Fitzpatrick: Good morning. My name is Mary Fitzpatrick, and I am a medical science liaison from Biogen. I'm trained as a nurse practitioner, and prior to joining Biogen, I had a clinical practice working with MS patients for 20 years. So, I would like to speak with you today about three of our products. Tecfidera, I testified about last year, and I'd like to provide an update on a couple of items. Tecfidera is currently on the PDL list, and we would like to maintain that status. So, Tecfidera has been available for three years and has been used to treat 200,000 MS patients with 250,000 patient years of experience. I've testified in the past regarding the efficacy and safety of the phase-3 trial, but I think what's important to look at is, what does the drug look like once it's in the real world. So, we have an endorsed trial, which is an eight-year extension trial, and recently the five-year interim data was published in the MS journal authored by Dr. Gold. So, in the five year integrated analysis, the continuous Tecfidera group showed a consistent and sustained efficacy throughout the five years with an annualized relapse rate, otherwise known as ARR for an abbreviation, of 0.138, which equates to one relapse every seven years. There were two other arms, placebo and copaxone, and for those two groups of patients, they showed substantial reductions in ARR in disability progression after they went on the active treatment of Tecfidera. So, Tecfidera has had four cases of PML in 200,000 patients. So, that is one in 50,000 patients, which is a low risk. The current label was recently updated the beginning of this year and provides guidelines to the provider on management of low lymphocyte counts of lymphopenia. If there is any questions about the ARR risk mitigation strategy, I'd be happy to address that. So, in conclusion, Tecfidera has a proven track record in the clinical setting. It has the combination of sustained efficacy and well-defined safety profile supports Tecfidera as a valuable longterm treatment option for patients with MS, and we ask to have Tecfidera remain on the PDL list. So, Plegridy, I'd like to say a few words, is our pegylated interferon beta-1a. So, it's given by subQ injection twice a month. That has been on the market for two years, and

one of the benefits of pegylation is it prolongs the half-life of the drug. So, the current recommended dose in the label . . .

Michael Johnson: I'm sorry. The time is up.

Mary Fitzpatrick: Thank you.

Donna Sullivan: So, we're just ready for a motion, then.

Lisa Chew: I move the Medicaid Fee for Service Program implement the limitations for the multiple sclerosis drug class listed on slide 17 and to also include that patients must step through all preferred drugs of each active ingredient that was discussed.

Eric Harvey: I'd like to make one correction. I believe it's slide 18, but I will second with that.

Donna Sullivan: Thank you.

Michael Johnson: All in favor, say aye.

Group: Aye.

Michael Johnson: All opposed, same sign. Great. Motion carries.

Donna Sullivan: And I believe that's it.

Michael Johnson: We're adjourned. Thank you.