Daniela Clape: Hello everybody. My name is Daniela Clape. On behalf of Medical Learning Institute, the Endocrine Society, and Xpeer Medical Education, welcome to this accredited symposium thanks to an educational grant by Lilly.

Our tremendous faculty, as you see there, has worked hard over the past several months creating this presentation to meet your needs. So, I leave you with our great faculty.

Goals of diabetes care

Bernhard Ludvik: So, let me share some thoughts about the goals of Diabetes Care with you. Every year generally we wait for the first issue of Diabetes Care, and there they publish the “Standards of Medical Care in Diabetes.” And basically, what are we doing? What are we trying to do? We try to improve cardiometabolic health. We try to prevent complications, and very important for the patients themselves, to improve health-related quality of life.

Where do we stand in optimal diabetes care?

So where do we stand in optimal diabetes care, and these are data from the NHANES study. And I think on the left side, on the far left side, you can see the HB1C, achievement of an HB1C goal below 7%; then the blood pressure goal of less than 130/80; and the non-HDL cholesterol less than 130. And these data are from 1999 to 2018, and you see different time periods.

And what you can see up to 2010, it’s getting better actually with HB1C achievement, blood pressure achievement, and non-LDL cholesterol achievement. But then it levels off and it’s even getting worse, and this is something which is really striking. So, if you look at the far right, you see a triple endpoint, having an HB1C less than 7%, blood pressure less than 140/90, non-HDL cholesterol less than 130. And you see
it’s, it’s improving over time. But then it, there’s some sort of stagnation; and this is something which is, actually, it’s sad looking at the new medications, the availability of new medications over the last time.

**Twin epidemics of T2D and obesity**

But what we see in the same time, we see twin epidemics of Type 2 diabetes and obesity. And, and here you can see data from the prevalence of Type 2 diabetes in the US population. And you see around 2000, it was about 9.8%. And now it’s, it’s about 14.3%. And this is true; this is an increase by 46%, which is tremendous. And what you can see, we have a stagnation with the undiagnosed population, which is good because, obviously, we might catch it earlier.

If you look at obesity, BMI above 30, what you can see in 2000 with a prevalence of 30.5% and now by 2018 it was 42.4. This is an increase of 36%; and what else you can see here down, it’s, the increase in severe morbid obesity, there’s a doubling, doubling over the time period.

**The obesity and diabetes syndemic**

So, there is, we call it, might call it "syndemic." The obesity, obesity leads to different changes and, in, of the metabolism of muscle, in muscle, in pancreas, and in adipose tissue. And this, based on the genetic predisposition, promotes to core defects of Type 2 diabetes which is insulin resistance and beta-cell decompensation. You’re well aware of that.

However, we also have some other factors promoting Type 2 diabetes which are sleep disorders, the inability to be active, and, of course, stigma and impaired mental health. So, then we, of course, have the social environment, the disadvantage, sociocultural barriers, and income inequalities.

And the problem is this is like a vicious circle because Type 2 diabetes per se can promote obesity. For example, think of medication-induced weight gain, neuropathy and the decreased activity level, hypoglycemia, and stimulation of food intake, stigma again, and impaired mental health. And then you have the physical environment, which is food, availability of food, physical activity, lack of physical activity, safety, and alcohol.

**Moderate weight loss has benefits — greater weight loss is associated with greater benefits**

We know from studies with diets, like the DiRECT study or bariatric or metabolic surgery, that weight loss matters. And the amount of weight loss is also very important. We know that small amounts of weight loss are capable to improving measures of glycemia, triglycerides, blood pressure. However, if you want to achieve better outcomes, you have to have a greater weight loss.
So, for example, for hepatic steatosis, for NASH activity, apnea-hypoxia, hypopnea index, and reduction in CV events, which you have only seen so far for bariatric or metabolic surgery. So, it matters how much people lose weight when they have diabetes.

**Treatment for T2D to minimize weight gain/promote weight loss**

And this is acknowledged by the joint EASD/ADA recommendations for pharmaceutical treatment. And the cleanest state, you guys know atherosclerotic vascular disease. If there’s no renal or cardiac disease, heart failure, then one should focus on minimizing weight gain or promoting weight loss; and this is preferably done with GLP-1 receptor agonist or dual agonist, as you will see in a moment, or SGLT2, but to a lesser extent.

**Social determinants of health**

But we must not forget that we have social determinants of health, which are equally important like genetic background, obesity, lack of exercise. This is, first of all, education and access to education and quality of education. This starts early in childhood. We have healthcare, the access to healthcare and to quality. We have, of course, neighborhood and built environment. It makes a difference when you can walk, when you can bike. It’s social and community context. We have seen that in the pandemic. And it’s economic stability. And many of those determinants, actually, are under enormous pressure in these times.

**Emergence of new classes of T2D therapeutics**

So, when we go back, we see over the last 15 years new medications, new classes of medications. In 2007, we saw the GLP-1 receptor agonists which show favorable weight loss profiles, a risk reduction of cardiovascular disease. In 2015, we had the launch of SGLT2 inhibitors, again with less but still weight loss. And better blood pressure profiles, CV risk reduction, and renal and cardiac protection.

And now it’s already launched in the US and in the United Arab Emirates, hopefully soon in the EU. We see the dual GIP/GLP-1 receptor agonist, tirzepatide in that case. It’s a normal receptor agonist. It’s a completely new class, once weekly injected. And as you will see from the subsequent talks, you will see with enhanced glycemic control and weight loss benefits.

Thank you so much, and I will proceed and ask Professor Nauck to come to the stage. I don’t have to introduce him. He has been introduced many times, and everybody who’s in this field knows his name. Thank you.
Michael A. Nauck: So, I will be talking about "Delineating the Incretin Effect and the Roles of GLP-1 and GIP," the two incretin hormones; and that is related to the potential benefits of agonism of multiple receptors. And I want to shed some light on the potential mechanisms of action.

**The incretin effect in healthy subjects**
And really what is important to start with is the incretin effect. In panel A, you see glucose going up and down again, once with oral glucose and, secondly, almost hidden behind the same symbols, with intravenous glucose. So, the glycemic stimulus is the same. But as you can see in panels B&C, insulin goes up much higher and C-peptide as well with oral glucose. I'm sorry, this is E and F I'm talking about. And the reason behind this is really the secretion of incretin hormones, GIP and GLP-1. They’re not secreted at all with intravenous glucose, but they are profoundly stimulated to be secreted from specialized endocrine cells in the gut. So, it’s going up like seven-fold for GIP and three-fold for GLP-1. And that explains the difference in insulin and C-peptide curves.

**The incretin effect in T2D**
And if you now look at the right-hand panels, the left-hand panels more or less repeat what you have seen in the first slide. This is now the same experiment in Type 2 diabetes; and you can see, of course, the levels of glycemia are different in the fasting state and post-load. But the difference that you typically see in the rise in insulin and C-peptide is much less. So, there is a reduced and, in some patients, even absent incretin effect.

**GIP and GLP-1 administered as single agents or in combination in T2D patients**
And we now know, and I will just briefly mention this in words, that there is no general difference in how GIP and GLP-1 are secreted between healthy subjects and Type 2 diabetic patients. So, it’s not a difference in secretion, a lack of availability of incretins, but it's their effect. And this is a very simple experiment in patients with Type 2 diabetes who received a therapy with basal insulin. We stopped that therapy, and the next day when they were hyperglycemic, they received an infusion of either placebo in gray, GIP in blue, GLP-1 in green, and the combination in red.

And what you can see in blue, not much difference in blood sugar compared to placebo, at least no significant difference. And if you compare the gray and blue lines with respect to insulin or C-peptide and
insulin secretion, not much of a difference. However, GLP-1 in green, first of all, is sufficient to normalize glycemia. So, after six hours, they all had normal blood sugar. And also, you see the transient stimulation of insulin, C-peptide, and insulin secretion rates. And surprisingly, if you add GIP on top of GLP-1, it doesn't make a difference.

**The traditional view**

So basically, what this indicates to us is that in Type 2 diabetes, there is an inability of GIP to stimulate insulin secretion, certainly if you aim at a sufficient stimulation to lower blood sugar.

**Is GIP the obesity hormone?**

The next role of GIP that is being discussed is in the role of body weight regulation. And I will present to you the old view, the traditional view which is mainly based on the examination of GIP receptor knockout mice. If they are overfed with a high fed diet, that means GIP is expressed more in the gut. They absorb more glucose from the gut. GIP is insulinotropic, so there is more insulin around. And this increases the ability of becoming a fat animal. So basically, GIP was viewed as an obesogenic hormone.

**Recent findings on GIP receptor agonism and body weight in animal studies**

But now we have recent findings on GIP receptor agonism or combined agonism on the GIP and GLP-1 receptor that challenges this old view. So, GIP receptor stimulation may lead to reduced food intake and weight loss…

**GIP reduces food intake and body weight by interacting with CNS-GIPR**

…and some cells in the hypothalamus that have GIP receptors have also been identified. So basically, this is summarized in this, in this cartoon, so you lose body weight by reducing your food intake if you are a wild-type mouse with an intact GIP receptor. And you don’t see this whether you inject acyl-GIP into the intracerebral ventricular fluid or into the periphery as long as you have the GIP receptor. But, unfortunately, simple studies in humans have not confirmed this. So, if you infuse even large amounts of GIP into human subjects and then test what is their appetite and how much food did, they eat, you will no longer see an effect. And if you
combine it with GLP-1, that is one published study mentioned in the bottom of this slide, they even say it compromises the effect that they usually see with a single infusion of GLP-1. So, some discrepancy between animal experiments and human experiments.

**GIP and GLP-1**: The two incretin hormones

Last, I want to show you how in healthy subjects GIP and GLP-1 interact in the postprandial stimulation of insulin secretion.

The influence of GIP and GLP-1 on postprandial glucose tested by use of specific receptor antagonists in human subjects

And what you can see here is experiments employing specific antagonists at the GIP receptor, that is GIP (3-30) amide. And at the GLP-1 receptor, that is exendin (9-39). And what you can appreciate, if you inhibit both incretin hormones — that is what you see in red dots — that gives you the highest increase in glycemia following an oral glucose load; and it gives you the high, the greatest reduction in the insulinogenic index, which b-, means both incretin hormones together with the major part played by GIP explain the physiological incretin effect. But that says that under normal physiological conditions, they interact in an additive manner in order to stimulate insulin secretion to meet the needs of such a meal situation. So, with this, I will finish and ask Juan Pablo Frias to come on and give us his information on tirzepatide.

**Juan Pablo Frias**: Okay, thank you, Michael. I can say my disclosures and Professor Nauck’s can also be found on, on the app.

So, I’m now going to sort of go translating what, what Professor Nauck was just speaking of and what we’ve seen in the clinic. We’ve had a, a great opportunity over the years to be very involved in this clinical development program as have the other two speakers and now for me using it in clinic as well over the past three months or so since its approval in the US.
Tirzepatide: A novel GIP and GLP-1 receptor agonist

So tirzepatide, as you probably know, is a dual agonist of both the GIP and the GLP-1 receptor. It is based on the backbone peptide sequence of GIP, and it’s been modified to be able to bind to and stimulate both GIP and GLP-1 receptors. And importantly, it has, it’s acylated with a 20-carbon fatty diacid moiety, which binds to albumen, extending its half-life to approximately 5 days. And what this does is allow for once weekly dosing. So, it’s, it’s once-a-weekly subcutaneous injection. A number of trials or studies have been done looking at the mechanism of action. Certainly, it enhances the incretin effect, so it enhances first and second phase insulin secretion compared to selective GLP-1 receptor agonists, such as semaglutide, and actually reduces glucagon concentrations as well versus dulaglutide. We’ve looked at that and semaglutide. And studies in patients with various degrees of renal and hepatic dysfunction have shown that the pharmacokinetics for tirzepatide concentrations are similar, irrespective of, for example, their degree of renal function. So, there’s no need to make any dose adjustments based on renal function.

The SURPASS program: clinical trials across the spectrum of T2D

Now if we look at the Phase III clinical programs, so the clinical development program, it really spans the spectrum of Type 2 diabetes. On your left as monotherapy, so patients treated with or not well treated with diet and exercise versus placebo. And all the way on your right versus, versus placebo in patients poorly controlled on basal insulin. And you’ll also note that SURPASS-2 was a study with an active comparator, and this is the one trial in the Phase III program comparing tirzepatide to a selective GLP-1 receptor agonist, in this case once weekly semaglutide at a dose of 1 milligram. And I think very importantly also, there is an ongoing dedicated cardiovascular outcomes trial, the SURPASS-CVOT. This has an active comparator which is dulaglutide and is expected to report out in 2024.

SURPASS trial design: tirzepatide 5, 10, and 15 mg versus active comparator or placebo

This is the general design of all of the Phase III studies, so basically it was three arms of tirzepatide or a dose of 5, 10, and 15 milligrams, either versus placebo in SURPASS-1 and SURPASS-5 or versus an active comparator; SURPASS-2 with semaglutide; SURPASS-3, which Dr. Ludvik was the first author of, was versus insulin degludec; and SURPASS-4 versus insulin glargine was titrated. And the studies were either a 40- or 52-week duration for the primary endpoint. And in all of these trials, the primary
Potential Benefits of Incretins Beyond Glycemic Control in T2D

And you can see the way that tirzepatide was initiated, and this is also the way in which it’s used, or it’s labeled in the United States, which is initiation with 2.5 milligrams once weekly for the initial 4 weeks of therapy and then escalating the dose in 2.5 milligram increments every 4 weeks until in these studies the randomized dose was reached, the 5, 10, or 15 milligrams. So, the 5-milligram dose is reached after 4 weeks, the 10 milligram after 12 weeks, and the 15-milligram dose, which is the maximal dose, is reached after 20 weeks of therapy.

Tirzepatide at all doses significantly reduced A1c versus placebo or active comparators
I’ll just quickly review the key endpoints here. So, this looks at the change in hemoglobin A1C from baseline to end of study across the five SURPASS trials. And sort of the key here is, you know, very robust reductions in A1C with the 5, 10, and 15 milligram dose statistically significantly greater reductions versus placebo and also versus the active comparators.

Tirzepatide significantly reduced HbA1c and more patients achieved A1c targets compared with semaglutide 1mg
And here I show the SURPASS-2 data with respect to A1C lowering. You can see on your right from a mean A1C of 8.3%, and this is looking at the efficacy estimate, you can see a 2.4 to 2.5% reduction in A1C with the 15-milligram dose down to an A1C of less, an average A1C of less than 6%. And again, with the three tirzepatide doses, 5, 10, and 15 milligrams, by week 40, significantly greater reduction in A1C than what was seen with the 1 milligram dose of once weekly semaglutide.

I’ll also point out if you look very early during the first four weeks of this study, and I point this out a lot when I’m speaking to clinicians in the US, there was already, all patients at that point were on 2.5 milligrams. During that four-week period, you see a mean reduction in A1C from 8.3 to 7.5 during four weeks. So, a 0.8% mean reduction in A1C. So very powerful even at the starting dose of 2.5 milligrams. And on your right, you see target attainment of hemoglobin A1Cs less than 7%, almost 90% of the patients treated with the higher doses of tirzepatide.

And as we saw in the Phase II studies, a large proportion of patients actually normalizing their glycemic control, as evidenced by an A1C of less than 5.7%, up to 46% of the patients in, in SURPASS-2 and higher in some of the other SURPASS trials. But generally, anywhere between 45 and then 55%. 
Potential Benefits of Incretins Beyond Glycemic Control in T2D

I don’t have a slide here, but in SURPASS end with the three doses of tirzepatide versus the comparators.

This was a secondary endpoint, and again in each case, a greater reduction in body weight at study end with the three doses of tirzepatide versus the comparators.

And then SURPASS-3, and here are the, this is out to 52 weeks. You can see that it’s just starting to level off with respect to, to the loss in body weight at about week 52. And as expected, the comparator here was insulin degludec. You see an increase in body weight with, with the degludec.

I don’t have a slide here, but in SURPASS-4, which went out to two years, so 104 weeks, you saw that the, the plateau in body weight occurred generally, shortly after, on average, after 52 weeks – maybe between 52 and 60 weeks or so.

**More participants achieved ≥10% weight loss with all doses of tirzepatide vs comparators**

And we also, obviously, looked at clinically relevant body weight reduction. This is just showing the proportion of patients who had greater than or equal to 10% weight reduction, again, very consistent in these trials, anywhere from 40 to 60% at the highest dose having greater than 10% weight reduction which is, obviously, very clinically significant, as Dr. Bernhard explained in his talk.

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**Tirzepatide decreased weight (kg and %) more than comparators in SURPASS trials**

Similar slide now for change in body weight. So double-digit reduction in body weight with respect to the proportion or the relative reduction in body weight. You can see in SURPASS-2, for example, a 13% reduction in body weight on average; and very consistent across the five studies. And I think it’s important what, to take into consideration that these were not weight loss studies. So, these were not studies where patients were seeing

**No plateau in body weight loss at 40 and 52 weeks (SURPASS 2 and 3)**

And again, I’ll show a couple of the studies. So, SURPASS-2 versus semaglutide, you see dose-dependent reduction in body weight with the three tirzepatide doses. And again, with each of the three doses, significantly greater weight reduction with tirzepatide, up to 13% mean reduction in body weight with the, with the highest dose versus semaglutide.

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dietitians at a calorie deficit diet, etc., etc.
Up to 60% of participants on tirzepatide achieved composite endpoint compared to 22% on once-weekly semaglutide 1 mg (SURPASS-2)

And lastly with respect to the data, one prespecified endpoint that we looked at in SURPASS-2, again tirzepatide versus semaglutide, and it was a composite endpoint. The proportion of patients at study end, so at week 40, that achieved all three of these – a hemoglobin A1C of less than or equal to 6.5%, greater than or equal to 10% weight reduction, and no clinically significant hypoglycemia, so no Level 2 or severe hypoglycemia. And it was reached by 60% of the, of the patients treated with a 15-milligram dose compared to 22% of the patients treated with semaglutide.

**Tirzepatide safety and tolerability**

With respect to safety and tolerability, a very comparable safety and tolerability profile to the selective GLP-1 receptor agonists. So, GI side effects being the most common. You can see here nausea was the most common of these, occurring anywhere from 17 to 22% of the patients treated with tirzepatide at any given time during the study.

Incidence of nausea over time through 40 weeks (SURPASS-2)

And this shows nausea now in, the incidence in four-week blocks throughout the study. And the things to point out here is that as with the selective GLP-1 receptor agonist, it occurs generally during dose escalation. So early in the course of therapy, most was mild to moderate in severity, you see in green and in orange there, and tended to dissipate over time. And again, quite comparable to what was seen with a selective GLP-1 receptor agonist.

I will tell you in this study though, we were not, we were blinded actually, I should say, to what tirzepatide dose patients were on; and we were not allowed to deescalate the dose, which certainly is something I would do in clinic in a patient who wasn’t tolerating.
Low incidence of hypoglycemia in SURPASS trials

With respect to hypoglycemia, given the mechanism of action, you would not expect significant hypoglycemia either as monotherapy or in combination with agents that make, that do not cause, I should say, hypoglycemia. So, metformin or an SGLT2 inhibitor. But you may get an increase in sulfonlurea or insulin-induced hypoglycemia. So, from, again, from a clinical perspective, when these drugs are initiated, when tirzepatide’s initiated, we should certainly consider proactively reducing the dose of insulin secretagogues or insulin if the patient, particularly the patient is very close to their target.

Pooled tirzepatide vs pooled comparator effect on time to first MACE-4

And lastly, there, the, the official sort of cardiovascular outcomes trial was ongoing, as I mentioned, SURPASS-CVOT. But there was a pooled analysis of seven clinical trials of over 26-week duration which looked at 4-point MACE; and you could see that there was a, or, over the course of, of these trials, the, the hazard ratio showed a 20% reduction, which was not statistically significant, but this was not powered for that. So, we could certainly say that from a cardiovascular perspective, it is safe; and again, we’re awaiting the results of SURPASS-CVOT.

Tirzepatide indication in EU and key prescribing information from US label

Now in Europe, it has, tirzepatide has received a positive opinion. We’re waiting on the label, but here’s a European indication that would likely be, which is “indicated for adults with insufficiently controlled Type 2 diabetes, as an adjunct to diet and exercise, as monotherapy in patients who cannot use metformin, or in addition to other medicinal products, for diabetes,” and this is very similar to the US indication.

In the US, and I imagine this will be in Europe as well, it comes in a single-dose pen with, with, with an autoinjector, very similar to the pen for dulaglutide. And it’s available in six doses, a starting dose of 2.5 milligrams and then the maintenance dose of 5, 7.5, 10, 12.5, and 15 milligrams; and you can see the recommendation for initiation and subsequent dose escalation based on the patient’s response is similar to what we did in the clinical trials.

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Tirzepatide: contraindications, limitations of use, and warning/precautions in the US label

And lastly, the contraindications, similar to the long-acting selective GLP-1 receptor agonist, contraindicated in patients with either a family or personal history of medullary thyroid carcinoma or a personal history of MEN2. It was not studied in patients with a history of pancreatitis and not indicated for Type 1 diabetes. And very comparable warnings and precautions to what’s seen with a selective GLP-1 receptor agonist.

Summary and conclusions

So, to summarize, tirzepatide is a unimolecular dual GIP and GLP-1 receptor agonist. Based on preclinical and clinical studies, its mechanism of action, and this is, as Michael mentioned, an area of very active investigation. It’s probably both synergistic and complementary effects of binding and activating both the GIP and GLP-1 receptors. Phase II and Phase III clinical trials have shown A1C and body weight reductions versus placebo and active comparators, including selective GLP-1 receptor agonists across the spectrum of Type 2 diabetes.

Recently approved, and we’ve been using it in the US outside of clinical trials for about three months now but also received a positive opinion in Europe. And it’s currently being studied for a number of other therapeutic indications, including obesity, fatty liver disease, and many comorbidities that are associated with obesity and obesity complications.

So, with that, I would like to thank you for your attention, and we are going to have about five minutes or so of Q&A now.

Maryann Galatan: Maryann Galatan, from Denmark. Impressive data. I’m really, really amazed to see really, really so great data in the Type 2 population. Have you any data on how long time that potentially these subjects will regain weight when they stop treatment? And if so, if or how long period of time would you expect it to if you don’t have any data?

Michael A. Nauck: Yeah. So, I think we have experience with GLP-1 receptor agonists that also have an indication for the treatment of obesity; and it, it is very obvious that it takes a long time, a year or so in the case of tirzepatide to reach the new plateau, but you will always reach such a new plateau. And with the GLP-1 receptor agonist, it’s the same when you discontinue. Then they will regain weight and probably end pretty much where they started at baseline. So, it is meant for, for a continuous therapy.

Maryann Galatan: (INAUDIBLE)
Juan Pablo Frias: Yeah, and although we do not have data, that is being looked at in one of the SURMOUNT trials, which are the obesity trials that are ongoing where everyone initiated with tirzepatide and then subsequently were randomized either to go to placebo or to continue tirzepatide. So, we’ll see that, but I, I completely agree with Michael. Probably needs to be chronic therapy for there to be continued effect.

Maryann Galatan: Thank you. Thank you for very nice data.

Bernhard Ludvik: Let’s put this, what you have heard in the SURPASS-3 studies in some clinical context. And you all know and heard it repeatedly. We don’t have it yet, and it’s around in the US for three months. So, we don’t have really long, they don’t have long-term data, but you have heard that it’s really working pretty soon.

Patient communication is key to weight management success

So, first of all, we have to talk in addition before we just prescribe medications for the treatment of diabetes. We have to think about our communication regarding weight management, and I think it’s very important because the patients just don’t like the terms "excess fat," "obese," and "obesity." So, we probably have to change a little bit our wording and prefer terms like "excess body weight," the "BMI," or "above ideal body weight," and "maintaining a healthy weight" because that’s very important, a healthy weight.

So, first of all, of course, this is indicated for treating patients with diabetes; but what we see, again, is a very pronounced weight loss. And I’m quite sure the patients are going for that. So, but still, we have to discuss weight. So, what we can do is actually when we ask the patient about further treatment, it’s a shared decision approach. So, let’s say as we get our glucose under control, do you have additional goals concerning your weight? And I, I think most of the patients, 90% are overweight or obese, we go for that. And maybe you can also ask what kind of help from me do you want for, for your weight from your reduction? I think this is, we have to have a very sensitive approach about that.

Case 1: Rudolph, 63 years

So, we have cases here, typical cases you all see in your clinics and practices. And this is Rudolph. He is 63 years. He has Type 2 diabetes since 2017. He always was struggling with obesity. His current BMI is 31, and he’s treated with metformin and empagliflozin and his HBA1C is 8.1%. There’s no evidence of cardiovascular disease, and he goes to a yearly screening with an exercise test. And so usually we
recommended insulin as a failure of oral glucose lowering therapy. But if you look closer into the recommendations that we have seen over the last years, that GIP1 agonist in that case should be preferred because of their, the effect on weight and hypoglycemia.

So, what we also agree is that the treatment with a GLP-1 receptor agonist or GIP/GLP-1 receptor agonist like tirzepatide is considered as an alternative to basal insulin because we can achieve even greater weight loss. We can achieve weight loss and a greater decrease in HBA1C without risk of hypoglycemia.

So, in that specific patient, we would go for, and we have proof from the status, go for tirzepatide because it has been shown as you’ve seen that in SURPASS-2 it has superiority over GLP-1 receptor agonist, which is semaglutide 1 milligram. And we have seen the SURPASS-3 study. It was also superior compared to degludec insulin, which is the most advanced basal insulin analogue; and in that study we saw a drop in HBA1C of 2.1% and a drop in body weight 11.3 kilograms.

So, what would we expect from treating Rudolph with tirzepatide for one year? We could expect to have an HBA1C of 6.0% and a BMI of 28.6 kilograms, which puts him in another category from obesity into overweight. So, this is one likely candidate for the initiation of tirzepatide following failure of oral therapy.

Case 2: Monica, 69 years
And this is Case 2 is Monica. She’s slightly older, 69 years. She has Type 2 diabetes since 2013. She’s likely obese, BMI is 31, and she’s treated with metformin, empagliflozin, and semaglutide once weekly. And her current HBA1C of 7.4. There, again, is no evidence of cardiovascular disease, but there is evidence of nonalcoholic steatohepatitis. And as you will agree, her HBA1C is not where we want to have it. We want to have it at least below 7%. So again, in this patient, addition to reach the HBA1C goals.

However, what you could do, and you have seen that in the SURPASS-2 study, one could alternatively, of course, switch from semaglutide to a GIP/GLP-1 agonist like tirzepatide because it’s most likely that we achieve an HBA1C goal less than 7% together with weight loss.

And so tirzepatide was, indeed, chosen or would be chosen, actually. It’s, it’s over semaglutide because we have the results of the SURPASS-2 study; and the difference between both agents was an HBA1C difference of -0.4 and a body weight difference of 5.5 kilograms. So, what could we expect after one-year treatment when Monica is treated with tirzepatide in addition to her current metformin and SGLT2 inhibitors? We could expect an HBA1C of 6.7% further weight reduction and again putting her
from an obesity category, her weight from obesity category to overweight category. So, I hope I could set these, these results you have heard with the SURPASS-2 studies in patient cases and thank you for your attention.

**Juan Pablo Frias:** All right, thank you. Great, great cases. I received a question, and maybe, Bernhard, you can answer this, which has to do with whether tirzepatide can be used in patients with a past history of pancreatitis. What are your thoughts on that?

**Bernhard Ludvik:** Cautious with that. Cautious with that because pancreas-, and you have seen it. I mean there is no proof that any of those drugs cause pancreatitis. I know with the SURPASS program, there was no, no indi-, no indication that there’s an increase in the risk of pancreatitis. But still, I think it’s, we would be very careful in those patients.

Of course, we’ll have also to consider what type of pancreatitis. If it was a stone, for example, then I would say, “Yes, there’s no problem.” But if you don’t know the right reason for pancreatitis, I would be really careful, unless we have other data.

**Juan Pablo Frias:** Yeah, I would agree, particularly in unexplained pancreatitis, you know, which is what you alluded to. I, I agree with that 100%. And Michael, the-, there was a follow-on question to that which had to do with people with gallbladder disease.

**Michael A. Nauck:** Yeah, so let me talk about the first question first. About 12 years ago, there was real concern that GLP-1 receptor agonist caused acute pancreatitis and even pancreatic cancer. And now the CVOTs have very carefully looked at this, and this is no longer true. So, there is no increased risk for pancreatitis with GLP-1 receptor agonists. But most of the studies, because this was unclear, have never included patients with a history of acute pancreatitis. So basically, there is a knowledge gap now. I would, would be prepared to study such patients in a controlled trial. But since we don’t have the data, we have to be cautious.

And now the, the second question is about retinopathy-.

**Bernhard Ludvik:** Gallbladder.

**Michael A. Nauck:** Gallbladder disease, sorry. That is a fact with GLP-1 receptor agonists, that there is always an imbalance in all kinds of gallbladder-related or biliary complications. It is like 30 to 40% higher relative risk to develop such complications but at a very, very low level. And what we know is that in an obese, Type 2 diabetic population, we expect many of them to have preexisting gallstones. And we do not really know is it those patients where then suddenly it becomes painful and, therefore, is diagnosed or is the weight loss associated with these agents the cause that you have more gallstones because if you lose body weight through any method, the risk for gallstones is increased.
There is no general recommendation that you should not use it, but I think I would inform my patient that there is this imbalance that this may happen and that they should simply tell you if they have symptomatic gallstone-associated disease because independent from this kind of treatment, this would always mean you should do something about it. Usually, you then recommend cholecystectomy.

Bernhard Ludvik: But that is true for bariatric surgery. We see it after massive weight loss. You have gallstones, and our bariatric surgeon have to remove the gallbladder. Sometimes when they have stones there because, because of the risk, it’s simply related to weight loss. Don’t you agree?

Michael A. Nauck: Yeah.

Juan Pablo Frias: Yeah, and I would say that’s probably the, the mechanism. It, it’s just more of a weight loss-related mechanism.

The other, the other question that came out was should all patients before initiating tirzepatide have an eye exam? And patients, patients who had preexisting proliferative retinopathy or retinopathy that required acute treatment or maculopathy were not studied in, in the SURPASS programs. So, all of these patients went to an ophthalmologist or an optometrist, had retinal photographs. There is no thinking that it causes worsening of retinopathy in and of itself. But certainly, with very rapid reductions in A1C, folks with unstable retinopathy can have temporary worsening. It is not recommended necessarily that they have to go have fundal photographs; but these patients should have a retinal exam in the office and be, we should be very cautious with patients with unstable retinopathy in these trials. Michael?

Michael A. Nauck: May I add something? So, I think this, this question came up with the SUSTAIN 6 study.

Juan Pablo Frias: Right.

Michael A. Nauck: With semaglutide. And so, it’s always asked in connection with starting a therapy with a potent incretin mimetic. In fact, I think this is a question totally independent from that kind of treatment because it is relevant for those with preexisting advanced retinopathy who start a therapy that will bring that blood sugar and HBA1C down considerably. And always they should be seen by an ophthalmologist. You have to know in your patients whether they have advanced retinopathy, and action is indicated totally independent from the prescription of an incretin mimetic.

Bernhard Ludvik: And we have seen that in Type 1 diabetes. DCCT, it led to worsening in the very beginning; and then it got better. So, I think we know that for many, many years.

Simon from India: Hi, this Simon from India. __________ completions on the SURMOUNT-1 data. Just wanted to get a couple of insights on the commercial side of things. Earlier I think that the Q2 results, company had indicated that they would be discussing with the FDA regarding findings. So, do we think they would go ahead based on the SURMOUNT data, or are we going to wait for the other data?
Juan Pablo Frias: Yeah, you know what, we didn’t focus on SURMOUNT data here; and that’s probably a better question for, for the company, unfortunately. We do know, as you know, that SURMOUNT was presented, SURMOUNT-1, the initial part, and, and it was, it was published in the New England Journal. There, there are three other studies that, that are being conducted as well. But I think that’s a better answer or question for, for Eli Lilly folks than for us.

Simon from India: Fine. This one is a follow-up. Around Asian patients, there was an article recently stating that we might see too much weight loss in the Asian population. Any thoughts on that?

Juan Pablo Frias: Yeah, I think, I think that’s true of any, certainly the, the, these studies from Japan were recently published. I think with, with any patient, and certainly a lot of my patients in the US as well, you may not want the degree of weight loss that you may get with the 15-milligram dose. But you know what, I mean there anyway, we have 5, 7.5, 10, 12.5, and 15. So I think we need to individualize care, and I think it’s actually something very positive to have a very wide spectrum of doses. And we see that the 5-milligram dose is very effective. So, if you have a patient that, you know, weight loss may not be their main concern or don’t want to lose, don’t want to lose too much weight, you certainly have the option to go to a lower dose. That’s what I would say. I don’t know if my colleagues have any other comment.

Michael A. Nauck: Yeah, so I, I think what we have learned is that you predominantly lose fat mass; and that is usually not bad for most of the patients.

Bernhard Ludvik: Yeah, and I think the SURPASS-3 MRI study really clearly demonstrated you lose mass, fat in the liver.

Juan Pablo Frias: No, absolutely. I think it was over 80% of the patients had greater than 30% relative reduction in liver fat content, which is a very clinically relevant metric. So, you, you really do clear fat out of the liver.

But some people still, you know, par, elderly patients who are frail, for example, patients who just do not want to lose that much weight, you have the option of having other doses that are very effective from a glycemic and a weight loss perspective but may not be as potent. Because you saw the, the weight loss was definitely dose dependent.

Thank you. I think we’ll; we’ll wrap up. I want to thank Dr. Ludvik, Dr. Nauck, Professor Nauck. And thank you all very much.