Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board
P&T Meeting Notes
February 19, 2020

Virginia Buccola: Good morning everyone. This is Virginia Buccola, Committee Chair. We'll convene the meeting for this morning. If we could go ahead and have everybody do introductions, state your name, and a reminder that the meeting is recorded.

Petra Eichelsdoerfer: Petra Eichelsdoerfer, United Healthcare.

David Johnson: David Johnson, Molina Healthcare.

Diane Schwilke: Diane Schwilke, committee member

Constance Huynh: Constance Huynh, committee member.

Alexander Park: Alexander Park, committee member.

Jordan Storhaug: Jordan Storhaug, committee member.

Virginia Buccola: Virginia Buccola, committee member, committee Chair.

Catherine Brown: Catherine Brown, committee member.

Nancy Lee: Nancy Lee, committee member.

Susan Flatebo: Susan Flatebo, committee member.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Umang Patel: Umang Patel, Magellan Health.

Ryan Pistoresi: Ryan Pistoresi, Health Care Authority.

Luke Dearden: Luke Dearden, Health Care Authority.

Jose Zarate: Jose Zarate, Health Care Authority.

Amy Irwin: Amy Irwin, Health Care Authority.

Virginia Buccola: I don't know if we have our members on the phone logged in yet.

Rosalie Kelly: Hi. This is Rosalie Kelly from the Center for Evidence Based Policy. Good morning.

Virginia Buccola: Good morning, Roz.

Jaymie Mai: This is Jaymie Mai from Labor and Industries.

Virginia Buccola: Good morning. I think Dr. Chen might be joining us later. Okay. Again, thanks everyone for being here this morning, as this is my first meeting that I am chairing. I'm looking to my experts to poke me with sticks, if there is anything that falls off the rails. I don't know if there are any announcements at all? Okay. We're just meeting until noon today, so the agenda is pretty packed. We'll move forward, as quickly as we can. So, we'll go to the first agenda item. Roz Kelly with DERP, you're going to go ahead and do a review for us.

Rosalie Kelly: Thank you, so much, for the introduction.

Virginia Buccola: Yes, sorry. Your slides are up and ready to go.

Rosalie Kelly: Okay. Great. Thank you, so much. I'm very excited to speak to you all this morning. So, I'm a little eager. Alright. So, yes, I am here today to present a newer diabetes drug and cardiovascular disease outcome reports. So, let's get started. Alright, turning to slide one, just a brief overview of the presentation today. I will go through a little bit of background information, our PICOS, our key questions, our methods, findings and finally, our conclusions.

So, on slide 2, you will see a brief topic history. This is an updated report for DERP that was previously presented in September of 2017 looking at newer medications and combinations.

Turning to our background on slide 3, several new diabetic drugs have been approved for adults with type 2 diabetes. Primarily, these drugs fall into three main categories. We have our glucagon like peptide 1 agonist, or GLP-1 agonist, our dipeptidyl peptidase-4 DPP-4 inhibitors, and our sodium glucose cotransporter 2, SGLT-2 inhibitors.

Turning to slide 4, just a little bit of introduction on our cardiovascular focus today. So, in 2005, the drug muraglitazar was found to be associated with an increased incidence of death, MACE, which stands for major adverse cardiovascular event, which is typically a composite of three events consisting of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death, and chronic heart failure. Additionally, in 2007, rosiglitazone was found to be associated with an increased risk of myocardial infarction and cardiovascular death. Obviously, this raised concern, because an estimated 32.2% of individuals with type 2 diabetes around the world are effected by cardiovascular disease, which is also the main cause of death for individuals with type 2 diabetes. So, this prompted the FDA to release 2008 guidance requiring new diabetic drugs demonstrate no association with an unacceptable increase in risk of cardiovascular events. The FDA defined an unacceptable risk increase as more than 30%.

So, now here on slide 5, we will get into our PICOs for our presentation today. So, our population is adults with type 2 diabetes. Our interventions fall into three main categories. We have oral drugs, subcutaneous injection drugs, and fixed dose combination products. And I will go into more detail on which specific interventions were covered in a few moments. Our comparators were combination therapy compared to monotherapy, head-to-head comparisons, and placebo with standard of care. We had five grade rated outcomes that we will discuss this morning, and there are additional outcomes detailed in your report, but due to time, I will focus on these five this morning. So, we have all cause mortality, fetal or nonfatal stroke, fetal or nonfatal myocardial infarction, hospitalization for heart failure, and serious adverse events. I just

wanted to briefly mention that serious adverse events were investigator determined. So, they included SAE's, as related to study treatment, as well as pre specified events of interest. So, for example, pancreatitis, neoplasm, hypoglycemia, allergic reactions, etc.

Turning to slide 6, you will see our first group of drug classes this morning are GLP-1 agonists. This is just to orient us to the rest of the process this morning. So, I will go through each drug class individually, in terms of our outcomes and findings. Let's take a moment to orient ourselves to this table here. So, on the left we have the class of drug, including some of our combination drugs you can see in the sort of second section there. Then, we have our generic names, our brand names, and our FDA approval date. There are quite a few drugs in our GLP-1 class.

Moving onto slide 7, we see the same format here. So, these are our DPP-4 inhibitors that were eligible for this report, which included some fixed dose combination products, as well as oral drugs.

Moving onto slide 8, we can see our eligible SGLT-2 inhibitor interventions. So, again, we see some oral drugs and fixed dose combination products.

Let's move on to slide 9. So, this is our key question slide. So, our first key question is what is the effectiveness of newer diabetes medications for cardiovascular events, including mortality in adults with type 2 diabetes. Our second key question, what are the characteristics of ongoing studies for newer diabetes medications and CVD outcome.

Let's move to slide 10. This slide details the methods that were used in this report. So, just briefly, DERP evidence sources were researched to identify new eligible studies of newer diabetes drugs for CVD outcome from January 1st, 2017, up to October 2nd, 2019. An additional eligibility criteria included publication in English in a human study population. We extracted data for outcomes of interest from eligible studies and redid the quality of the body of evidence using the grade approach. Additionally, we calculated risk ratios, instance rate ratios, and 95% confidence interval to P-value by using OpenEpi, and these statistics are denoted with italics.

Moving onto slide 11, we just have a brief refresher here on our DERP methodological quality rating scale. So, for us, our studies can range from good, fair, to poor quality. So, our methodologic quality ratings assess each individual study on its own.

Turning to slide 12, we have our grade quality of evidence rating scale. The body of evidence can range from high, moderate, low to very low. So, this looks at the body of the evidence, as a whole, rather than individual studies on their own. Factors that can effects these quality ratings include the number of studies that report a specific outcome, a consistency of findings between those studies, the methodological quality of the studies themselves, and the statistical precision of the estimates of the effect.

Moving onto slide 14, so for findings, we identified six eligible RCT's in 50 publications. This is the large body of evidence here. For our eligible RCT's, we had sample sizes that range from just about 3200 individuals to just over 17,000. In all of our RCT's, they were sponsored by manufacturers of the interventions themselves. All RCT's were multisite international, and all [RD] standard of care therapy for glycemic and/or cardiovascular risk management adhering to local guidelines. So, just taking a moment here just to point out that these were multisite international RCT's. So, there is no standardization, and it's possible that some interventions using standard of care included therapies that may not have been approved in the U.S. We found no head-to-head studies of included interventions identified. No studies assessing cardiovascular outcomes between monotherapy and combination therapy were identified.

Moving to slide 15, this is just a brief summary of our overall key findings for this presentation this morning. So, for our grade rated outcome of all-cause mortality, we found small absolute risk reduction with GLP-1 agonists. We found no evidence of an effect on all-cause mortality risk for DPP-4 or SGLT-2 inhibitors. For stroke outcome, we found no evidence of an effect for any of the drugs covered in this report, including GLP-1 agonists, DPP-4 inhibitors, or SGLT-2 inhibitors. For myocardial infarction, we found uncertainty in the effect of GLP-1 agonists, and no

evidence of an effect on myocardial infarction risk for SGLT-2 or DPP-4 inhibitors. For hospitalization for heart failure outcome, we found significant relative reductions with SGLT-2 inhibitors. However, there is no evidence of an effect observed for GLP-1 agonist or DPP-4 inhibitors. For a final serious adverse event outcome, we have significant relative reductions with GLP-1 agonists and SGLT-2 inhibitors, but no evidence of an effect was found on serious adverse events risk with DPP-4 inhibitors.

Turning to slide 16, this slide is just to orient ourselves to the remainder of the presentation this morning. So, I will go through each drug class and each of our five outcomes and talk about findings for each.

Let's get into the GLP-1 agonists class on slide 17. The GLP-1, as some of you may know, is a type of hormone found naturally in the body that is lower than normal in people with type 2 diabetes. GLP-1 helps the pancreas release insulin by suppressing glucagon secretion. Glucagon is the hormone that prevents blood sugar from dipping too low. However, in type 2 diabetes, glucagon can remain in the body and actually cause the opposite, high blood sure. The GLP-1 agonist also decrease stomach acid and slow gastric emptying, both of which can make you feel fuller longer and often lead to weight loss. However, there may be some GI side effects experienced, due to the GI motility effect of these drugs.

Moving to slide 18, these are our included RCT's for the GLP-1 agonist class. So, we have seven studies overall. Three fair quality RCT's. So, briefly, we have leader trials, liraglutide. Harmony outcomes assessing albiglutide. Rewind looking at dulaglutide. You can see here that we have fairly large sample sizes for these fair quality RCT's, which were over 9000 participants in each. We also identified four poor-quality RCT's. Pioneer 6 looking at oral semaglutide. Exscel looking at exenatide ER. Sustain-6 looking at semaglutide. Elixa assessing lixisenatide. In each of these studies, the study population contained complex patients with several comorbidities. So, just briefly on the side, you can see individuals had established CVD or CVD risk factors, but they may have also had cerebrovascular disease, metabolic syndrome, etc. The average HbA1c or blood glucose levels for the seven RCT's at baseline ranged from 7.2% to 8.7%. The average age range of participants in this class were 62 to 66 years. These individuals were living with type 2 diabetes for an average

of 9 to 15 years. Our report gives more detail on our methodologic quality ratings, which I encourage you to check out.

So, moving to slide 19, this is our grade rating table here. So, just a moment to orient ourselves to the table. The left most column, we have our outcomes, as well as the number of studies and associated publications. In the next column we have our quality of the evidence rating. The third column contains the relationship or overall findings. The right most column, or the fourth column, contains our rationale for the rating. Again, the report goes into more detail on our individual justifications for each rating. So, overall, we found moderate quality evidence for our all-cause and hospitalization for heart failure outcomes. We found low quality evidence for stroke and serious adverse events, and very low quality evidence for myocardial infarction in this class. I will go through each of our findings individually, but just briefly, we found generally small absolute risk productions for risk of all-cause mortality, uncertainty in the effect surrounding a myocardial infarction, and reduction in risk for serious adverse events, but GLP-1 agonist did not affect stroke or hospitalization for heart failure and risk compared to placebo.

So, moving to slide 20, our first outcome, all-cause mortality, and at the top here, the outcome is colored according to its grade rating. So, yellow signifies a moderate quality evidence rating. So, we found no evidence of an effect with albiglutide, dulaglutide, lixisenatide, or semaglutide. However, significant relative reductions of 14 to 51% compared to placebo did occur. However, these were very small absolute risk differences of 1 to just under 1.5%. Two of the drugs in this class, exenatide extended release, reduced risk by 14%, liraglutide by 15%, and oral semaglutide by 51%, as compared to placebo, but you can see our first drug, exenatide, is very small reduction. However, oral semaglutide you can see a large separation between the groups. These were very and frequently occurring at 1.4 versus 2.8%, so just something to keep in mind.

Moving to slide 21, we have our stroke outcome. This outcome was not assessed in semaglutide, and no evidence of an affect was observed with albiglutide, exenatide ER, lixisenatide, or oral semaglutide. However, one

drug in this class, dulaglutide, significantly reduced risk by 24% over placebo. However, this is a small effect, given the absolute risk difference, less than 1 percentage point between treatment groups. Just to call your attention, we had a sample size of over 9000 in this trial.

Moving to slide 22, we have our myocardial infarction outcomes. Overall, there was uncertainty around the effect on MI risk as a class, but there was some evidence of reductions in relative risk. So, within the class, no evidence of an effect was observed with dulaglutide, exenatide extended release, lixisenatide, or oral semaglutide. However, significant relative reductions of 14 to 25% over placebo did occur with two drugs in the class, but yet again, these were small absolute risk differences of 1 percentage point. So, the two drugs in class that did reduce risk, relative to placebo, albiglutide and liraglutide respectively.

Moving to slide 23, you see our hospitalization for heart failure outcomes. So, this outcome was not assessed in albiglutide, and there was no evidence of an effect within this class on risk, including our eligible interventions of dulaglutide, exenatide extended release, liraglutide, lixisenatide, semaglutide, or oral semaglutide.

Moving to slide 24, our serious adverse events outcome. So, we found evidence for small but meaningful reductions in risk. There was no evidence of an effect on risk for serious adverse events observed with exenatide extended release, liraglutide, or lixisenatide. We found significant relative reductions of 4 to 23%, as compared to placebo with absolute risk differences of 3.1 to 8.2 percentage points. So, you may be looking at this and wondering, well, why did some of these drugs not reduce risk. Just take a moment to think about the way that type 2 diabetes progresses in some of the sort of complicating factors. So, some of our outcomes, it's hard to differentiate whether or not these may have been related to treatment or the natural progress of the disease. For example, hypoglycemia, we know that some medications can increase this risk. However, this is something that doesn't actually occur within type 2 diabetes.

Moving to slide 25, we looked at individuals with and without prior cardiovascular disease. So, this slide here is just broken out by each

individual drug, just what was reported in identified studies and publications. So, no significant difference in MACE risk. Again, this is a composite event containing nonfatal myocardial infarction, nonfatal stroke, or cardiovascular related death. So, no significant difference in risk was found between individuals with and without prior CVD treated with dulaglutide. All-cause mortality risk was reduced by 21% for individuals without previous heart failure treated with exenatide extended release, but had no effect on risk for individuals with prior heart failure who took exenatide extended release. Again, no significant difference in MACE risk was found between individuals with and without prior heart failure treated with lixisenatide.

Moving to slide 26, our final report here on liraglutide. Risk of MACE was reduced by 18%, and risk of cardiovascular death by 33% in individuals with single vascular disease treated with liraglutide. No evidence of an effect on either one of those risks, the risk of MACE or cardiovascular death occurred for individuals with polyvascular disease treated with liraglutide. Liraglutide also reduced risk of MACE by 31% in individuals with EGFR less than 60 mL. It had no effect for individuals with a baseline EGFR greater than or equal to 60 mL. Just a quick reminder, EGFR estimated glomerular filtration rate, so that's a blood test here that gives you sort of a function of the waste products of the kidneys here. So, depending on the clinician that you speak to, you might hear normal renal function at a rate of greater than or equal to 90 mL, but some individuals suggest that in an older population, which these studies mostly took place in, somewhere around 60 might be considered normal to mild renal impairment. So, I will let that differentiation lay with you, but you can think of sort of less than 60 mL as maybe more moderate to mild impairment.

Moving to slide 27, we have our DPP-4 inhibitor class. The DPP-4 works similarly to GLP-1 agonist. However, the DPP-4 inhibitors work by blocking the DPP-4 enzyme, which slows degradation of endogenous, so naturally occurring GLP-1 hormone in the body. As you saw with the previous class, more GLP-1 hormone then stimulates insulin secretion and suppress enzyme secretion after eating. However, DPP-4 inhibitors do not effect GI motility. So, that leads to more neutral effect on weight,

but it does alleviate some of the GI side effects that can be experienced with GLP-1 receptor agonist.

Moving to slide 28, we identified 5 RCT's in 14 publications assessing GLP-1 agonists. So, we had one fair quality RCT, the Tecos trial looking at sitagliptin. It was a very large sample size. We also identified four poor quality RCT's, the Examine trial, Carmelina, Carolina, and the Savor-Timi 53 trial. Again, these study populations contain complex patients with several comorbidities or aggravating factors, and in these trials, the average HbA1c level ranged from 7.2 to 8% at baseline. The average age range of these individuals was 61 to 66 years. The average diabetic duration for these trials ranged from 7 to 15 years. Again, we rated these trials as poor to fair methodologic quality for various things that are detailed further in our report, including short followup duration, etc. I would like to call out that one trial, the Carolina trial, looked at linagliptin, as compared to glimepiride, and the Carmelina trial assessed linagliptin as compared to placebo with standard of care.

Moving to slide 29, we again have our grade table here. For our five outcomes, we found moderate quality evidence for all-cause mortality, stroke, and serious adverse events. However, no evidence of an effect was observed within the class for each of these previously mentioned outcomes. However, there was some evidence of a very small but increased risk for serious adverse events with DPP-4 inhibitors. We found low quality evidence for hospitalization for heart failure and myocardial infarction risk. Overall, no evidence, in fact, within the class. Again, more details are in the report surrounding our rational and justification for our grade rating.

Turning to slide 30, hospitalization for heart failure, so this outcome was not assessed in alogliptin. I'm sorry. Slide 30 is all-cause mortality, stroke risk, and myocardial infarction risk. So, our two outcomes within an asterisk were not assessed in alogliptin. So, no evidence on the effect was observed with alogliptin, saxagliptin, or sitagliptin on all-cause mortality risk. Linagliptin had no evidence of an effect when compared to placebo or glimepiride on any of our three outcomes. No evidence of an effect was observed with saxagliptin or sitagliptin on stroke or MI risk.

Turning to slide 31, hospitalization for heart failure. This outcome was not assessed in alogliptin. No evidence in the effect was observed with sitagliptin. Linagliptin had no evidence of an effect when compared to placebo or glimepiride. However, saxagliptin significantly increased risk by 27% relative to placebo, but when we look at the absolute risk difference between groups, it was less than 1 percentage point.

Turning to slide 32, for serious adverse events risk, no evidence of an effect on risk was observed with alogliptin or sitagliptin. Linagliptin had no evidence in effect when compared to placebo or glimepiride. However, a significant 5% increase in risk of serious adverse events was found with saxagliptin relative to placebo, but again, a small absolute risk difference between groups overall when you take a look between groups as reported.

Turning to slide 33, now looking at individuals with and without prior CVD. So, we had two trials that reported differences. So, no significant difference in risk of hospitalization for heart failure or risk of cardiovascular death was found between individuals with and without baseline heart failure treated with linagliptin in the Carmelina study. No sign difference in MACE risk between individuals with baseline CVD and individuals with just cardiovascular risk factors treated with saxagliptin was found.

Turning to slide 34, we have our SGLT-2 inhibitor class. So, these drugs work a little bit differently. So, SGLT-2 inhibitors prevent the kidney from reabsorbing sugar during blood still drained by blocking a protein called SGLT-2. Typically, these proteins cause sugar resorption into the body from urine. So blocking them signals the kidneys to lower blood sugar by excreting excess glucose through the urine.

Turning to slide 35, we have our included RCT's. We identified two fair quality RCT's looking at SGLT-2 inhibitors. We have our Declare-Timi 58 study looking at dapagliflozin. Empagliflozin-Reg Outcome study assessing empagliflozin, both with fairly large sample sizes. We had two poor quality RCT's. Our Canvas trial looking at canaglifozin, and our Credence trial also looking at canaglifozin. However, Credence was assessing canaglifozin in individuals with type 2 diabetes with established

chronic kidney disease. So, overall, again, individuals in each trial had average HbA1c levels ranging from 8.1 to 8.3%. So, just of note, that's a little bit less variation in baseline HbA1c than we had seen in our other two classes. Individuals in these four trials had an average age of 64 to 64 years old. Again, more narrowed range of individuals. The average diabetic duration for individuals in these trials ranged from 11 to 16 years. So, more longstanding disease than our other drug classes we have seen, so far. Again, we reviewed these trials as poor to fair methodologic quality for various things that we detailed further in our report. I encourage you to check them out.

Moving to slide 36, overall we had 4 RCT's and 19 publications. We found moderate quality evidence for our all-cause mortality, myocardial infarction, hospitalization for heart failure, and serious adverse events outcomes. Low quality evidence for our stroke outcome. SGLT-2 inhibitors did not have evidence of an effect on risk of all-cause mortality, stroke, or myocardial infarction, as a class. However, we found small absolute reductions in risk across the class for hospitalization for heart failure and serious adverse events. Again, more details are included in our report on the justification and rationale for our grade rating.

Moving to slide 37, our first outcome, all-cause mortality, there is no evidence of an effect observed with canaglifozin or dapagliflozin on all-cause mortality risk. However, empagliflozin significantly reduced risk by 32% relative to placebo. This is actually a very strong effect with an absolutely different in risk between treatment groups of over 2.5% percentage points. Again, benefit was seen at both the 10 mg and 25 mg doses of empagliflozin.

Turning to slide 38, our outcomes of stroke and myocardial infarction. Again, no evidence of an effect is observed with any of the three individual drugs covered in this class, canaglifozin, dapagliflozin, or empagliflozin.

Turning to slide 39, hospitalization for heart failure. So, we saw significant relative reduction across the class ranging from 27 to 39%, as compared to placebo with small absolute risk differences ranging from 0.8% to 2.5%. So, there's some variation in this class on this outcome.

Canaglifozin shows minimal reduced risk by 33% in Canvas and reduced risk of hospitalization for heart failure by 39% in credence. Dapagliflozin reduced risk by 27% and empagliflozin reduced risk by 35%. Again, benefit was seen with empagliflozin at both the 10 mg and 25 mg doses.

Turning to slide 40, we have our serious adverse events outcomes. The significant relative reductions in risk ranging from 6 to 10% were seen in this class with absolute risk differences of just over 2 to just over 4 percentage points. So, some strong absolute risk differences there. What's interesting is, canaglifozin did not reduce risk for serious adverse events in the Canvas program. However, it did reduce risk by 9% in Credence. Dapagliflozin reduced risk by 6%. Empagliflozin also reduced risk by 10%.

Turning to slide 41, looking at individuals with and without previous cardiovascular disease. So, for our canaglifozin intervention, no significant difference in the risk of cardiovascular events. This included several things, including myocardial infarction, stroke, hospitalization, heart failure, etc. Was found between individuals with and without baseline heart failure in Canvas. No significant different in risk for cardiovascular events was found between individuals less or equal to 30 years of age with ASCVD or just over 50 years with CV risk factors in both the Canvas and Credence trials. Canaglifozin reduced the risk of hemorrhagic stroke by 75% in individuals with baseline cerebrovascular disease in Canvas. Dapagliflozin significantly reduced MACE by 16%, and risk of recurrent myocardial infarction by 22% in individuals with previous myocardial infarction history. However, no evidence of an effect was found for individuals without previous MI.

Turning to slide 42, this is a continuation here of our dapagliflozin intervention. So, dapagliflozin reduced risk of hospitalization for heart failure by 36%, risk of all cause mortality by 41%, and risk of cardiovascular death by 45% for individuals with baseline heart failure with reduced ejection fraction, and had no effect on these three outcomes for individuals with baseline heart failure with preserved ejection fraction. So, interesting difference there. With empagliflozin, so no significant difference in risk for cardiovascular events between individuals with and without prior MI or stroke, or between individuals

with and without peripheral artery disease treated with employee was found. Greater reductions in risk for cardiovascular death, risk of hospitalization due to heart failure, and risk of all-cause mortality were reported for individuals with prior CABG than without prior CABG treated with empagliflozin.

Turning to slide 43, so just talking briefly about some of our ongoing studies here.

On slide 44, you can see that we identified four placebo-controlled ongoing studies which have been named. So, our Soul trial is looking at semaglutide compared to standard of care. The Prehypd study is looking at empagliflozin as compared to metformin. The Vertis CV trial is assessing ertugliflozin as compared to standard of care. Our fourth unnamed trial, dapagliflozin in combination with pioglitazone, as compared to standard of care. We also identified 1 completed randomized control trial. However, no publications have been identified yet. And this looked at the exenatide implant, as compared to a placebo implant. We also identified two large cohort studies, 1 looking at empagliflozin or any SGLT-2 inhibitor, as compared to DPP-4 inhibitors. Emprise trial, also looking at empagliflozin as compared to DPP-4 inhibitors, and there are more details on these ongoing studies detailed in our report.

Turning to slide 45, this is just some brief limitations of the evidence here. So, included RCT's were designed as non-inferiority trials and gained marketing approval if the drug displayed one of two things. So, one, if the drug was noninferior or did not cause an 80% excess risk for cardiovascular events when compared to placebo. Two, if the drug demonstrated superiority or did not cause a 30% excess risk for cardiovascular events when compared to placebo.

Turning to slide 46, additionally, these trials were only powered to detect a 15 to 20% reduction in the primary composite MACE endpoint. Then, you might want to ask, what does a 15% reduction in the risk of three composite events outcome mean clinically? Does that actually translate to a 5% reduction in each of our three events? We don't know. Right? Additionally, all these trials... well, not all the trials. Most of the trials

used placebo run-in periods. So, again, this may have artificially reduced the number of treatment discontinuation rates and the number of adverse events reported with treatment.

Turning to slide 47, additionally, we had some population variations. So, individuals had a wide range of diabetic duration. So, the timeframe that they had been living with type 2 diabetes. We also had some variation in baseline characteristics, such as baseline HbA1c levels, baseline blood pressure, and concomitant medications, all of which are detailed for each individual trial in our report with some variation in the study populations themselves. So, the type of cardiovascular disease these individuals are living with compared to somebody living with just cardiovascular risk factors. Some trials had smaller proportions of female participants, which is important, because we know the risks for certain cardiovascular events can be different between men and women. The Framingham study, an analysis of the Framingham heart study also found that cardiovascular mortality with diabetes posed a greater risk for cardiovascular mortality in women than men. Additionally, background therapy was allowed for local guidelines. So, for example, one trial was conducted in 48 countries. Again, some of this background therapy may include drugs or therapies that are not approved in the U.S. and was not standardized throughout the trial.

Turning to slide 48, our conclusion slide which is on 49 here. So, overall, as classes, we found GLP-1 agonists have evidence of small, absolute risk reduction in all-cause mortality and evidence of risk reduction for serious adverse events. DPP-4 inhibitors had no evidence of an effect on risk for the 5 included outcomes. However, there were small absolute increases in risk for hospitalization for heart failure and risk of serious adverse events found with [inaudible] and SGLT-2 inhibitors have evidence of generally small but significant absolute risk reductions in hospitalization for heart failure and serious adverse events.

Turning to slide 50, they also found significant differences in cardiovascular event risk between individuals with and without established CVD in both the GLP-1 agonist and SGLT-2 inhibitor classes. To summarize again, we did not identify any eligible studies assessing cardiovascular effectiveness and safety of included interventions when

used as monotherapy compared to combination therapy. With no eligible head-to-head trials identified, we are unable to make direct comparisons between drug classes for our included intervention. Slide 51 is our question slide.

Virginia Buccola: Thanks, Roz. Are there any questions from the committee?

Nancy Lee: Thank you, Roz, for the presentation. I appreciated the limitations of the evidence slide. I was wondering, has your group explored some of those areas of population variation? I know that there is limited evidence, but as the evidence base grows, maybe to explore looking at some of those differences possibly? I just wanted to know if your group has kind of explored that right now?

Rosalie Kelly: Yeah. So, the reports, oh, sorry. The report actually detailed each individual trial. So, it actually pinpoints some of the specific population differences. So, for example, in some of the trials, more patients may have been using one type of diabetes drug compared to another. More individuals with preexisting conditions were in one treatment group, as compared to another. Those are all detailed by individual trial in the report.

Virginia Buccola: Great. Thank you, Roz.

Leta Evaskus: Roz, I wanted to verify, in your review, have ertugliflozin plus metformin not been fully reviewed for efficacy?

Rosalie Kelly: No. They were not detailed in this report as those cardiovascular focused trials, they have not published their final results, as of our final search date of October 2nd, 2019. So, I know they are coming down the pipeline. I believe it should be in the first quarter of the year.

Leta Evaskus: I'll change on the motion. I'm going to grey those two out. So, those won't be eligible to be preferred. Thank you.

Virginia Buccola: If there are no further questions, then I think we go to Umang Patel with Magellan for a review of disease states.

Umang Patel: Perfect. While the slides are coming up, just to remind the committee, per our December meeting, what I've done is, for most of the classes, the dosages and the formulations are in the appendices. Those are for your leisure to review. Usually, there's not too much clinical information there. Since this first bulk is going to be primarily diabetes related, I will go over the background and the guidelines once, out of respect for time.

Alrighty. Perfect. Okay. So, we'll jump right into the incretin mimetics enhancers, SGLT-2 inhibitors, and their combinations, as well. So, again, just to give a little bit of background on the next slide. It's estimated that roughly 30 million Americans have diabetes, of which nearly 95% are made up of type 2 diabetes. Diabetes is responsible for an increased morbidity and mortality, as one can imagine. Adequate glycemic control is crucial to minimize chronic microvascular and macrovascular. Microvascular is defined as things like blindness, renal dysfunction, and macro or things like CVD complications. Exogenous insulin supplements deficient levels of endogenous insulin and temporarily restores the ability of the body to properly utilize carbs, fats, and proteins. Multiple insulin products are available and are used as replacement therapy in management of both type 1 and type 2 when glycemic goals are not met with oral antidiabetic agents.

Jumping into some of the guidelines. The first one here is by the American Diabetes Association in 2019. The ADA standards of medical care and diabetes continue to include SGLT-2 inhibitors in the management algorithm for glycemic goals. The position statement recommends a hemoglobin A1c of less than 7%, as a reasonable target for most nonpregnant adult patients. A target A1c of 6 to 6.5% is recommended in most pregnant women. A relaxed A1c goal is recommended in some older patients, defined as 65 years of age or older, to reduce the risk of hypoglycemia, particularly in those with chronic comorbidities, cognitive impairment, and functional dependence. Based on the diabetes care decision cycle, designed to prevent complications and optimize quality of life, therapy should be individualized, based on A1c target, impact on weight and hypoglycemia, side effects, frequency and mode of administration, patient adherence, and patient preference, and cost. In terms of therapy for type 2 diabetes, the ADA guidelines state to start with metformin, unless it is

contraindicated, in patients without atherosclerotic CVD. If monotherapy with metformin at a maximum, tolerated dose does not achieve or maintain A1c target over three months, an oral agent, such as a sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonist, or basal insulin should be added. If the patient does have ASCVD, the addition of an agent with known CV risk reduction, such as empagliflozin and liraglutide is preferred. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels, such as over 300 mg/dL, or an A1c of greater than 10%, basal insulin therapy typically plus metformin with or without additional noninsulin should be considered from the beginning. If the target A1c is not achieved after three months, then the addition of a rapid acting mealtime insulin or a GLP-1 agonist, or a change to premixed insulin should be considered. Insulin therapy is the treatment of choice in type 1 patients and type 2 patients who are pregnant. In general, the ADA advised that prescribers used SGLT-2 inhibitors with caution in patients at risk for bone fracture, as well.

Continuing on with the ADA guidelines. Key revisions include for patients with type 2 who require an injectable drug. GLP-1 receptor agonist is preferred over insulin. Routine glucose self-monitoring is of limited additional benefit for patients with type 2 diabetes not on insulin. A 1-year ASCVD risk should be part of a patient's overall risk assessment. Criteria for the diagnosis of diabetes was changed to include two abnormal test results from the same sample. So, for example, two fasting plasma glucose and an A1c from that same sample. The guidelines stress the importance of diabetes care team, revision to lifestyle management recommendations, and a recommendation was added to reevaluate glycemic control targets over time. There was a new section on diabetes technology. Changes were made to alight with the ADA-EASD consensus report. Speaking of that report, so the ADA-EASD report, in 2018, a decision cycle for patients centered glycemic management of type 2 diabetes to prevent complications and optimize quality of life. It included factors that impact treatment of choice, including A1c goals, the agent's impact on weight and hypoglycemia, and its side effect profile, the frequency and mode of administration, and the probability of patient adherence. Additional focus was placed on lifestyle management and diabetes self management, education, and support.

Efforts targeting weight loss, including lifestyle, medication, and surgical interventions are recommended for those with obesity. The first injectable medication recommended was a GLP-1 receptor agonist. These guidelines recommended a patient with CVD, they should receive a SGLT-2 inhibitors, a GLP-1 receptor agonist with proven CV benefit, similar to previous guidelines. And a patient with CKD or clinical heart failure recommended a SGLT-2 inhibitors with proven benefit is recommended. If contraindicated, a GLP-1 receptor agonist shown to reduce CKD progression should be used.

On the next slide here, according to the American Academy of Clinical Endocrinologists, and the American College of Endocrinology, in 2019, in terms of glycemic goals, they recommend diabetes treatment with a goal of A1c less than or equal to 6.5%, if it can be reached without substantial hypoglycemia or other adverse effects. For patients with concurrent illness who are at risk of hypoglycemia, an A1c goal of greater than 6.5% is appropriate. In terms of treatment, antidiabetic therapy, the initial choice should be based on glycemic profile, their A1c, their bodyweight, and the presence of comorbidities. If the patient has type 2 diabetes and the A1c is less than 7.5%, they recommend starting monotherapy, preferably with metformin. Monotherapy with a thiazolidinedione or a sulfonylurea should be used with caution. Alternatives to metformin, as initial therapy include a GLP-1 receptor agonist, SGLT-2 inhibitors, DPP-4 inhibitors, and alpha glucosidase inhibitors. Patients with type 2 diabetes and an A1c greater than or equal to 7.5%, the guidelines recommended dual therapy with metformin, unless contraindicated and a second agent, which could be a GLP-1 agonist, SGLT-2 inhibitors, DPP-4 inhibitors, a TZD, or basal insulin. TZD, basal insulin, and sulfonylurea, again, should be used with caution. Patients with an A1c greater than 9 with no symptoms of hyperglycemia should be started on a maximum of two antihyperglycemic agents, and if they have an A1c of greater than 9 with symptoms, they should begin insulin therapy with our without other agents. Patients who are pregnant, they recommend the preferred treatment for postprandial hyperglycemia in pregnant women is regular or rapid acting insulin analogs and basal insulin needs can be met with the use of rapid acting insulin via infusion pump or longacting insulin. Lastly, the guidelines recommend that the A1c should be reassessed

every three months and failure to improve glycemic control may warrant additional complementary therapy for optimal glycemic control.

Continuing on with this guideline, additionally, in terms of dapagliflozin, they demonstrated reduced all-cause mortality and a composite of CV death and heart failure hospitalization. However, it did not significantly lower the combined risk of CV death in nonfatal MI and stroke. These guidelines also acknowledge the risk of initial renal impairment, hypotension, syncope, and falls due to dehydration related to increased diuresis with SGLT-2 inhibitors. In clinical trial, canaglifozin and dapagliflozin were associated with an increased incidence of bone fracture, as I mentioned earlier. Guidelines recommend stopping SGLT-2 inhibitor therapy 24 hours before scheduled surgeries and expected metabolically stressful activities, such as extreme sports. They also recommend avoiding therapy with SGLT-2 inhibitors with insulin in patients on a very low carbohydrate diet, or with excess alcohol intake.

On the next slide here, continuing with those guidelines, further insulin recommendations, again, since we're kind of going over diabetes in one haul, we'll go over insulin here, but it is later on. Insulin is required in all patients with type 1 diabetes. They advise that insulin therapy can be considered for patients with type 2 when A1c is greater than 8%, or therapy with two or more antidiabetic agents, or a GLP-1 therapy fails to achieve target glycemic control. When insulin therapy is indicated in patients with type 2 diabetes, therapy with longacting basal insulin analogs should be the initial choice in most cases. Basal insulin analogs are preferred over intermediate acting NPH insulin, because basal insulin provides a relatively flat serum, insulin level and is associated with less hypoglycemia. Rapid acting insulin is preferred over regular for postprandial hyperglycemia, because they have a more rapid onset and offset of action and result in less hypoglycemia. Basal bolus insulin therapy is flexible and is recommended for intensive insulin therapy. Pivoting over to the American College of Physicians, in 2018, they developed a statement to guide clinicians in selecting targets for pharmacologic treatments for type 2 diabetes, including recommending an A1c level between 7 and 8% in most patients. They state that clinicians should consider deintensifying therapy in patients who achieve an A1c level less than 6.5%, treat patients to minimize symptoms related

to hyperglycemia, and avoid targeting an A1c level in patients with a life expectancy of less than ten years, due to advanced age, because the harms outweigh the benefits in that population. Lastly, according to the World Health Organization in 2018, they released guidelines for the treatment intensification in patients with type 2 diabetes. They recommend introduction of human insulin in patients with type 2 diabetes who do not achieve glycemic control with metformin and/or a sulfonylurea in adults with type 1 or adults with type 2 where insulin is indicated. Human insulin should be used to manage blood glucose. Longacting insulin analog should be considered for type 1, or adults with type 2 who experience frequent severe hypoglycemia with human insulin. Lastly, they recommend the addition of a DPP-4 inhibitor, a SGLT-2 inhibitor, or a thiazolidinedione if insulin is unsuitable in patients with type 2 diabetes who do not achieve glycemic control with metformin and/or sulfonylurea.

Now, moving over to the medications. As you can see, the indications are stratified. We have amylin analogue, Symlin. We have DPP-4 enzyme inhibitors with their respective indications. I was gonna go over the mechanism of action, but our colleague from DERP kind of went over it in a much more articulate way than I would have. So, I'm just gonna skip over the MOA again.

In terms of going to the next slide here, we have our finals, the GLP-1 receptor agonists along with their respective indications, as well. To pause on this slide here for one second, please note that there is a REMS requirement for Trulicity, Byetta, and Victoza, along with liraglutide and insulin degludec combo. It was eliminated, since the FDA determined the program goals were met. Medication guides were maintained for all incretin mimetic agents, regardless of REMS requirement. Keep in mind that the REMS requirement for Symlin was also eliminated, as well. In terms of patients who are pregnant, Symlin and Victoza are pregnancy category C. Otherwise, Glyxambi, Qtern, Steglujan, are not recommended during the second and third trimester of pregnancy based on animal data. A pregnancy registry exists to monitor pregnancy outcome in women exposed to sitagliptin containing products during pregnancy.

Going over here to the next slide, there were some studies that evaluated the impact of SGLT-2 inhibitors on macrovascular, cardiovascular outcomes, and included the EMPA-reg outcome and the Canvas/Canvas-R. The EMPA-reg outcome trial reported approximately a one-third relative risk reduction for cardiovascular death, hospitalization due to heart failure, and an all cause death with use of Jardiance, as compared to placebo. The Canvas and the Canvas-R trials demonstrated a 14% risk reduction in first occurrence of major adverse cardiovascular event in patients with type 2 diabetes treated with Invokana. Lastly, the Declare-TIMI trial, dapagliflozin did not result in a lower rate of a major adverse cardiovascular event compared to placebo. However, it did lead to a lower incidence of heart failure related hospitalizations.

Moving onward over here to the SGLT-2 inhibitors, FDA MedWatch in 2018, there was a new MedWatch where FDA's warning that cases of necrotizing fascitis of the perineum have been reported with SGLT-2 inhibitors based on the results of a case series between March 2013 and May 2018, 12 cases of Fournier's gangrene were found in patients taking an SGLT-2 inhibitor, resulting in significant medical care needed and one death. A new warning will be added to the PI of all SGLT-2 inhibitors regarding this risk, and healthcare practitioners should assess patients of Fournier's gangrene, if they present with symptoms consistent with this diagnosis. Patients should be treated accordingly immediately. Please keep a note, there is a black box warning for canaglifozin containing products. So, these are Invokana, Invokamet, and Invokamet XR. In patients with type 2 diabetes who have established CVD or are at risk for CVD, canaglifozin has been associated with lower limb amputations, most frequently of the toe and midfoot. Some also involved in the leg. Before initiating, consider factors that may increase the risk of amputation, and monitor patients receiving this medication for infections or ulcers of the lower limb and discontinue if these occur.

On the next slide here, we have our SGLT-2's with their respective indications. In terms of pediatrics, the safety and efficacy has not been determined in patients under the age of 18. For patients who are pregnant, Invokana, Invokamet, Farxiga, Xigduo XR, Jardiance, Synjardy XR are pregnancy category C, as in Charlie. For patients who have renal impairment, the safety and efficacy of SGLT-2 inhibitors have not been

studied in patients with severe renal impairment, ESRD, or patients in dialysis. Any questions?

Virginia Buccola: Thank you, Umang. I appreciate that. We're going to go ahead and move to stakeholder input. We have five stakeholders, Dr. Anthony Hoovler, Dr. Bob Fell, Dr. Anthony Wheeler, Greg Sellman, and Mae Kwong. So, if Dr. Anthony Hoovler could step up. Thank you. So, step the podium. If you could state your name and your affiliation, and you'll have three minutes to speak. Thank you.

Anthony Hoovler: Can you guys hear me? Okay. So, good morning. My name is Anthony Hoovler. I'm an endocrinologist and senior medical liaison with Novo Nordisk. Today, I would like to share some highlights with you regarding Ozempic, including a very important and timely label update. Ozempic is a once weekly GLP-1 receptor agonist first approved in December of 2017, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. However, just last month, the FDA approved a label expansion for Ozempic for the indication of reducing the risk of major adverse cardiovascular events, including cardiovascular death, nonfatal MI, nonfatal stroke in adults with type 2 diabetes with established cardiovascular disease. The label expansion is based on a sustained six cardiovascular outcomes trial of 3297 adults with type 2 diabetes and established CV disease, or high risk of CV event. The trial demonstrated that Ozempic, statistically significantly reduced the risk of CV death, nonfatal MI, or nonfatal stroke by 26% versus placebo when added to standard of care in people with type 2 diabetes and increased CV risk. Ozempic is the only once weekly GLP-1 receptor agonist approved for CV event reduction. The safety and efficacy of Ozempic has been established in a sustained clinical trial program, which enrolled more than 8000 adults with type 2 diabetes, six phase 3A studies sustained one through six. Those six studies are all in the label. There is also one phase 3B study, sustain 7, which is consistent with the label. Regarding efficacy, A1c reductions, 1.4 to 1.8% were achieved with the Ozempic 1 mg dose, and while not indicated for weight loss, weight effect was a secondary endpoint in the sustained clinical trial program and mean weight loss of 10 to 14 pounds over 30 to 56 weeks was noted with the 1 mg Ozempic dose. Two head-to-head trials comparing Ozempic to other once-weekly GLP-1's have been published. Sustain three compared

Ozempic to Bydureon, and sustain seven compared Ozempic to Trulicity. Both trials demonstrated that therapy with Ozempic resulted in greater A1c reductions, a greater percentage of patients achieving A1c targets, and greater weight loss versus both comparators. With respect to safety, there is a boxed warning with Ozempic regarding potential risk of thyroid C-cell tumors and as such, patients with a personal or family history of MTC, and patients with [inaudible] should not use Ozempic. I would refer you to the PI for additional safety information. So, with the data presented, including two head-to-head trials against other once weekly GLP-1 receptor agonists, and a recent very time-appropriate label expansion, which makes Ozempic the only once weekly GLP-1 receptor agonist approved for CV event reduction, I would respectfully request that you add Ozempic to the PDL. Thank you, and I am happy to answer any questions.

Virginia Buccola: Thank you, Dr. Hoovler. Next up is Dr. Bob Fell.

Leta Evaskus: I'm just going to make sure that's on. 'Cuz, I didn't see it lighting up red.

Bob Fell: Good morning. My name is Bob Fell, pharmacist with Sanofi 20 years. The average lifespan of an MSL is about three years. I'm not sure what that says, but I've been around a long time. Prior to that, I noticed on some laptops here, there are some micromedics on your display there. I worked at Micromedics as a senior editor. So, what I appreciate from this committee is how much effort it takes to review. Living in a cave writing monographs that are published in 126 countries takes a lot of work. What I'm looking on my iPad right now is a clock. It's the only thing I'm looking at, but I'm going to represent to you here now in the two and a half minutes is a class, which you actually indirectly talked about in the ADA guidelines, and that is fixed ratio combinations. Currently, there are two products on the market for fixed ratio combination products. What that means is a combination of a basal insulin and a GLP-1 receptor antagonist. Soliqua is the product that Sanofi carries. What's really critically important to understand, and I... looking at the approximate number of folks in this room, about five of you have type 2 diabetes, it's very difficult to get A1c below 7. It's very difficult. At some point in the guidelines, as you appropriately pointed out, is there is a particular situation when the guidelines, according to the ADA and EASD suggest a

fixed ratio combination. Now, you can go sequentially or simultaneous. The benefit of fixed ratio combination like Soliqua, for example, it covers about 85 to 90% of the type 2 defects that are occurring in these patients at the same time. The advantage of having one injection, when it's appropriate, and according to the guidelines where it sticks out is a patient with type 2 diabetes, the A1c is over 10. Or a difference in adults who have an A1c of two percentage points above their goal. It is the only class of injectable agents that can get a patient whose A1c is over 9% below 7%. It's the only product that can do that as a class. Advantages to the patient, and I have 45 seconds left, single injection. One of the issues around GLP-1 receptor antagonists is, of course, the GI toxicity. It effects persistency, and usually with a fixed combination product, like, Soliqua, you cut down the GI adverse events by two-thirds, a single injection, and it addresses all the major defects, except for kidney, which you're reviewing here, in a fixed ratio combination product. Lastly, I just want to point out, and I'll address any questions, I appreciate the CVOT review. I'm not addressing that here. I just want to point out that there is a cardiologist out of UT Southwestern, Darren Maguire, who has published two very important reviews in circulation. Also, an editorial on CVOT outcomes by an FDA ad com person, Cecilia Lawang. Excellent review, published last year. Any questions on Soliqua or the approach with a fixed ratio combination product? This stuff is not really long, but I appreciate your attention. Go ahead.

Virginia Buccola: No, just going to say thank you, very much. I appreciate it. Yeah.

Bob Fell: My pleasure. Thank you for your time and attention. We ask that you consider this class of agent and consider the use of Soliqua.

Virginia Buccola: Thank you. Next is Dr. Anthony Wheeler. Dr. Wheeler, when you come to the podium, if you could state your affiliation. You'll have three minutes.

Anthony Wheeler: Alright. Thank you. I am Anthony Wheeler. I am an employee of Eli Lilly and Company, which manufacturers Trulicity. This is part of the GLP-1 receptor agonist class. It's indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. This is administered once a week. It's a subcutaneous injection. It's delivered

using a single dose auto-injector pen. There's no mixing or reconstitution necessary to use it. It has a hidden preattached needle. I know you've reviewed this drug before. So, I just want to provide two quick research updates for you, since your last review. First is the completion of the Rewind study. This is a large scale cardiovascular outcomes trial where Trulicity showed superiority to placebo on a three-point composite of major adverse cardiac events. The other update was the continuation of a real world evidence study that we previously conducted, but now it's been extended to a year of data. It's showed patients initiating Trulicity had significantly higher adherence and lower discontinuation than those initiating Bydureon or Victoza. Thanks for letting me provide the update. I'm happy to try to answer any questions you have. Thanks.

Virginia Buccola: Thank you, Dr. Wheeler. Next is Greg Sellman. As a reminder, when you come to the podium, if you could let us know who you're with. You'll have three minutes.

Greg Sellman: Thank you. Good morning. My name is Greg Sellman. I am the Boehringer Ingelheim diabetes business manager for the Northwest. I'm here today to say a few words about Jardiance or empagliflozin. Jardiance is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Jardiance is also indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes and establish cardiovascular disease. Jardiance is the only SGLT-2 inhibitor indicated to reduce the risk of CV death in patients with type 2 diabetes and establish CV disease. And it is the most prescribed SGLT-2 inhibitor in the United States. This indication is based on the findings of the landmark EMPA-reg trial published in 2015 in the New England Journal of Medicine in the significant reduction of three-point MACE, particularly the 38% relative risk reduction in CV death. The most common adverse events for Jardiance have been UTIs and genital mycotic infections. Contraindications include severe renal impairment, end stage renal disease, and dialysis. Jardiance is part of the empagliflozin family, which also includes Synjardy and Synjardy XR, which are combination products of empagliflozin and metformin, as well as glixambi, which is a combination product of empagliflozin and Tradgenta or linagliptin. Jardiance is recommended as part of the SGLT-2 inhibitor class by the 2020 American Diabetes Associated standards of care and

also the American College of Cardiology expert consensus decision pathway to reduce the risk of CV death in adults with type 2 diabetes and established cardiovascular disease. So, we're here requesting that Jardiance or empagliflozin remain on the State of Washington PDL second line choice after metformin. Today, I have with me our medical scientific liaison, John Beatty, if there are any question that you could have. Thank you.

Virginia Buccola: Thank you, very much. Mae Kwong is up next.

Mae Kwong: Good morning. My name is Mae Kwong. I am with Johnson scientific affairs. Invokana is an SGLT-2 inhibitor indicated for glycemic control in adults with type 2 diabetes and also to reduce the risk of three-point [inaudible] events, including cardiovascular death, nonfatal MI, and nonfatal stroke in adults with type 2 diabetes and established cardiovascular disease. In September of last year, Invokana received approval to reduce the risk of endstage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria making Invokana the only SGLT-2 inhibitor approved to protect the kidneys. There has been no medications approved in 17 years to protect the kidneys, since ACEs and ARBs. So, I think this is an important addition to treat patients with type 2 diabetes. The newest indication is based on the data from the Credence trial, which was published in the New England Journal of Medicine. Credence enrolled over 4400 type 2 diabetes patients with stage 2/3 chronic kidney disease and albuminuria to evaluate whether Invokana 100 mg would have a renal and/or cardiovascular protective effect compared to placebo. Patients in both arms were also receiving standard of care, including ACEs and ARBs, antihypertensives, as well as antihyperlipidemic therapy. The Credence trial was stopped early based on the achievement of prespecified efficacy criteria. Invokana significantly reduced the risk of the primary composite outcome of endstage kidney disease, doubling of serum creatinine, and renal or cardiovascular death by 30%. The impact of Credence is transformational to clinical practice. Investigators estimated that if 1000 patients were treated for 2.5 years, only 22 patients need to be treated with Invokana to prevent endstage kidney disease, doubling of serum creatinine, or renal or cardiac death. In addition, among the same 1000

patients, Invokana treatment would prevent 22 hospitalizations for heart failure and 25 composite MACE events. Regarding safety, rates of overall adverse events were similar with canaglifozin and placebo, except for diabetic ketoacidosis and genital mycotic infections. I am pleased to report there was no imbalance in rates of fracture or amputation. The overall safety profile was otherwise consistent with known adverse effects associated with Invokana. On June 3rd, the ADA issued an update highlighting the efficacy and safety endpoints of Credence. This update elevates the recommendation of SGLT-2 inhibitors over GLP-1 in type 2 diabetes patients with chronic kidney disease and states that renal effects should be considered when selecting antihyperglycemic agents. Given that Invokana is the only type 2 diabetes medication that has demonstrated a significant renal and cardiovascular benefit in patients with diabetic kidney disease and type 2 diabetes, we thank the committee for keeping Invokana on the PDL and making Invokana available to Washington Medicaid patients. Thank you.

Virginia Buccola: Thank you, very much. So, we're gonna move to our motion. We're going to look at the P&T motion right now. Then, afterwards when we convene the DUR, we'll look at the same classes.

Ryan Pistoresi: So, this is for the Washington PDL.

Virginia Buccola: Thank you.

Ryan Pistoresi: So, just a reminder. So, since this was a report and kind of like a supplemental report, really, this focused in on the cardiovascular data only and not really on the diabetes. There's the no scan as adequate as what's shown in the motion. So, really, you're just looking at reiterating the prior motion or changing the motion if you so decide.

Virginia Buccola: Thank you.

Jordan Storhaug: I move that we reiterate the prior motion.

Susan Flatebo: I second.

Virginia Buccola: All those in favor, say aye.

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries.

Diane Schwilke: I move to reiterate the prior motion for the DPP-4 inhibitor class.

Female: Second.

Virginia Buccola: All those in favor, say aye.

Group: Aye.

Virginia Buccola: All those opposed? The motion carries. So, we're going to adjourn the P&T…

Donna Sullivan: One more.

Virginia Buccola: ...oh, sorry. Delete that. I missed it. There it is. Thank you.

Susan Flatebo: I make a motion that we reiterate the prior motion for the GLP-1 agonists.

Alexander Park: I second.

Virginia Buccola: All in favor, say aye.

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We can adjourn the P&T portion of the meeting. I would propose a five-minute break. Then, we'll come back and head into DUR? Okay.

Donna Sullivan: Sounds good.

Umang Patel: Just to recap, since it is relatively short, they recommend introduction of human insulin in patients with type 2 diabetes who do not achieve glycemic control with metformin and/or sulfonylurea. They also

recommend insulin in patients with type 1 diabetes or adults with type 2 whom insulin is indicated. Human insulin should be used to manage blood glucose, longacting insulin analog should be considered for type 1 or adults with type 2 who experience frequent severe hypoglycemia with human insulin.

Pivoting right along to the list of insulin medications. They are stratified by, as I'm sure most of the committee knows, their duration and onset. So, we have rapid acting insulin, which we have Afrezza, Fiasp, Novolog, Apidra, Admelog, Humalog, and Humalog Junior. For regular insulin, we have Humulin R and Novolin R. For intermediate insulin, we have NPH, Humulin N. Longacting, we have Tresiba, Levemir, Basaglar, Lantus, and Toujeo. Then, we have combinations. So, we have a rapid and intermediate acting combination of Novolog mix of 70/30, and a Humalog mix of 50/50 or 75/25. Lastly, the regular intermediate acting combinations of Humulin 70/30 or Novolin 70/30 and their respective indications. So just to stay on this slide a little bit to give a little bit of background, in terms of mechanism of action, I'm sure most of the committee knows, but insulin is secreted by the pancreatic beta cells. It lowers blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat. It inhibits gluconeogenesis. It also inhibits lipolysis in the adipocytes. It inhibits proteolysis and enhances protein synthesis. In terms of pregnancy, available data from published studies over decades have not established an associated between the use of human insulin during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. Notably, tere are risk to the mother and fetus associated with poorly controlled diabetes during pregnancy. In terms of renal impairment, renally impaired patients are subject to increased levels of circulating insulin, as one can imagine. It can increase hypoglycemia. Therefore, more frequent insulin dose adjustments may be warranted. For hepatic impairment due to increased risk of hypoglycemia, more frequent dose adjustment and blood glucose monitoring may be needed. Lastly, in terms of a REMS requirement, there was a REMS requirement for Afrezza, but that was eliminated in April of 2018. Again, the dosing and availabilities are all in the appendices, in case anyone in the committee wanted to take a look.

Moving along here. So, we have an FDA statement just from December 2019. They published this statement regarding the pathway for approval of a chemically synthesized polypeptide. In March 2020, the majority of protein products, including all current insulin products, will have the potential for biosimilar and interchangeable products to increase competition through FDA approval under abbreviated pathways. However, products that are deemed 'chemically synthesized' polypeptides are not eligible for the abbreviated approval pathways utilized for biosimilars and interchangeable products. The statement addresses how removal of this exclusion would allow for chemically synthesized follow on insulins and other products to become approved through abbreviated pathways, as well. For the FDA safety communication in September 2019, they issued a safety communication regarding the use of pen needles when injecting medicine. The FDA received reports of patients using standard pen needles to administer insulin without removing the inner needle cover. So, the safety communication was put out resulting in the insulin not being injected and a result of hyperglycemia. This included one case that resulted in hospitalization and subsequent death. The FDA advised healthcare practitioners to instruct patients on the proper use of pen needles for medication delivery and insure that the patient can demonstrate proper technique at the time of dispensing. Healthcare practitioners should remind patients of the type of pen needles and how to use it. The final FDA safety communication was in May of 2019 regarding the use of devices for diabetes management that are unauthorized for sale in the U.S., devices that are unauthorized, have not received FDA review and approval to assure their safety and efficacy. As a result, use of these devices could lead to incorrect blood glucose level measurements and/or an improper dose of insulin, which could result in serious or potentially life-threatening medical complications. Combining devices not appropriate for use with other devices should also be avoided. Lastly, the FDA recommends that patients only use diabetes management devices that have received authorization from the FDA for sale in the U.S. Any questions regarding insulin?

Leta Evaskus: So, let's do... if there's any stakeholders before the motions.

Virginia Buccola: There is one stakeholder. It's Dr. Bob Fell. Would you come to the podium, please? You'll have three minutes.

Bob Fell: Thank you for the invite back. I just went on the CDC website. So, diabetes, we're all here for a real important reason. It's number six for mortality. Number six, diabetes. So, we all have a common goal here. Number four is accidents. So, be careful driving home is the way I would put that. So, we just talked about fixed ratio combinations. I'm going to transition here to longacting second generation insulin. So, Soliqua, for example, approved after diet and exercise and lots of data on patients that have failed oral agents. We're kind of talking about a second generation insulin, and that's Toujeo. We talked about NPH. That's been out, since 1945. NPH went unabated 55 years until a product we all know as Lantus, which significantly changed the landscape for diabetes. Then, a few years went by. The advantage, obviously, with Lantus was improved kinetics, less hypo, but we still have issues with first-generation basal insulins. Toujeo was a significant improvement on Lantus. Think of it as Lantus but a much improved molecule. The other thing I saw was a subtle difference in the slide that you just showed on all the insulin categories is, like Lantus, Toujeo is approved in pediatrics. That's a new update to the label and something to consider now so we have a broader population. What patients really care about, by the way, it's kind of a board test, a very common adverse event in insulin, and PI is nasal pharyngitis, completely unrelated. So, it's contextualizing the label, but hypos. That's the number one concern that patients have. As you improve the insulin, going from first to now second generation basal insulins, you improve the hypoglycemic risk in these patients. It's really critical, as we start basal insulin. This is why patients get off the insulin is because of hypos. Toujeo significantly improves that over the first generation class. With 52 seconds left, I would love to entertain any comments or questions. There's got to be one. I appreciate your time and attention.

Virginia Buccola: Thank you, Dr. Fell. So, we'll move to the motion. So, we have two for this section, it looks like, insulin and related agents. The first one is here for antidiabetics.

Constance Nguyen: I move that all products in the drug classes listed on slide 19 are considered safe and efficacious for the medically accepted indications and are eligible for preferred status and grandfathering at the discretion of the HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Alexander Park: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We'll move to the next motion then for insulin. All the drugs listed on slide 22.

Jordan Storhaug: I move that all products in the drug classes listed on slide 22 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of the HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Susan Flatebo: I second.

Virginia Buccola: All in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. The third motion for this section is the SGLT-2 inhibitors. So, we'll be looking at which slide?

Donna Sullivan: This one did not have a slide.

Virginia Buccola: Okay. Thank you.

Susan Flatebo: I move that all products in the antidiabetics SGLT-2 inhibitors drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Constance Huynh: I second.

Virginia Buccola: All in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. I just wanted to clarify a minute, before we moved on to the next topic. Were there any stakeholders for SGLT-2 inhibitors? Those were done during the P&T right before. Thanks.

Virginia Buccola: Okay. Thank you.

Umang Patel: Okay. Moving right along to thiazolidinediones or TZDs. We'll jump right into the list of medications that comprise this TCR. So, we have pioglitazone, or Actos, and rosiglitazone, or Avandia. Then, we have combinations, so TZD and glimepiride, which is pioglitazone/glimepiride. We have pioglitazone metformin with Actoplus Met and Actoplus Met XR and their respective indications here. While we stay on this slide, just to give a little bit of background here. So, how thiazolidinediones work is, they bind and activate the PPAR gamma in the skeletal muscles. The adipose tissues in the liver, and that results in improved insulin action by enhancing the sensitivity of the peripheral muscle, glucose uptake, and possibly reducing hepato glucose productions. The TZDs require the presence of insulin to exert their antihyperglycemic effects. In terms of this class, I'm sure many of the committee has heard, side effects with these medications. I do want to clarify some of those. There was a REMS program for both pioglitazone and rosiglitazone containing products, but

that has been eliminated. There are still medication guides that are still maintained as part of an approved labeling. In terms of edema and congestive heart failure, TZD should be used with caution in patients with edema. Edema was reported more frequently in patients treated with pioglitazone or rosiglitazone and then placebo, and it appears to be dose related. Lastly, there is a black box warning. Thiazolidinedione containing products carry the warning regarding a development or exacerbation of congestive heart failure in some patients. In terms of pregnancy, all rosiglitazone containing products are category C. For pediatrics, the safety and efficacy has not been established for Actos or Avandia, or their combined products, in pediatric patients.

Then moving right along to the next slide here. The FDA safety communication for the bladder cancer risk, in 2016, the FDA issued an updated safety communication concluding that all pioglitazone containing products may be linked to an increased risk of bladder cancer. This is a followup to the initial announcement in 2010 that reported a possible increased risk of bladder cancer when used for over one year. The FDA urged patients taking pioglitazone to contact the medical professional if they experience signs or symptoms associated with bladder cancer, such as blood in the urine or pain while urinating. Also, in 2016, the results of an observational cohort study of over 145,000 patients initiated on antidiabetic medications over a 13-year period suggest that the risk of bladder cancer increases with duration of time and the amount or dose of pioglitazone. However, an increased risk of bladder cancer was not associated with the rosiglitazone use. Consequently, use of pioglitazone is not recommended in patients with active bladder cancer and should be used with caution in those with a prior history of bladder cancer, considering the benefits of glycemic control versus unknown risks of cancer recurrence. Since there was no background in guidelines, since we covered it, this is somewhat of a short TCR. Any questions?

Virginia Buccola: Thanks Umang. There are no stakeholders for the TZDs. So, we'll move right to the motion.

Alexander Park: I move that all products in the antidiabetics thiazolidinediones drug class are considered safe and efficacious for their medically accepted

indications and are eligible for preferred status and grandfathering at the discretion of the HCA. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Constance Huynh: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We will move to pancreatic enzymes.

Umang Patel: Alrighty. Moving right along, so the pancreas, the exocrine functions of the pancreas include the secretion of pancreatic enzymes necessary for digestion. The secretions also neutralize gastric acid in the duodenum and achieve an appropriate pH for maintaining the activity of the enzymes. When this pancreatic function is lost, supplementation of the pancreatic enzyme is needed. Conditions such as cystic fibrosis, chronic pancreatitis, pancreatic tumors, and absence of all or a part of the pancreas are associated with the lack of pancreatic enzyme in the body. In terms of cystic fibrosis, reduced pancreatic enzyme affects occur due to thickened secretions in the GI tract, specifically the pancreas. Pancreatic enzymes are unable to move into the duodenum, leading to malabsorption of nutrients and malnutrition. This is the main cause of poor growth, fatty diarrhea, and deficiency in fat soluble vitamins in this population. In terms of pancreatic enzymes, supplemental pancreatic enzymes are available in a variety of formulations and strengths. All formulations are measured by their content of amylase, lipase, and protease. In order to avoid gastric inactivation, enteric coating and buffering may be used to deliver enzymes to the intestine. Historically, pancreatic enzyme products were available over the counter. However, due to reports of problems associated with their use, such as intestinal stricture and lack of therapeutic effect, the FDA announced that all exocrine pancreatic insufficiency drug products are new drugs and announced the conditions for continued marketing of these drug products.

Moving right along to the indications. Again, more information is in the appendices. The medications on the next two slides, as I said, are stratified by their product name and their units of amylase, lipase, and protease. Again, the indication is all the same. So, there is no indication column here. Going right along to the next slide, to give information in terms of patients who are pregnant, all these medications are pregnancy category C. Since there are no major guidelines or anything to review here, it's a relatively short TCR. Any questions?

Virginia Buccola: Thanks, Umang. We have two stakeholders, Dr. Margaret Olmon and Dr. Meredith Manville.

Margaret Olmon: Hello. I'm Dr. Margaret Olmon with Global Medical Affairs with Abbvie. I want to thank you for the opportunity today to speak with you about Creon. Please review the full prescribing information at rxabbvie.com for comprehensive safety and efficacy data. Creon is available in 3000, 6000, 12,000, 24,000, and 36,000 lipase unit strengths for dosing flexibility. Today, I will share with you two key points for your consideration. Creon is an FDA approved delayed release pancreatic enzyme indicated for the treatment of exocrine pancreatic insufficiency or EPI due to cystic fibrosis, chronic pancreatitis, and pancreatectomy, and other conditions. Two pivotal studies in adults and children with EPI due to cystic fibrosis and one in adults with EPI due to chronic pancreatitis and pancreatectomy, evaluated the efficacy and safety of Creon. The primary efficacy endpoint was the mean difference in the coefficient of fat absorption between Creon and placebo. Statistically significant higher values were seen with Creon compared to placebo in all three studies with no difference in response by age or gender. Creon is not interchangeable with any other currently approved pancrelipase product and product substitution is not recommended. These pivotal studies also evaluated Creon safety, GI complaints, cough, dizziness, and headache were the most commonly reported adverse events. Fibrosing colonopathy, a rare serious event reaction, has been reported in patients with cystic fibrosis taking high doses of pancreatic enzyme replacement therapy. Caution should be exercised when taken by patients with gout, renal impairment, hyperuricemia, and with known pork allergies. Care should also be taken to ensure that Creon is not chewed, retained in the

mouth, or mixed with food with a pH of greater than 4 to avoid inner irritation of the oral mucosa. In patients unable to swallow capsules, the contents may be sprinkled on applesauce to be eaten. Creon should be initiated at the lowest recommended dose and gradually increased. In summary, I'd like to respectfully request that Creon remain as a preferred medication for Medicaid patients in Washington. Thank you for your time and consideration, and I'd be happy to answer any questions you might have.

Virginia Buccola: Thank you, Dr. Olmon. Dr. Meredith Manville is up next.

Meredith Manville: Hi. My name is Meredith Manville. I'm a pharmacist from Seattle Children's Hospital in the cystic fibrosis center. So, thank you, so much, for letting me come today to speak to the committee. I'm just gonna read a letter that we've composed with our parent advisory committee. So, a lot of the statements that I'm reading are quotations from our parents and from our patients. So, mucus obstruction in CF, as previously stated, can prevent the pancreas from releasing critical enzymes to digest fat and cause malnutrition. Starting pancreatic enzymes and fat soluble multivitamin products as soon as patients are diagnosed can optimize early aid nutrition and overall health outcomes. Washington State has invested in newborn screening for CF since 2006, and most infants are diagnosed at birth. Washington State in 2019 incorporated testing for common DNA variants, as part of newborn screening for CF. We anticipate these changes will lead to earlier diagnoses and increased opportunity to start patients and maintain necessary enzymes and CF agents, such as fat soluble vitamins and pancreatic enzymes. So, quotation from one of the parents, my son was diagnosed with CF six days after birth. His weight was rapidly decreasing, and our pediatrician was very worried he would require hospitalization. Once we were able to get him onto the correct amount of enzymes, he gained weight back right away. Children with CF struggle with weight gain, because their pancreas can't release enzymes that are needed to digest fat. By taking these enzymes with every meal, we've been able to reach the 70th percentile weight for age. So, our advocacy is, we're asking for our center, we would like for all pancreatic enzymes to be placed on formulary due to the inter-patient differentiation between our patient populations. We have certain patients that are unable to take medications orally. So, we

have a lot of patients that are tube fed. So, we're asking that all the available FDA recommended pancreatic enzymes are added to formulary. Thank you, so much. I'm available for questions.

Virginia Buccola: Thank you, very much. So, we will move to the motion for digestive aids, pancreatic enzymes.

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

Diane Schwilke: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We'll move now to growth hormone and growth factors.

Umang Patel: For this one, Magellan has growth hormones and growth factors as two separate TCR buckets. So, what I'll do is, I'll break them out. First, we'll go over growth hormones. Then, I'll jump into growth factors and then the motions. So, first, growth hormones. Growth hormone deficiency, or GHD moving forward, results from inadequate production of growth hormone and can produce various medical conditions, depending on age. Adults with GHD may have diminished lean body mass, poor bone density in a number of physical and psychological manifestations. It can be congenital or acquired in childhood or adult life, in addition to be partial or complete. The condition is usually permanent and may be an isolated deficiency or occur in association with deficiency of other pituitary hormones. In most cases, the diagnosis of GHD should be based on results from two provocative tests, as recommended by the pediatric endocrine society. The 2009 American Associated of Clinical

Endocrinologists Guidelines for Clinical Practice indicate no evidence exists to support any specific growth hormone product over another. Another disease background here is. Moving forward, it will be PWS. It is a genetic disorder in which several genes on chromosome 15 are missing or unexpressed on the paternal chromosome. It is characterized by hyperphagia and food preoccupations, as well as small stature and mental retardation. The major manifestations of PWS are neurobehavioral and endocrine abnormalities, hypothalamic obesity, hypotonia, short stature, developmental delays, and aspects of hypothalamic endocrine dysfunctions in pubertal delay or absence. In some cases, the impaired GH secretion, which can persist into adulthood, may be the result of hypothalamic dysfunction. Daily growth hormone injections support linear growth, increase muscle mass, and may lessen food preoccupation and weight gain in patients with PWS.

Moving onward, chronic renal insufficiency, so children with CRI may have difficulty attaining a normal height and weight for several reasons, including malnutrition, renal osteodystrophy, electrolyte, calcium, and vitamin D imbalances, inadequate use of protein by the body, and abnormalities in the growth hormone insulin like growth factor axis. Babies born small for gestational age, or SGA, are defined as babies with birth weights that fall below the 10^{th} percentile for their gestational age. Typically, intrauterine growth retardation is the causative factor. Although the majority of these children catch up in height to normal range during the first two years of life, approximately 10% of SGA children fail to exhibit catch up growth by age 2 years. Growth hormone levels in these children may be lower within normal range, and decreased growth may be due to insensitivity to growth hormone, as well as low IGF-1 levels. It is thought that administering exogenous growth hormone may overcome the growth hormone insensitivity. Lastly, we have short stature homeobox gene, or SHOX. A gene on the X and Y chromosomes that control the formation of many body structures, including the growth in maturation of bones in the arms and legs. Patients with this deficiency, which is a gene mutation, were present in only copy, may present with a broad phenotypic spectrum ranging from isolated short stature with no distinguishing clinical features to short stature with moderate to severe skeletal dysplasia. Approximately 1 to 4% with

clinical features consistent with idiopathic short stature may test positive for this SHOX deficiency.

Next, we have Turner Syndrome, or TS, in patients with TS female sexual characteristics are present but are underdeveloped due to several chromosomal abnormalities. At least 95% of all patients with TS have short stature. Short stature in patients with TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, and growth failure during childhood and adolescence. These factors lead to a diminished final height, which can be positively affected by growth hormone therapy. Next, we have idiopathic short stature. It's a condition in which the height of an individual is more than a two standard deviation score below the corresponding mean height for a given age, gender, and population group without evidence of systemic endocrine, nutritional, or chromosomal abnormality. The pediatric endocrine society identifies ISS as height standard deviation score less than or equal to -2.25 with a predicted height less than the normal range, which is 63" in men and 59" in women. Specifically, children with ISS have normal birthweight and are growth hormone sufficient.

Next, for short bowel syndrome, SBS, it's a malabsorption disorder caused by either the surgical removal of the small intestines, or the loss of its absorptive function, due to various diseases. Intestinal mucosa contains receptors for growth hormone, and for IGF-1, which is known to mediate many of the cellular actions of growth hormone. In human clinical studies, the administration of growth hormone enhanced the transmucosal transport of water, electrolytes, and nutrients. Zorbtive is indicated for the treatment of SBS in patients receiving specialized nutritional support. The final disease state, we have Noonan Syndrome. It's a congenital disorder that includes heart malformation, short stature, indentation of the chest, learning disabilities, impaired blood clotting, and a certain configuration of facial features. Short stature is present in as many as 80% of patients. Growth hormone has been used successfully to correct short stature associated with the disorder.

Moving onto the next slide, there is a variety of disease states here. The reason we went over that is, these medications here on this next slide are

stratified by their subsequent indication, again GHD, Turner Syndrome, SGA, ISS, and others. That includes Prader-Willi Syndrome, SHOX, and Noonan Syndrome, as well, along with Serostim having an HIV wasting or cachexia to increase lean body mass and weight, and improved physical endurance. Just a little more information on these for other populations, in terms of pregnancy, humatrope, nutropin A1-P1 NuSpin, and norditropin are all pregnancy category C. In terms of hepatic function impairment or reduction in recombinant human growth hormone clearance has been noted in patients with severe liver dysfunction. The clinical significance of this decrease is unknown. For renal hepatic function, excuse me. For renal function impairment, patients with chronic renal failure may experience a decreased clearance compared to patients with normal renal function, and dose adjustment may be required. Again, the dosing and availability for all of this is available in the appendices for the committee, as well. Any questions before pivoting over to growth factors? Okay.

Moving right along to growth factors, so for growth factor, growth hormone and sensitivity or insulin-like growth factor IGF-1 deficiency refers to a variety of disorders characterized by the resistance to growth hormone. Growth hormone insensitivity can be defined by deficiency in the production of growth hormone or peripheral action of IGF-1 on linear growth. Severe primary IGF-1 deficiency is due to a mutation of the growth hormone receptor or post-growth hormone receptor signalling. Severe primary IGF-1 deficiency is also characterized by the development of growth hormone inactivating antibodies in pediatric patients with growth hormone gene deletion. Patients are considered to have severe primary IGF-1 deficiency when the following criteria is met: Height standard deviation score is less than or equal to -3, basal IGF-1 standard deviation is less than or equal to -3, and normal or elevated growth hormone. Moving over to HIV lipodystrophy. Soon after combination antiretroviral therapy was found effective in treating HIV infected patients. Adverse side effects from the medications reported, including metabolic changes, morphological abnormalities, and lipodystrophy. HIV lipodystrophy is found in patients on highly active antiretroviral therapy. Patients with HIV lipodystrophy were described as having a loss of subcutaneous fat in limbs, face, and buttocks, and an accumulation of fat in other areas of the body, including the abdominal viscera. Patients who

have increased visceral abdominal fat and waist circumference are at an increased risk for metabolic syndrome, cardiovascular disease, atherosclerosis, and diabetes.

Moving right along to the indications. I also put the dosing availability here, since it's two medications. You can see the two medications, Increlex and Egrifta. Both are indicated. Their subsequent indications, treatment for growth failure in children with severe primary IGF-1 deficiency or with growth hormone, gene deletion who have developed neutralizing antibodies to growth hormone. That's for Increlex. For Egrifta, growth hormone releasing factor analog indicated for the reduction of excess abdominal fat in HIV infected patients with lipodystrophy.

Moving on to the next slide here. In terms of guidelines, so the severe IGF-1 deficiency growth hormone gene deletion, Increlex is the only available product approved for indication of longterm treatment of growth failure in pediatric patients with severe primary IGF-1 deficiency, or with growth hormone gene deletion with development of neutralizing antibodies to growth hormone. Patients with diagnoses that are not growth hormone deficient and will not respond well to exogenous growth hormone. Likewise, Increlex should not be used as a substitute for patients who require growth hormone therapy. It should not be used in patients with secondary forms of IGF-1 deficiency in all thyroid and nutritional issues should be corrected prior to starting Increlex therapy. It should not be used for weight loss management. In terms of HIV lipodystrophy, this medication, for Egrifta, it has been used with success in patients with AIDS related wasting syndrome, since it has been shown to improve muscle mass. However, studies have shown that it can cause a reduction in visceral adiposity, but supraphysiological levels of IGF-1 and symptoms of excess growth hormone occurred, causing treatment cessation. Egrifta offers a specific treatment option for the reduction of excessive abdominal fat in HIV patients with lipodystrophy, as it appears to target the visceral fat compartment with little effect on subcutaneous fat or fat in the limbs. Any questions?

Virginia Buccola: Thank you, Umang. We have one stakeholder, Piao Ching. If you could come to the podium. Thank you.

Piao Ching: Good morning. My name is Piao Ching. I'm a pharmacist with Pfizer medical affairs team. I am here today to present genotropin in support of Pfizer's request to retain genotropin on the formulary. Genotropin is a recombinant human growth hormone indicated for treatment of children with growth failure due to growth hormone deficiency, Prader-Willi syndrome, small for gestational age, Turner Syndrome, idiopathic short stature, and treatment of adults with adult onset or childhood onset growth hormone deficiency. Umang has done a good job going through it, so I am not going to go through it again. Genotropin is contraindicated in patients with acute critical illness, children with prader-willi syndrome who are severely obese, or have severe respiratory impairment, active malignancy, and hypersensitivity to somatropin. Pfizer International growth database and Pfizer International metabolic database are the largest patient databases available for patients with growth hormone disorder. Pfizer International growth database has collected data on 83,000 children, and Pfizer International metabolic database has data on 16,000 adults. Data includes patients from 30 to 50 countries and has generated over 100 publications. The longitudinal analyses of Pfizer International growth database found increased in the proportion of patients in the normal weight range after growth hormone treatment. Genotropin also offers patients support with the Pfizer bridge program. The program provides comprehensive personalized patient support, including benefit verification, in-home device training, and telephone support 24/7. In conclusion, genotropin offers a wide range of indications in the patient support program with over 20 years of experience with genotropin. We are committed to growth hormone rare diseases and urge you to retain genotropin on the formulary. I would be happy to respond to any questions that you have. Thank you.

Virginia Buccola: Thank you, Mr. Ching. So, we'll move to the motion for growth hormone and growth hormone releasing hormones.

Susan Flatebo: All products in the drug classes listed above are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All nonpreferred products require a trial of two preferred products in

their respective class before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Nancy Lee: I second that motion.

Virginia Buccola: All in favor?

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries. We'll move to ulcerative colitis.

Umang Patel: So, moving right along to ulcerative colitis. So, ulcerative colitis is a chronic inflammatory disease, primarily effecting the colon and the rectum. It affects approximately 1 million people in the U.S., and the incidence continues to increase worldwide. The CDC estimates the current prevalence of ulcerative colitis at 238 of 100,000 adults. It can present at any age, but onset typically peaks between the 15 to 30 years of age. The disease is characterized by superficial infiltration of the bowel wall by inflammatory white cells resulting in multiple mucosal ulcerations and crypt abscesses. The predominant symptom of ulcerative colitis is diarrhea, which is usually associated with blood in the stool. Additional symptoms may include pain in the lower quadrant or rectum, along with systemic features, including fever, malaise, and weight loss, which are more common if a greater portion of the colon is affected. The initial attack may be fulminate with bloody diarrhea, but the disease, more commonly, begins indolently with nonbloody diarrhea progressing to bloody diarrhea. Ulcerative colitis can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to the entire large intestine. Most commonly, it follows a chronic intermittent course with long periods of quiescence, interspersed with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course. The primary goal of treatment of ulcerative colitis is essentially inducing, then maintaining, remission of the disease.

Moving right along, aminosalicylates remain the first line treatment option for mild to moderate active ulcerative colitis with 90% of patients

treated with this class shortly after disease diagnosis. Mesalamine agents currently available are an oral and rectal formulations. The rectal products achieve high luminal concentrations of the active component 5-ASA, while minimizing adverse events from systemic absorption. Several aminosalicylates are available and differ only in mode of distribution throughout the small intestine and colon. Second line therapy with a course of oral or rectal steroids, such as Uceris, is indicated for induction therapy in patients with mild to moderate disease who do not respond to oral and rectal mesalamine agents, or in patients with moderate to severe disease. Oral and rectal corticosteroids are not intended for maintenance therapy and can lead to serious adverse events with longterm use. For active ulcerative proctitis, an effective and rapid acting approaches nightly administration of mesalamine retention, edemas, or suppositories often supplemented with an oral aminosalicylate. Corticosteroid enemas can also be used, and another approach to proctitis is administration of an oral aminosalicylate alone, although therapeutic response may not be evident for three to four weeks. In patients with severe refractory ulcerative colitis symptoms, oral corticosteroids are indicated. Corticosteroids, while highly efficacious in the short term use have numerous adverse effects, especially in the elderly, which preclude longterm use. Patients who respond to oral prednisone can be fully withdrawn from the drug over a period of 60 days and should be maintained on an aminosalicylate. Patients with corticosteroid dependent or corticosteroid refractory disease, immunosuppression with azathioprine or mercaptopurine may prevent colectomy. Several TNF inhibitors, such as Remicade or Humira, are approved or inducing and maintaining clinical response, remission in patients with moderate to severe active ulcerative colitis who fail conventional therapy or are considered at high risk for colectomy. Entyvio is an IV integrin receptor antagonist approved for inducing and improving clinical response, remission in patients with moderate to severe active ulcerative colitis who show an inadequate response to or were intolerant of treatment with TNF inhibitor, immunomodulator, or corticosteroid. The oral JAK inhibitor, Xeljanz or Xeljanz XR is also indicated for moderately to severe active ulcerative colitis, as well.

Now, in terms of treatment guidelines, The American College of Gastroenterology, clinical guidelines state that the selection for ulcerative

colitis should be based on not only inflammatory activity, but also disease prognosis. In patients with mildly active proctitis and distal ulcerative colitis, it is recommended to treat with a rectal 5-ASA. Oral 5-ASA agents are used if needed as add-on for distal ulcerative colitis or to treat extensive disease. Mildly active ulcerative colitis who are intolerant or nonresponsive to 5-ASA, oral budesonide is recommended to induce remission. For moderately-active ulcerative colitis, it should be treated with an oral 5-ASA or budesonide. Moderate to severe active ulcerative colitis, the guidelines recommend induction of remission using systemic corticosteroids, anti-TNF therapy, vedolizumab, or tofacitinib with the exception of corticosteroids, the medications used to induce remission should be continued as maintenance therapy. The guidelines state that complementary therapy, such as probiotics, curcumin and fecal transplantation require further study and clarification of treatment and endpoints.

Moving along to the AGA guidelines. The 2019 AGA guidelines, treatment of mild to moderate ulcerative colitis recommend standard mesalamine or 5-ASA, such as balsalazide or olsalazine for induction and maintenance treatment. High dose oral mesalamine combined with rectal 5-ASA may be required for patients with suboptimal response to standard dose therapy or in those with moderate or extensive disease. Oral prednisone, or budesonide, may be added in those refractory to optimize oral and rectal 5-ASA. Proctosigmoiditis, or proctitis, can be treated with topical mesalamine rather than oral 5-ASA. In patients with suboptimal response or intolerance to rectal mesalamine, rectal corticosteroids may be used. Patients who do not respond adequately to the therapies, as outlined above, may need to escalate to systemic corticosteroids, immunomodulators, or biologic therapies. These guidelines make no recommendations regarding the use of probiotics, curcumin, or fecal transplant. While they appear to be safe, their use could delay initiation of proven efficacious treatments that potentially lead to worsening symptoms or complications.

The final guidelines here, we have the American Academy of Family Physicians from 2013. They state the incidence of colon cancer is increased with ulcerative colitis and achieving remission is critical in order to reduce the patient's lifetime risk. For firstline treatment, they

recommend 5-ASA via suppository or enema for patients with proctitis or proctosigmoiditis respectively. If unable to tolerate rectally administered 5-ASA therapy, you may try oral preparations, although response times and remission rates are not as favorable. Oral 5-ASA is effective in patients with active mild to moderate ulcerative colitis extending from the proximal to the sigmoid colon. A topical 5-ASA may be added if an oral formulation alone is inadequate. A short term course of oral corticosteroids may be appropriate, if oral plus topical 5-ASA therapy is not effective. Prednisone is given in dosages of 40 to 60 mg per day with the full dose continued until symptoms are completely controlled, followed by a gradual taper. Longterm steroid use is not recommended for chronic maintenance, due to significant side effects. To prevent relapse, oral probiotics have been shown to be effective, and the agent that is used to maintain remission is usually the same as that used to achieve remission. Symptoms refractory to oral mesalamine or oral corticosteroids may be treated with IV Remicade. Azathioprine is generally not recommended for active ulcerative colitis. However, it may be considered in patients who require corticosteroids or cyclosporine to induce remission. Keep in mind, these came out in 2013. So, Uceris was first FDA approved in January of 2013, but it's not specifically addressed in these guidelines.

So, pivoting over to the medications on the next two slides, you'll see the ulcerative colitis agents. On this slide, we have the oral prodrug forms, which constitute Colazal, Giazo, Dipentum, and Azulfidine and EN-tabs.

On the next slide, we have the oral delayed release forms, rectal forms, and the oral corticosteroids. So, for the oral delayed release forms, we have Asacol HAD, Delzicol, Lialda, Pentasa, Apriso. For the rectal form, we have Uceris, Rowasa, sulfite free Rowasa and, and Canasa. Lastly, for oral corticosteroids, we have budesonide extended release tablet, Uceris, as well. Any questions?

Virginia Buccola: Thank you, Umang. We have no stakeholders. So, we'll move right to the motion for gastrointestinal agents' inflammatory bowel agents.

Susan Flatebo: I guess I do have a question. What about the biosimilar agent in the infliximab. Was that reviewed at all?

Umang Patel: Yeah. That's a great question. So, we have that under... because a lot of those cytokine antagonists have multiple indications, not just ulcerative colitis, Crohn's, rheumatoid arthritis, all of that, it's actually it's own separate class, as well.

Catherine Brown: I move that all products in the gastrointestinal agents' inflammatory bowel agents drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. All nonpreferred products require a trial of preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Susan Flatebo: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries. We will move to cystic fibrosis agents.

Umang Patel: Moving right along to cystic fibrosis agents. So, cystic fibrosis is a serial autosomal recessive multiorgan disorder. It affects approximately 30,000 and adults in the U.S., and is the most common fatal genetic disease in Caucasians. Really quickly to the committee, I apologize if I speed up a little bit. 'Cuz, I realize I have about 40 minutes to do 40 slides. So, yeah. So, children are anticipated to live to approximately 40 years of age with current treatments. In 2017, adults comprised approximately 53% of the population, while in 1987, it was about 30%. Mutations lead to the disease of the exocrine gland function, resulting in the formation of a thick mucus that builds up in the lungs, digestive tracts, and other parts of the body. CFTR, cystic fibrosis transmembrane conductance regulator functions as a chloride channel. Mutations in this result in abnormalities of chloride transport across epithelial on mucosal epithelial cells on mucosal surfaces. Goals of cystic fibrosis treatment include maintaining lung function by controlling infection and clearing mucous in the airway,

maintaining appropriate growth by providing nutritional support, and managing disease complications.

On the next slide, goals of cystic fibrosis treatment, CFTR modulators or potentiators or correctors are the newest class of medications available for the disease and improve chloride ion transport abnormalities. Treatment of cystic fibrosis is mainly dependent on the type and severity of cystic fibrosis symptoms, and this can differ widely from person to person. Medication therapy for respiratory complications primarily include antibiotics, as well as other treatments for airway clearance. CFTR modulators... I mentioned earlier CFTR modulators are the newest class that are available to improve chloride ion transport abnormalities. So, in 2012, the FDA approved Kalydeco, in 2015 Orkambi, 2018 Symdeko, and there's a fourth class that I will go over... a fourth medication I'll go over in a second. Each agent is approved for different CFTR genotypes. If a patient's genotype is unknown, FDA approved CF mutation test should be used to detect the presence of the mutation. This should be followed by verification if needed, based on the results of the mutation test. Use of these agents does not eliminate the need for other symptomatic and preventative therapy. Rather, their use is intended to improve the functionality of the protein.

In terms of guidelines, here on the next slide, we have the Cystic Fibrosis Foundation in 2013. Inhaled treatments, such as tobramycin, dornase alfa, saline, corticosteroids, and oral treatments for treatment of symptoms, exacerbations, and/or infections are recommended. Chronic treatment of Ivacaftor for individuals 6 years of age and older with at least one G551d CFTR mutation to improve lung and quality of life, and to reduce exacerbations. Keep in mind, some of these indications have changed, but these guidelines are from seven years ago. So, I'm repeating what the guidelines say back then. Ivacaftor has not received approval in younger patients or the additional mutations at the time of the publication. Likewise, lumacaftor/ivacaftor, and tezacaftor/ivacaftor were not approved in 2013. The committee also published guidelines on newborn screening, diagnosis, nutritional care, GI related issues, other respiratory care, infection control, and general clinical care by age group. The guidelines recommend use of ivacaftor in preschoolers with specific mutations, which I've put here. Other treatments recommended in this

age group for select individuals include oral, IV, and inhaled antibiotics, which we'll go over on the next TCR, hypertonic saline, dornase alfa, and inhaled antipseudomonal antibiotics. No agent in this class is approved for treatment of children less than 12 months with cystic fibrosis, and notably, ivacaftor has received approval for an expanded number of mutations, since the recommendation. According to the Clinical Pharmacogenetics Implementation Consortium in 2014, they recommend ivacaftor therapy based on CFT or genotype in cystic fibrosis 6 years of age or older who are homozygous or heterozygous for the G551d CFTR variant. The guidelines further state that there are no data regarding whether or not ivacaftor can replace other established therapy. Like CFF guidelines, the CPIC developed these guidelines prior to the approval of lumacaftor/ivacaftor, tezacaftor/ivacaftor, and the expanded indications of ivacaftor. However, following the expanded approval, the CPIC Allele Definition Table in this has been updated with the additional variants.

On the next slide here, we have the four medications that I mentioned. There is a fourth recently added. We have ivacaftor or Kalydeco. We have lumacaftor/ivacaftor combination, known as Orkambi. Tezacaftor/ivacaftor, Symdeko. Lastly, elexacaftor/ivacaftor, which is Trikafta.

Just moving right along, so on the next slide, and these three are newer changes that have happened recently. So, we'll focus on three of them that did receive either an expanded indication or something different. For Kalydeco, in May 2019, the FDA expanded the indication for use in patients as young as 6 months to 11 years who have 1 CFTR mutation that is responsive to the ivacaftor potentiation based on clinical and/or in vitro assay data. The bolding on these slides will indicate the changes or the updated changes here and the respective dosing is below for this new expanded indication and availability of a 25 mg. This medication is pregnancy category B, as well.

On the next slide here, we have Symdeko. In June 2019, FDA expanded approval of Symdeko to include pediatric patients aged 6 years or older with cystic fibrosis who have a certain genetic mutation. Previously, it was only 12 years of age or older with that said same mutation. Again, the dosing is stratified by age and weight base, which you can see below.

Lastly, we have here the newest medication that came out around Halloween. We have Trikafta, which is elexacaftor/tezacaftor/ivacaftor combination. This medication has an indication for the treatment of cystic fibrosis in patients 12 years of age or older with at least one F508del mutation in the CFTR gene. If the patient's genotype is unknown, as I mentioned earlier, the FDA mutation test should be used to confirm the presence before starting treatment. That is primarily the cystic fibrosis oral agents, if anyone has any questions.

Virginia Buccola: So, we have two stakeholders. I just want to clarify, Leta, for time, the additional time is for, did you say there was an additional time request?

Leta Evaskus: Yeah. There is somebody who has, like, what, six drugs? If we don't get through all of these DUR topics, we'll just stop and finish them next time. So, it's okay.

Virginia Buccola: Okay. So, our first stakeholder is Dr. Lisa Allen. Then, after that will be Dr. Meredith Manville.

Lisa Allen: Good morning. My name is Lisa Allen. I'm with Vertex Medical Affairs. Thank you for the opportunity to provide public testimony on behalf of Trikafta, the elexacaftor/tezacaftor/ivacaftor medication, which as Umang said, was approved by the FDA on October 21st for patients with CF 12 years of age and older who have at least one F508del mutation in the CFTR gene. Trikafta works by targeting the underlying cause of cystic fibrosis, which is that defect in the CFTR protein. The objectives of CF care include, but are not limited to, preserving lung health, optimizing nutritional status, and overall improvement in respiratory symptoms. FDA approval of Trikafta was based on a clinical program including two phase three pivotal trials that enrolled over 500 patients with CF and studied endpoints that were in line with those CF care objectives. The two phase trials enrolled patients 12 years of age and older who had either one F508del CFTR mutation and another specific mutation, which we call F-minimal functional study, or FMF study, or patients who were homozygous for the F508del mutation, referred to as the FF study. Those studies met their primary endpoint of an absolute change from baseline at week 4 in lung function, as measured by percent predicted FEV-1. The

FMF patients treated with Trikafta also experienced a significant increase in their BMI and had a 63% reduction in the number of pulmonary exacerbations, as compared to placebo. These reductions in pulmonary exacerbations resulted in reduced hospitalizations and reduced IV antibiotic use. The warnings and precautions associated with Trikafta are in the USPI, include important information on liver function test elevations, drug interactions with [inaudible] 3A inducers inhibitors, and cataracts. Elevated transaminases and bilirubin have also been observed in Trikafta treated patients. So, guidance around monitoring of LFTs are included in the USPI. Cases of cataracts have also been reported in pediatric patients treated with ivacaftor containing regimens. Therefore, baseline and followup exams are recommended. In addition to the USPI, I encourage the committee to read the peer-reviewed manuscripts in the New England Journal of Medicine and the landset that detail these studies. Approximately 60% of the U.S. CF population, based on age and genotype, are now eligible for Trikafta. For approximately 5900 of these patients, Trikafta will be their first and only available CFTR modulator therapy. So, I respectfully ask the committee to add Trikafta to the PDL in accordance with the FDA approved indication.

I'd also like to take a little bit of time to speak to our other medications. I'd like to begin with Kalydeco. There are patients with CF who are not eligible for Trikafta based on the genotype and her age. For this reason, I'd like to summarize a little bit. So, the FDA expanded indication for Kalydeco in 2018 and 2019, now include patients with CF 6 months of age or older who have one mutation in the CFTR gene that's responsive to ivacaftor based on either clinical data or in vitro assay data. These labels were based on the results of phase-3 open label 24 week study of ivacaftor in children less than 24 months of age with a CFTR [inaudible] mutation. Moving next to Orkambi, the most recent update was in August of 2018, which expanded the indicated patient population to include patients with CF 2 years of age and older who are homozygous for the F508del CFTR mutation. Finally, Symdeko. In June of 2019, the FDA expanded the indication to include patients with CF 6 years of age and older who are homozygous for the F508del mutation, or who have at least one mutation in the CFTR gene responsive to tezacaftor/ivacaftor, based on in vitro data. This label expansion was based on the results of a phase-3 open label 24 week safety study. I would like to conclude by

reminding the committee of the warnings and precautions associated with Kalydeco, Symdeko, and Orkambi, which have been shared previously. These can be found in the U.S. prescribing information. Based on these updates I provide here today, I respectfully ask the committee to continue to provide coverage for Kalydeco, Orkambi, and Symdeko in accordance with their approved indications, and continue with inclusion for those three agents, as well, to the preferred drug list. Thank you, very much, for your time. I'd be happy to answer any questions that you might have.

Virginia Buccola: Thank you, Dr. Allen. Dr. Manville?

Meredith Manville: Hello again. My name is Meredith Manville. I'm from Seattle Children's Cystic Fibrosis Center. Dr. Allen pretty much went over most of the clinical data. So, mostly, I just wanted to share some of the stories that we've heard from some of our patients who have been able to access Trikafta so far. So far, our families are telling us that they are breathing better without a cough, and the rest of these are patient quotations. "I'm trying to remember how to breathe properly, now that I can, with tears in her eyes, for the first time over 10 years I didn't have to check the symptom of cough on my clinic intake form." "This new medication is working so good. I've had the sniffles, and they're getting better. Usually, I'm in the hospital and needing oxygen at this point." Patients are also telling us that they had previously struggled and having now improved nutrition. Mom says, "He's gaining weight, which has been so hard for him before. My son has had a problem being underweight since he got severely ill six years ago. Within one month after starting Trikafta, he's gained 15 pounds and informed me that he needs to buy new pants. I'm ecstatic." Our families are now leading more active lives. "I don't need oxygen anymore to take my dog on a walk." "I've skied for the first time in ten-plus years today. Not a single cough." "I've been able to do things that I couldn't do in years. I'm making plans for my life again." The most poignant quotations that we've heard is that they are now learning that they are going to live longer lives and planning for their futures. "I promised my mom I would open a retirement account this year rather than traveling, and I've never thought about retirement like this before." This last quotation is, "I never thought that I would have to take care of my parents in their old age, because I didn't think that I

would live long enough. Now, that's very likely. Thank you, so much. I'm happy to answer any questions.

Virginia Buccola: Thanks very much. So, we'll move to the motion for respiratory agents cystic fibrosis agents.

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

Alexander Park: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We'll move to inhaled antibiotics.

Umang Patel: So, moving over to inhaled antibiotics, as I mentioned when we were going over the cystic fibrosis guidelines, these inhaled antibiotics play a role in preventing infections in the airways. So, I won't go over that again, but there are some added indications, as well, that these medications have. So, I'll briefly go over them.

So, mycobacterium avium complex, or MAC lung disease is the most common non-tuberculosis mycobacteria lung infection. Treatment is continued until sputum cultures are consecutively negative for at least 12 months. Typical duration exceeds 18 months. Eradication is difficult, and recurrence and relapse are common. The timing of treatment depends on the type of disease and the risk of progression. While fibrocavitary disease has a rapid progression and warrants prompt treatment, a course of observation may be reasonable for patients with nodular

bronchiectasis disease, if the patient has minimal symptoms or radiographic findings, or the patient has comorbid conditions that are considered to be more serious than the MAC lung infection. During observation, sputum cultures are generally monitored every two to three months. Repeat imaging occurs after approximately six months. Signs of disease progression, such as increased bacterial load, development of cavitation, or worsening nodularity indicate the need for antibiotic therapy.

According to the American Thoracic Society and the IDSA, the diagnosis of NTM lung disease should be based on the minimum of chest radiography, or HRCT scan. Three or more sputum specimens for acid fast bacilli analysis, and exclusion of other conditions, such as tuberculosis or lung malignancy. Due to the long therapy duration and potential for intolerance, treatment should only be considered in patients who meet the clinical, radiographic, and microbiologic criteria for the diagnosis of NTM. The current recommended treatment for NTM includes a macrolide, such as clarithromycin or azithromycin, rifampin, and ethambutol. An IV aminoglycoside, amikacin or streptomycin, is added to treat rapidly progressing disease, extensive cavitary MAC, or after failure of standard multidrug therapy. For infections that are macrolide resistant, a regimen of rifabutin, ethambutol, plus a parenteral aminoglycoside is recommended. The guidelines are in the process of revising this statement. The Cystic Fibrosis Foundation, and the European Cystic Fibrosis Society in 2016 recommends susceptibility testing for MAC infections on isolates recovered prior to initiation of treatment, and sputum samples are recommended for cultures every four to eight weeks for the duration of the treatment. IV amikacin is recommended in select patients. A daily oral antibiotic regimen containing a macrolide, such as azithromycin, rifampin, ethambutol is recommended for clarithromycin sensitive MAC pulmonary disease. Monotherapy with a macrolide or other antimicrobial should never be used for MAC pulmonary disease. Treatment is recommended for 12 months beyond culture conversion if no positive cultures are obtained during these 12 months.

So, moving right along to the medications that make up this class, we have Arikayce, Cayston, Bethkis, Kitabis Pak, TOBI, and TOBI Podhaler

along with their respective indications here. The TCRs that are uploaded for the committee, they pretty much have, they are updated every either semi-annually or annually, and if there are any new medications or indications that have come out after that update, I kinda highlight them a little bit. So, on the next slide here, you'll see the reason Arikayce has its own little update here is because in November of 2018, FDA approved Arikayce for cystic fibrosis, previously approved for MAC lung disease as part of a combination antibacterial drug regimen. The limitation of use only indicated in adults who have limited or no alternative treatment option. It has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of six consecutive months of a multidrug background regimen therapy. Use is not recommended for patients with nonrefractory lung disease. Any questions?

Virginia Buccola: We have one stakeholder for this section. It is Dr. Meredith Manville.

Meredith Manville: Last time, I promise. So, I'm here to talk about our inhaled antibiotics. Some bacteria are prone to infect CF mucus, which can provoke inflammation and destruction of the airways and the lungs. Untreated, and/or repeated lung infections can lead to the decline of lung function. Inhaled antibiotics decrease acute and chronic infection and CF agents, such as dornase alfa and hypertonic saline, as previously discussed, improve airway clearance of mucous to improve lung function and health. One of our patient shares, I can't participate in what I want because of CF, but I feel better months that I am on tobramycin. I'm breathing better. We advocate for at least one inhaled tobramycin product be added to formulary, continue to be on formulary, including aztreonam lysine and then also the addition of Arikayce, primarily for our patients who we had previously been doing IV amikacin for nebulization. Now, our patients are telling us that they are more likely to be compliant to their therapies by using Arikayce, due to the taste of it and overall trying to get pediatric patients to take inhaled medications is challenging. Thank you, very much. Any questions?

Virginia Buccola: Thank you, very much. Let's move to the motion for aminoglycosides, inhaled.

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

Alexander Park: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries. Now we have monobactams inhaled.

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

Constance Huynh: I second.

Virginia Buccola: All those in favor?

Group: Aye.

Virginia Buccola: Any opposed? The motion carries. We'll move to anticoagulants.

Umang Patel: So, as you can imagine, there are a lot of guidelines with anticoagulants. I know it's almost lunch, but just bear with me here. Alright. So, for anticoags, the first disease state, VTE, venous thromboembolism. It

manifests as a deep vein thrombosis, or DVT, and a pulmonary embolism, PE, and is a major consequence of various surgical procedures and medical conditions. It occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portion of the extremities, most commonly the legs. The exact number of patients impacted by DVT and PE is unknown. However, it is estimated that these conditions effect between 300 and 600,000 people in the U.S. every year. If left untreated, approximately 30% of patients who develop PE will die within the first few hours of the event. Generally, the risk of VTE increases with the number of risk factors present, major trauma, and age. Due to the risk of morbidity and fatal PE associated DVT, prophylaxis has become the standard of care for patients at high risk for thrombosis. CAD, or coronary artery disease, and PAD, or peripheral arterial disease, approximately 14 million Americans have CAD and 8.5 million over the age of 40 years have PAD. Prevention and treatment of atherosclerosis focus on modifiable risk factors. Therapy includes lifestyle changes and the medical treatment of hypertension, hyperlipidemia, and diabetes. Antiplatelet medication, such as aspirin, clopidogrel, prasugrel, ticagrelor, vorapaxar, are indicated for the reduction of thrombotic CV events in patients with established CAD or PAD.

In terms of atrial fibrillation, it is a common arrhythmia ranging in prevalence from 2% in patients under 65 years of age to 9% of those 65 years of age and older. It is higher in men than women and increases with age. More than a third of patients with atrial fibrillation are 80 years of age or older. Patients with a-fib can have a reduction in cardiac output resulting in pooling of blood in the heart, the atrial thrombus formation and potential systemic embolization. Ischemic stroke is the most frequent clinical manifestation of a-fib associated embolization, and it increases the risk of stroke five-fold. In patients with a-fib, ACCP recommends measuring the thromboembolism risk using a CHADS-2 VASc score, which considered risk factors, such as gender, age, history of stroke, TIA, or thromboembolism, as well as history of CHF, hypertension, diabetes, vascular disease such as prior MI, peripheral artery disease, or aortic plaque. The scores range from 0 to 9 with higher numbers indicating more of a risk. In terms of guidelines for VTE, the American Society of Hematology in 2019 recommendations included prophylaxis for medical patients, VTE diagnosis, management of anticoagulation

therapy, hyperinduced thrombocytopenia, VTE in pregnancy, and pediatric VTE treatment. When anticoagulants are used for VTE prophylaxis, the guidelines prefer low molecular weight heparin over unfractionated heparin, or direct acting anticoagulants. They also note that managing anticoagulation therapy is complex. Therefore, an order to optimize management of anticoagulation therapy, the guidelines suggest patients receive care from specialized anticoagulant management service centers versus primary care physicians whenever possible. Additionally, for patients at low to moderate risk of recurrent VTE who require interruption of vitamin K antagonist therapy for invasive procedures, the guidelines recommend against periprocedural bridging with low molecular weight heparin or unfractionated. In patients with acute HIT suggested treatment options include argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant. Additional guidance on the DVT/PE treatment, VTE in cancer patients, thrombophilia, and VTE in surgical patients is anticipated in the near future.

According to the ASCO, the American Society of Clinical Oncology guidelines in 2019, they state that cancer patients are significantly more likely to develop VTE than people without cancer. Additionally, cancer patients exhibit increased rates of VTE recurrence and more bleeding complications during the VTE treatment. Both prophylaxis and treatment regimens are generally more aggressive in cancer patients than in other populations. For example, most patients hospitalized for any condition who also have an active malignancy should also receive anticoagulation therapy, as prophylaxis, unless there is active bleed or another contraindication. In the outpatient setting, routine thromboprophylaxis is not recommended for cancer patients. However, the use of apixaban, rivaroxaban, or low molecular weight heparin, as prophylaxis may be indicated for certain high risk patients, including those with a Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen. Patients with multiple myeloma receiving thalidomide or lenalidomide based regimens with chemotherapy and/or dexamethasone should be offered prophylaxis with either aspirin or low molecular weight heparin depending on risk assessment. Cancer patients undergoing major surgery should have anticoagulation continued for at least 7 to 10 days postoperatively, and possible extended prophylaxis with a low

molecular weight heparin for up to four weeks for select high risk patients undergoing pelvic or abdominal surgery. Initial anticoagulation for treatment of VTE in patients with cancer may include low molecular weight heparin, unfractionated heparin, fondaparinux, or rivaroxaban. Per the guidelines, patients initiating VTE treatment with parenteral anticoag, low molecular weight heparin is preferred for the initial five to ten days, unless the patient has severe renal impairment. There is strong evidence to support recommendation for longterm anticoag with a low molecular weight heparin. Edoxaban, rivaroxaban for at least six months rather than vitamin K antagonist.

According to the American College of Chest Physicians, guidelines suggest no antithrombotic therapy in patients with a-fib without valvular heart disease, including those with paroxysmal a-fib who are at low risk for stroke. Guidelines recommend oral anticoagulation therapy for patients with a-fib, including those with paroxysmal a-fib without valvular heart disease who have a score of 1 on the CHADS-2 VASc score, and it's suggested they receive oral anticoagulation while patients considered at high risk CHADS-2 VASc score of 2 or higher in male or 3 or higher in female. Where oral anticoagulation is recommended or suggested, the guidelines suggest using a novel oral anticoagulation therapy, rather than an adjusted dose vitamin K antagonist therapy. According to the AHA, ACC, HRS guidelines, in 2019 all NOACs are now preferred over warfarin in NOAC eligible patients with a-fib. Exceptions to this are patients with moderate to severe mitral stenosis or mechanical heart valve. In NOAC eligible patients, NOACs were shown to be at least noninferior to warfarin in preventing stroke and systemic embolism and have a lower risk of bleeding. Apixaban is preferred in patients with endstage renal disease or on dialysis while other NOACs are not recommended in this population due to lack of evidence. Edoxaban is now included in the guidelines as an option for stroke prevention, and the anticoagulant reversal agents, Praxbind and Andexxa are recommended in the event of life threatening bleeding or an urgent procedure.

Continuing the update, there is consensus throughout the published guidelines that all a-fib patients with mechanical heart valve should be treated with warfarin. Pradaxa is contraindicated in patients with mechanical heart valves, due to increased risk of bleeding. Patients with

a-fib and endstage CKD or those receiving hemodialysis should be treated with warfarin. Pradaxa and Xarelto should not be used in patients with endstage CKD or receiving hemodialysis due to lack of evidence regarding the balance between risks and benefits. Dosage recommendations are available for the use of Pradaxa, Eliquis, Xarelto, and patients with moderate to severe CKD, and a CHADS-2 VASc score of greater than 2. Bridging therapy with unfractionated heparin or low molecular weight heparin for patients who require interruption of oral anticoagulant therapy should be contemplated. Considerations include the oral anticoagulant being interrupted whether or not the patient has a mechanical heart valve, and the duration of time a patient will not be anticoagulated. These decisions should balance the risk of stroke versus bleeding.

In terms of stroke, according to the CDC, stroke is the fifth leading cause of death behind heart disease, cancer, chronic lower respiratory disease, and accidents. According to the AAN guidelines in 2014 reaffirmed in 2017 for the prevention of stroke, Pradaxa 150 mg twice daily is likely more effective than warfarin with a decreased risk of intracranial hemorrhage. Xarelto is probably as effective as warfarin in preventing stroke or systemic embolism with a lesser frequency of intracranial hemorrhage and fatal bleeding. Eliquis 5 mg twice daily has been shown to result in a reduced mortality compared to warfarin due to a decreased risk of bleeding, including intracranial bleeding rather than its effect on reduction of cerebral systemic embolism compared to warfarin. These guidelines also provide comparison between the effectiveness and safety of the oral anticoagulants to antiplatelet agents, such as aspirin and clopidogrel. Edoxaban and Bevyxxa were not available at the time the guidelines were published, and they were not included. Unresolved issues surrounding the use of new anticoagulants in the setting of NVAF include the lack of data comparing these drugs to one another. In addition, drug activity cannot be assessed in routine clinical practice, which may lead to under or over treatment of patients, questionable safety treatment for acute ischemic stroke with a thrombolytic agent in patients receiving Eliquis, Pradaxa, Xarelto, edoxaban, and the lack of an antidote in the setting of an acute hemorrhage.

Moving right along to the ACC 2017 guideline on management of bleeding. For major bleeds, anticoagulants should be interrupted. For most patients, an anticoagulant reversal agent is recommended if available. Lab evaluation to identify residual anticoagulant activity is recommended in patients with severe renal impairment, particularly those taking dabigatran, which is 80 to 85% renally excreted. Platelet transfusion may be considered in select patients, particularly after other measures, such as oral anticoagulant reversal have failed. For nonmajor bleeding, the guidelines do not recommend routine reversal of an oral anticoagulant; however, interruption of oral anticoagulant therapy, until the patient is clinically s table, may be advised depending on individual patient characteristics, the nature of the bleed, and the intensity. The patient's current underlying bleeding risk and relevant medical comorbidities should be considered. The final guidelines here, the ACC and the AHA guidelines in 2016 focus on prevention and treatment of atherosclerosis focus on modifiable risk scores. The therapy includes lifestyle changes in the medical treatment of hypertension, hyperlipidemia, diabetes, antiplatelet medications are indicated for reduction of thrombotic CV events in patients with established CAD or PAD. In October of 2018, Xarelto became the first oral anticoagulant approved for use in combination with low dose aspirin to reduce the risk of major CV events in patients with chronic CAD and PAD.

The next three slides on here, I have just DVT prophylaxis broken down by specific surgical procedures and DVT treatment. The next two slides, for sake of time, I'm not going to go over them in detail, but it shows the other additional indications that these medications have, and I leave it for the committee members' leisure. On the final slide here, we have the dosing and availability. Any questions from the committee?

Virginia Buccola: Thank you, Umang. We have two stakeholders for anticoagulants, Piao Ching and Mae Kwong.

Paio Ching: Hello again. My name is Piao Ching. I am a pharmacist with Pfizer medical affairs team. I am here to provide medical information on Eliquis in support of Pfizer request to retain Eliquis on the formulary. As detailed in the prescribing information, Eliquis, or apixaban, is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular

atrial fibrillation, prophylaxis, and treatment of deep vein thrombosis and pulmonary embolism. There is a box warning for premature discontinuation of any oral anticoagulant increases the risk of thrombotic events and spinal or epidural hematoma. The most common and most serious adverse reactions reported with Eliquis, or apixaban, were related to bleeding. The apixaban for reduction in stroke and other thromboembolic event study was the clinical trial that garnered the FDA approval. Eliquis, or apixaban, was found to be superior in reducing stroke and systemic embolism and had fewer major bleeds than warfarin, as stated in the guideline earlier. It is the only direct oral anticoagulant in this phase that has shown superiority. The other agents have shown noninferiority to warfarin. Eliquis has demonstrated continued efficacy and safety in other retrospective analyses. In closing, I urge you to maintain Eliquis on the formulary, given its consistency in efficacy and safety reward data. Thank you for your attention. I would be happy to answer any questions you may have.

Virginia Buccola: Thank you, Mr. Ching. Mae Kwong?

Mae Kwong: Hello again. I guess I can say good afternoon. My name is Mae Kwong. I'm with Janssen scientific Affairs. I want to thank the committee for making Xarelto or rivaroxaban a direct oral anticoagulant available to Washington Medicaid patients. Xarelto received its first indication in 2011 and last October received its eighth indication for the prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications, not at high risk of bleeding. For the medically ill indication, Xarelto is dosed at 10 mg once daily with or without food in the hospital and after hospital discharge for a total recommended duration of 31 to 39 days. Xarelto is the only DOAC approved for the reduction in risk of major cardiovascular events, including cardiovascular death, myocardial infarction, and stroke in patients with chronic coronary artery disease or PAD. Xarelto 2.5 mg twice daily in combination with aspirin yielded a 24% reduction in MACE events versus placebo, as demonstrated in the Compass trial, which was stopped a year early, due to efficacy. As Dr. Patel already highlighted, the 2019 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation now prefer NOACs as a recommended drug class over warfarin to reduce stroke risk and appropriate a-fib patients, unless

patients have moderate to severe mitral stenosis or a mechanical heart valve. Xarelto is the DOAC with the most FDA approved indications to treat and help protect against thrombotic events, further differentiating Xarelto as a must have option, as it is the most studied anticoagulant available for the most groups of patients. I want to thank the committee for keeping Xarelto, or rivaroxaban available to Washington Medicaid patients for all approved indications. I'm happy to take any questions. Thank you.

Virginia Buccola: Thank you, Ms. Kwong. We'll move to the motion for anticoagulants factor Xa and thrombin Inhibitors.

Nancy Lee: I just had a question of clarification. So, in the tables and charts include warfarin. Are you considering that as part of this factor Xa thrombin inhibitor class? Or is that just there as a reference? I just wanted to clarify whether this is more like the direct oral anticoagulants. I understand warfarin inhibitors factors 2, 7, 9, and 10, but I wasn't sure if you wanted, if the intent was to include that within this specific, or if it was just the NOACs?

Marissa Tabile: So, the way that we have it organized on the PDL, the warfarin is its own class. So, they're, I believe, the coumadin agents, or they're their own specific class. So, they're separated. So, it is really only the Factor Xa.

Alexander Park: I move that all products in the anticoagulants Factor Xa and thrombin drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Susan Flatebo: I second.

Virginia Buccola: All those in favor.

Group: Aye.

Virginia Buccola: Any opposed? And the motion carries. Now, before we move to antiparasitics, I want to check in with the...

Leta Evaskus: We will do the last two classes in April. So, the topical antiparasitics and the lipotropics. We have another meeting starting at 1:00. So, I'm going to ask everybody to clear the room. You can go ahead and adjourn.

Virginia Buccola: We'll adjourn the DUR portion.

Leta Evaskus: Thank you.