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https://reachmd.com/programs/cme/ultra-long-acting-insulins-the-future-of-insulin-therapy/15478/

Released: 07/10/2023
Valid until: 07/09/2024
Time needed to complete: 60 minutes

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Ultra-Long-Acting Insulins: The Future of Insulin Therapy

[CHAPTER 1]

Dr. Pablo Frias:
Hi, I'm Juan Pablo Frias. I'm an endocrinologist in Los Angeles, California, where I serve a medical director of Velocity Clinical Research. I'll be speaking today about once weekly basal insulins and discussing the rationale and proof of concept.

Here are my disclosures.

So we know that reducing the number of injections with many different agents can improve adherence, persistence, and potentially quality of life and reduce treatment burden for patients and caretakers really may, it has been shown to reduce quality of life, may improve adherence with therapy and persistence with therapy, which ultimately can improve short-term and even long-term outcomes and very importantly, since we've moved to once weekly GLP-1 receptor agonist there is the potential having a once weekly insulin of combining these two classes of agents with complementary mechanisms of action.

So if we look at the key of overarching principles and extending half-lives of therapeutics, it's important to understand that efficacy of a therapeutic depends on its availability at the target site, in this case the insulin reporter, at concentrations and for durations that maximize efficacy while at the same time minimizing side effects. And we know that many endogenous peptides, including insulin, have very short half-lives and for that reason, an unmodified peptide would have to be administered by subcutaneous infusion continuously or multiple daily injections to be efficacious.

And over the years a number of different technologies either modifying the protein and/or drug delivery technologies have been used to overcome these barriers and extend the half-life. Some of these include slowing absorption from subcutaneous tissue, generally with depot formulations using polymeric or lipid microparticulate systems, an example in diabetes would be extended release Exenatide. Also, increasing the hydrodynamic radius of the therapeutics, PEGylating the therapeutic and very importantly, increasing the molecular weight, and this can be done in a number of fashions, including noncovalent association of the peptide with a large carrier protein, such as albumin, or via covalent fusion to a carrier protein, such as the Fc region of an immunoglobulin, generally an IgG.

So if we look at this IgG-Fc fusion technology, the peptide of interest, in this case it would be insulin, is fused with the Fc region of an immunoglobulin, and this is usually an IgG and if you look at the figure there, you can see that this Fc fragment or region is very large, 50 kilodaltons. IgGs, along with albumin, which we'll discuss in the next slide, have the longest half-life among plasma proteins, generally around 20 days. And Fc fusion proteins have delayed subcutaneous absorption for a number of reasons, one because of their large size. Once in the bloodstream they recycle through what's called the neonatal Fc receptor, which increases the half-life of IgGs as well as these fusion proteins, and also based on the size, there's reduced renal elimination. And these have been used for many years, since 1998, the first one being Enbrel in rheumatologic and immunologic disorders, but also closer to diabetes would be Dulaglutide, which is a GLP-1 analog which is bound or fused to a modified IgG4 Fc region.

Now turning to albumin binding to enhance the, or prolong the half-life of a molecule, albumin is the most abundant protein in human blood, very large as with the Fc region, 65 kilodaltons, and again, has a half-life of approximately 20 days. And albumin binds to

endogenous ligands, such as free fatty acids and also to some exogenous medications such as Warfarin and Diazepam. Incorporation of fatty acids has been used to potentiate albumin association and binding to albumin, which is reversible, so the albumin drug complex that exists after administration of these drugs serves as a drug reservoir enhancing biodistribution and bioavailability.

And we're very familiar with some of the examples of this technology, including Semaglutide, which has an 18 carbon fatty diacid moiety, which reversibly binds to albumin. Tirzepatide for example, has a 20 carbon fatty diacid moiety and some of our insulins as well, including insulin degludec uses this methodology.

So there are two weekly basal insulins that are currently in clinical development. Efsitora alfa, which is also may be known as BIF, or basal insulin Fc, is a fusion protein, it combines a single chain variant of insulin with a human IgG Fc domain, this is in clinical development by Eli Lilly and we recently published two, or three actually, Phase 2 studies and it is now in Phase 3 of clinical development, a program termed QWINT. And the second one is insulin Icodec, and this is an insulin analog that strongly but reversibly binds to albumin. It is in clinical development by Novo Nordisk, and it has completed the pivotal Phase 3a clinical development program, which is the ONWARDS Program. So it has been submitted to FDA at this point.

So let's start with Efsitora alfa, so Efsitora again, is an insulin receptor agonist, it combines a single chain variant of insulin with an IgG2 Fc domain, that's what's shown in the figure. It is a homodimer, so there are two single chain variants that are attached if you will, or fused, to one Fc domain. It is a selective insulin receptor agonist, it has a half-life of 17 days, as I'll discuss briefly, in a brief moment, insulin Icodec is a half-life of eight days, but this allows once weekly dosing and the prolonged half-life is due to a number of reasons; slow absorption from the subcutaneous space due to the sheer size of the molecule, again, recycling via the neonatal Fc receptor, reduced renal clearance, this also has to do with its molecular weight, and importantly, reduced insulin receptor affinity.

And what this does is it reduces insulin receptor mediated endocytosis and clearance of the insulin. It's been shown to have a low mitogenicity potential and low immunogenicity risk. So if we look at the structure, the amino acid substitutions that have been made to both the B and the A chain of the insulin, what this does basically is it reduces insulin self-association, it enhances manufacturability, so chemical and physical stability, and again, it reduces insulin receptor affinity, increasing the half-life through this methodology.

If we look at a single ascending dose study, and this is in patients with type 2 diabetes, looking at Efsitora concentrations after a single administration, and this is over 28 days, you see a dose dependent increase in the pharmacokinetics and very low between day and between subject variability. If we now look at the pharmacokinetics, so again, Efsitora concentrations, after multiple doses, so it's steady state and here we're looking at concentrations over seven days after that last injection or administration, a very flat profile throughout the week, with a peak to trough ratio of 1.14. And looking at the pharmacodynamics after a single dose, you see that the pharmacodynamics matches the pharmacokinetics so dose dependent reductions in insulin with a nadir reach at about 4-6 days. So this is suitable for once weekly administration. And lastly, this is model data over a 12-week proud showing in the light blue, the daily fluctuations if you will, or the daily peak trough ratio of insulin glargine U100, which is about 1.8 and that of insulin Efsitora either given with a loading dose in red, or without a loading dose in black, and what you see is that the peak trough ratio of 1.14 never exceeds that of the daily peak trough ratio of insulin glargine, again making the point that this has a very flat profile which may result in more consistent glycemic control, more predictable control as well.

Turning now to insulin Icodec, so insulin Icodec is a novel ultralong-acting insulin with a 20 carbon fatty diacid moiety and it is designed for once weekly administration. It's half-life is eight days, as with Efsitora it's a selective insulin receptor agonist, it's prolonged half-life is due to this reversible albumin binding and also reduced insulin receptor affinity, which slows receptor mediated clearance. Also, there's a formation of essentially an inactive albumin bound depot for slow, continuous release after administration and as with Efsitora, low mitogenicity potential and low immunogenicity as well. If we look at the structure, there are three amino acid substitutions relative to human insulin and what this does is it reduces enzymatic degradation, it lowers insulin receptor binding affinity, again slowing the insulin clearance, and it improves solubility so the concentration of this insulin is a U700 and this limits the volume that needs to be given once weekly and is very clinically important. And the 20 carbon fatty diacid moiety slows the release and it also limits the number of Icodec molecules that are available at the insulin receptor for binding, further reducing the affinity and the clearance of the insulin.

If we look here at a multiple ascending dose study, and this is actually after five weeks of dosing so that it's study state, you see dose proportionality and also you see the extended, the extended Icodec concentration. So the extended half-life and again, with a half-life of approximately eight days.

So lastly, from that pharmacokinetic studies, there were glucose clamps done and modeling done to look at the stability or the glucose lowering activity of the insulin throughout a seven-day period. So what these bars represent is the preparation of glucose lowering and each day, relative to the entire week and you can see that it is very steady, as with Efsitora and should provide very smooth coverage throughout the week and after a once weekly injection.

So to summarize, once weekly basal insulin formulation may improve adherence and persistent, potentially improving quality of life, as well as long-term outcomes. The two once weekly insulins in development are Icodec and Efsitora, these are novel once weekly basal insulins in late stage of clinical development. Molecular modifications and different methodologies are used to prolong the time action profile, making these insulins suitable for once weekly administration. And the pharmacokinetic and pharmacodynamic data supports once weekly dosing of these insulins.

Thank you very much for your attention.

[CHAPTER 2]

Dr. Pablo Frias:
Hello. I'm Dr. Juan Pablo Frias. I'm an endocrinologist in Los Angeles, California where I serve as medical director of Velocity Clinical Research. And I'm here to discuss some of the clinical trial data of the once-weekly basal insulins Efsitora and Insulin Icodec.

Here are my disclosures.

So by way of introduction, there are two once-weekly basal insulins that are in clinical development. One of them is Efsitora alfa, which is in Phase 3 of clinical development. The program is called the QWINT Program. And the second is Insulin Icodec, which has completed the pivotal Phase 3a studies and is currently under regulatory review. So if we look at the clinical development program, this is looking at the Phase 2 program for Insulin Icodec. And there were two studies in patients who were insulin naïve, so on oral agents, and one study in patients who were already on basal insulin. If you look to your left, this is one of the studies in patients who were insulin naïve who were randomized either to Insulin Icodec once a week or to Insulin Glargine. And this was a 26-week study with hemoglobin A1C as the primary end point.

And then two shorter studies that were quite interesting. One was also in patients who were on oral agents, insulin naïve. And in this study, actually what was looked at was the target glucose, as well as the increment of adjusting the insulin once weekly to look at what the best targets would be. And what the best insulin dose adjustments would be. And this was a 16-week study. And the second 16-week study was in patients already on basal insulin switching to Insulin Icodec. And this one looked at whether you need a loading dose, so a higher dose initially of the once-weekly basal insulin versus not giving a loading dose. And in each of these Phase 2 studies, the comparator insulin was Insulin Glargine.

If we look at the Efsitora Phase 2 clinical development program, there was one study in patients who were already on basal insulin who switched to Efsitora. There was one study in patients who were insulin naïve, so they were on oral agents for the first time initiating basal insulin. And there was one study in patients with Type 1 diabetes. And all three of these trials compared Efsitora once a week to Insulin Degludec.

And then moving in to Phase 3, and these studies have been completed now and two of them were reported out during the American Diabetes Association meetings this week. And there were three of the trials and this is the ONWARDS program. Three trials, ONWARDS 1, 3, and 5, in patients on oral agents where Insulin Icodec was the first insulin. You see these ONWARDS 1 was a 78-week study which compared Icodec once a week to Insulin Glargine once daily. ONWARDS 3 compared Icodec to Insulin Degludec. And ONWARDS 5, a very interesting study because it was more real world, comparing initiating Icodec to whichever basal insulin the investigator thought would be best for the patient. And this study included an application to help with insulin dosings, so insulin dose adjustment.

And then there were studies in patients who were already on basal insulin. These were ONWARDS 2, 4, and 6, which was a study in patients with Type 1 diabetes. So ONWARDS 2, patients on basal insulin who were switched to Icodec versus Insulin Degludec. And then ONWARDS 4 were patients who were on basal-bolus insulin and had their basal insulin switched to Icodec. And again, all of these studies have been completed and reported out.

Now QWINT, which is the Phase 3 program for Efsitora, it is currently ongoing. And this program includes two studies in insulin naïve patients and you see here one versus Insulin Glargine and one versus Insulin Degludec. So these are patients who are seeing insulin for the first time. And QWINT-1 is interesting in that it has a fixed dose escalation of Efsitora. There's also a study in patients already on basal insulin switching either to Efsitora compared to Insulin Degludec once daily. And also a study in patients already on basal-bolus insulin compared Efsitora as the basal insulin to Insulin Glargine in a study in patients with Type 1 diabetes.

Now all of these studies are currently ongoing. So none have yet completed, so they have not reported out. And you can see in this timeline the QWINT-1, the rate-limiting study or the last study that will finish before registration or before regulatory filing of Efsitora. And that's estimated to complete sometime next year in 2024. So let's look at glucose lowering with these agents with respect to A1C lowering and this is looking at both Efsitora on the left and Insulin Icodec on the right. At the A1C reductions that we're seeing in the

Phase 2 programs. On the bottom line, you can see that across these, when you compare the once weekly insulin to once daily insulin, whether it's Insulin Glargine or Insulin Degludec. Very similar glycemic control is measured by the hemoglobin A1C.

You did see in the Type 2 diabetes initiation trial, the 16-week trial that looked at different glycemic targets or fasting targets and also different escalations of the Insulin Icodec. Slightly lower hemoglobin A1C with more aggressive targets but there was more hypoglycemia in this group, as well. So what was decided with Icodec moving into the ONWARDS program or the Phase 3 program was to use a target of 80 to 130 milligrams per deciliter. And use changes in insulin as I'll show later in 20 unit increments once a week. And to get what that would mean from a daily perspective, you need to divide seven. So that would be slightly less than three units once a week if you were using once-daily basal insulin. And again, more on that a bit later.

If we look at the Phase 3 Icodec program, so this is a program that has completed, and again, looking at hemoglobin A1C, actually this was I wouldn't say surprising but I think very good news. With Icodec, either compared to Insulin Glargine or Insulin Degludec, across these trials, in most of these trials, you actually had a significantly greater reduction in hemoglobin A1C with Insulin Icodec. So the once-weekly insulin, compared to the once-daily. And you can see that across the trials except for ONWARDS 4, which was in patients already on basal-bolus, where it was equivalent. And importantly, this slight improvement in hemoglobin A1C seen with Icodec did not result in clinically significant increases in hypoglycemia. Which is shown at the bottom of this slide which looks at rates of hypoglycemia less than 54 milligrams per deciliter. And I'll discuss a little bit more about hypoglycemia later.

So if we look at hypoglycemia, specifically, and this is looking at Level 2 or severe hypoglycemia. So glucose is less than 54 milligrams per deciliter, which is three millimolars, or requiring assistance of a third party. You can see that across the Phase 2 studies and the completed Phase 3 trials in insulin naïve patients. So patients who are on oral agents and were seeing either Efsitora, or Icodec, or any insulin for the first time. That there was very comparable rates, and this is per patient per year, in clinically-significant hypoglycemia.

And looking similarly now at Level 2 or 3 hypoglycemia in patients who were already on basal insulin, so who switched to either Icodec or Efsitora. You saw fairly comparable rates of hypoglycemia of clinically significant between the once-weekly and the once-daily insulins. And they tended to look a bit higher, you see on your left in the Phase 2 study with Efsitora. But I do have to say that in this study, we used continuous glucose monitoring which was not blinded to the patient or to the investigator throughout the trial. So we really were looking for the hypoglycemia, which might explain why there was a bit more here, but certainly it was not more with the once-weekly insulin with Efsitora compared to the once-daily. In this case, it was Insulin Degludec. So if we look at continuous glucose monitoring, I mean, one of the keys of all of these programs have been a lot of use of continuous glucose monitoring. So this looks at the Phase 2 study of Efsitora in patients who were insulin naïve and you can see the time and range, so between 70 and 180 milligrams per deciliter at baseline. Then at Week 12 and at Week 26, at the end of the study. And you see that increased with both insulins. There really was not a difference between the two insulins but certainly a difference between baseline and Week 26.

If we look at patients using Efsitora who switched from basal insulin, again, similar between the two Efsitora arms and the Insulin Degludec arm. They did not reach sort of the target we would like to see with time and range, which is greater than 70%, but again, the fasting glucose targets in this study were not very aggressive for the Efsitora arms. It was either less than 120 or less than 140 milligrams per deciliter with Efsitora and less than 100 milligrams per deciliter with Insulin Degludec. But importantly, we looked at variability, and what you see on the left is within day variability for daytime, nighttime, and the full 24 hours with Efsitora and with Insulin Degludec. And you can see that numerically there was less variability with Efsitora compared to Insulin Degludec. This could have something to do with the very flat profile of this weekly insulin and also there tended to be less in between day variability with the once-weekly insulin compared to Insulin Degludec.

If we look at ONWARDS 1, so this was a study looking at Insulin Icodec versus Insulin Glargine in patients who were insulin naïve. You can see here that at both between 48 and 52 weeks and then all the way out to 74 to 78 weeks, there was actually not only numerically but significantly greater amount of time spent within range. So 70 to 180 milligrams per deciliter with Insulin Icodec compared to Insulin Glargine, and really no increase in hypoglycemia that was seen here.

And looking also at ONWARDS 2 and 4, so these were studies that looked at patients who were switching from previous use of basal insulin. There really was no difference between the two at the end of these trials with respect to the time in range, so again, 70 to 180 milligrams per deciliter. And no significant excess in hypoglycemia in these patients. Now I think a clinical question that comes up with these very long-acting insulins is will they cause more hypoglycemia and potentially prolonged hypoglycemia if they inadvertently get overdosed, for example. And this was a study that specifically looked to try to answer that question. It also answered whether there was any difference in the counter regulatory response to hypoglycemia.

So this was a randomized open-label study. There was a two-period crossover trial. These were patients with Type 2 diabetes who were already on basal insulin with or without oral agents. And basically, you can see that they were treated for six weeks with once-weekly Icodec or 11 days with once-daily, in this case, Insulin Glargine. And at some point during this treatment period, they received a

double dose, and then later a triple dose, of either of the insulins. And then they were crossed over to the other arm. And the bottom line with this study was that there was comparable percentage of individuals who experienced clinically-significant hypoglycemia. So with this overdose of the Icodec, there was no difference in the proportion of patients who experienced significant hypoglycemia compared to Insulin Glargine, which I think is very reassuring. Also when counter regulatory hormones were looked at during hypoglycemia, they were similar with Icodec compared to Insulin Glargine. And we've seen also from CGM data that the duration of hypoglycemia is no different with Icodec compared to the once-daily basal insulins.

Another clinical question that I think is important is does it matter where I inject the Icodec, the Insulin Icodec? Could it be in the arm, in the abdomen, in the thigh, like other insulins? And this was a three-period crossover study in patients with Type 2 diabetes, again on basal insulin with or without oral agents. Which looked at the pharmacokinetics, so Insulin Icodec concentrations, and pharmacodynamics of the effect in lowering glucose. If it's administered in the thigh, versus the abdomen, versus the upper arm. And this is looking at the pharmacokinetics after a single dose in either thigh, abdomen, or arm, very similar on the left. And then at steady state after multiple doses, as well, there did not appear to be a difference whether the patients were administering in one of these three locations. And if we look at the glucose lowering effects, so the pharmacodynamics, was not different, as well.

So the bottom line from this study is that it appears that there's no difference with respect to Icodec concentrations or Icodec action if it's administered in the arm, in the abdomen, or in the thigh. Which I think leads to even more convenience for patients.

The last question is how should this be administered? What is the dose? So in the Icodec studies, what was done in patients who were on oral agents and they were initiating insulin therapy, the dose of Icodec that was started was 70 units. So to get the equivalent of what that would mean in a daily basal insulin dose, you would divide by seven. So they basically started with an equivalent of ten units daily. So in these trials, for example, if they were going to be comparing to Insulin Glargine. They would start with 70 units of Icodec and they would start with ten units of Insulin Glargine and then dose escalations or titrations if needed were done on a once-weekly basis.

And you can see what happened in this particular study in insulin naïve patients over the 26 weeks of the study. And this is looking at fasting glucose, maybe slightly higher with Icodec at the beginning but not really clinically significant. But certainly by the time you get to four weeks, on average they were quite similar. Now a different situation in patients who were already on basal insulin.

So this is looking at the Phase 2 study that looked at whether it's important to have a loading dose or not in someone who is already on basal insulin. And you can see here in the dark blue line where you see fasting glucose going up initially, this is no loading dose. So the patient basically stops the basal insulin they were on and initiates the equivalent dose in the weekly insulin and you do see a bit of a rise in fasting glucose. And this is because of the long half-life, the eight-day half-life of Insulin Icodec. It takes a while to reach the steady state. So what you see, though, in the light blue line, is Icodec fasting glucose is here with a loading dose. In this particular study, it was twice the basal insulin dose. So, for example, if a patient was on 20 units of basal insulin before initiating Insulin Icodec, they would have started on 20 times 7, so 140 units if there was no loading dose. And in this particular study, it would be 20 times 7, which is 140, times 2, which would be 280 units, so that would be the loading dose.

What was decided for the Phase 3 trials was actually to give a one-time loading dose 50% higher than the dose that was calculated based on the previous basal insulin. So, for example, if a patient was on 20 units, the calculated dose without a loading dose would be 20 times 7 or 140, and then here you would add 50% more, so 70 units more or 210 units. So the initial dose of Icodec in a patient on 20 units of basal inulin would be 210 units one time administration or injection. And then the following week, it would fall back to the dose that had been calculated basically one to one, if you will, which would be 140 units. So with respect then to titrating after initiation, what was done in the clinical trials was a target of 80 to 130 milligrams per deciliter. So if the patient is at that target and what was used were the three glucoses prior to or the glucose on the day of titration and the two days prior to titration. And this would be fasting glucose using the mean of those glucoses. If it was between 80 and 130, there was no titration. If the mean was higher than 130, there would be an increase of Icodec of 20 units. So this is just if we convert this in the equivalence of daily, it would be divided by seven, so slightly under three units.

With Insulin Glargine, the adjustments in the trial were done in three units if the mean was higher than 130. And then if there was a glucose lower than 180, and in this case, they used the lowest of the three glucoses, was less than 80, then there would be a reduction of 20 units of Icodec. And in the case of Insulin Glargine, it would be a reduction of three units. So I think this is relatively simple with respect to figuring out how to titrate with this target, again, of 80 to 130 milligrams per deciliter.

So to summarize, there's two weekly basal insulins that are in development, Insulin Icodec that has completed Phase 3 and has submitted to the FDA. And Insulin Efsitora alfa, which is in ongoing Phase 3 clinical trials. They both effectively lower glucose and they do so comparably to what we've seen with once-daily basal insulins, either Insulin Glargine U100 or Insulin Degludec. The rates of hypoglycemia in the Type 2 diabetes studies were generally low and they were similar between the two with only mild differences that probably were not clinically significant. And other side effects, such as weight gain, injection-site reactions, systemic reactions,

immunogenicity, appeared similar with the once-weekly insulins compared to the once-daily basal insulins.

And we do need more information with respect to Type 1 diabetes, in particular, to see how this will be used in Type 1 and additional data in these populations. I think we've been reassured from the CGM data, as well as the study I showed with twice and three times dosing. That although we should always be concerned about hypoglycemia with any patient with diabetes using insulin. Certainly there does not appear to be any increased risk with the once-weekly insulins, at this point, compared to the once-daily basal insulins.

So thank you very much for your attention.

[CHAPTER 3]

Dr. Mathieu:
Hello, I'm Chantel Mathieu, and I'm an endocrinologist from Leuven Belgium, and welcome to my clinical perspective on once weekly insulins.

Here are my disclosures.

When talking to people living with diabetes when I was recruiting them to take part in trials with once weekly insulins, I got some very interesting statements. First of all, there was a person with type 2 diabetes who didn't inject insulin before and so when I said, would you like to participate in a trial with a once weekly insulin, he said of course, why do you ask me even if I would like to inject once a day or once a week? But I was even more surprised by the reaction of one of my female patients I have been following for a long time. She is on multiple daily injections, she was in the ONWARDS 4 study with the once weekly Icodec, and she was in the arm where she received the once weekly insulin.

And so at the end of the trial she was very upset with me that I wouldn't continue giving her the once weekly insulin. So I said, but isn't it strange you inject your mealtime insulin? What's the difference? Just injecting one more basal insulin per day. And she said, you know, every injection matters so give me the once weekly insulin. So people are using it really like it and at the end of this talk I will be showing you some patient rated outcomes from the clinical trial programs.

When talking to doctors or dietitians or educators, the situation changes a little bit, comments from colleagues for instance, are fear of stacking, fear of hypoglycemia, fear of prolonged hypoglycemia. A dietitian told me oh, we will see a lot of weight gain with so much insulin on board. And primary care on the other hand they said, oh yes, we dig it, we understand the once weekly insulin, we have the once weekly GLP-1 receptor agonist, bring it on. So very different perspectives.

And so this brings me to my overall clinical perspective. Once weekly insulins for who? We are sure that people with type 2 diabetes who need basal insulin, this will be a very elegant way to start basal insulin but also those already on a once daily basal insulin will benefit from switching to a once weekly basal insulin. For type 2 diabetes, the jury is still out with two different studies, one in Phase 2, one in Phase 3, Efsitora and Icodec. More data will be needed also to find those people with type 1 diabetes who may benefit because I can already think of a few profiles that may benefit from having a once weekly basal insulin.

How to start Icodec? We do have a regimen, 70 units per week in insulin naive people, and when switching from already basal insulins that are being used daily, there you will multiply the dose that is being used daily by seven and then add a one-time 50 percent loading dose. For Efsitora, the jury is still out. Phase 3 studies ongoing, we will learn what the advice is there. How to titrate, again Icodec 3 SMBGs fasting measurements and then increase decrease by 20 units per week. Efsitora, more data will come.

And then what to do with the mealtime insulin in people on MDI again for Icodec we know that the mealtime insulin can be brought down and in some people we could even stop the mealtime insulin. Efsitora, again, the Phase 3 data are coming.

And then hypoglycemia, for Icodec we know that in type 2 diabetes, there's no increased risk, there's no longer duration difference in presentation or reaction, in type 1 diabetes, the one Phase 3 trial ONWARDS 6, did show an increased risk in hypoglycemia for people with type 1 diabetes. And Efsitora, the Phase 2, again shows similar data as what was presented for Icodec with the exception of the data in people with type 1 diabetes, but we need more data from the Phase 3. I didn't show the data on weight, weight increases were not different between the weekly insulin and the once daily basal insulins.

But the bottom line, the really important question is, what do people with diabetes think about this once weekly insulin use? Do they like it? And so fortunately many of the studies that have been conducted have included patient related outcomes. And so here I just took data from the ONWARDS 2 study, where they used, people who were already on a basal insulin and then switched to Icodec or to degludec, and as you can see, the treatment satisfaction was higher with the once weekly Icodec than with degludec, and also other PROs showed the same increased satisfaction for those using the once weekly basal insulin.

Still, not all questions have been answers, many questions are still out there and namely, what happens with exercise? What happens

with intercurrent illness? What happens with fasting? What happens with hospitalization? So, studies are ongoing, both for Efsitora as I introduced you already, but also for Icodec to answer these important questions. Also, how should we switch back to a once daily basal insulin if needed? Or how will we switch between Icodec and Efsitora and vice versa? What about pregnancy? What about children? What about the elderly? Where having the option of having a once weekly insulin administration may be very appealing to those needing insulin administration by third parties.

So, a final thing I want to highlight is that we will need a lot of communication, a lot of education, not only for endocrinologists but also for primary care doctors, for nurses, for diabetes educators, for dietitians, surgeons, internists, pediatricians, and of course, also for those using the once weekly insulins. So this is my conclusion, I do think there is a future for these products but more research is needed to really guide us clinicians in how to use these products.

Thank you.

[CHAPTER 4]

Dr. Goldenberg:
Hello, I'm Dr. Ron Goldenberg, I'm an endocrinologist in Toronto, Canada affiliated with the LMC Diabetes and Endocrinology Group. And I'd like to peer into my crystal ball as you see on the slide regarding the once weekly insulins and take a glimpse into the future outlook for ultra long-acting insulins.

These are my disclosures.

And the objectives for this session are to know the timeline of incredible basal insulin innovation, including the once weekly options moving into the future to contemplate the potential impact of the clinical data on the prescribing of once weekly basal insulins once they are available for prescription in the clinic and then take a little bit of a glimpse into the future of a fixed ratio combination of a once weekly basal insulin along with a once weekly GLP-1 receptor agonist.

The story of basal insulin innovation is quite incredible. We started off with NPH many decades ago, which has a relatively short half-life of 5-10 hours, and over the years there's been continuous improvement to extend the duration of action of basal insulins, start with the first generation analogues, which have a half-life of about half a day, moving to the second generation analogues with a half-life of about one day. But now we're very excited looking into the future and by 2020-- by 2024 hopefully we'll have access to the once weekly insulin Icodec, which has a half-life of about eight days and about a year later, probably in 2025 if all goes well, we'll be able to access insulin Efsitora, which has even a longer half-life of 17 days.

So the question I propose, looking to the future of these once weekly options is once weekly insulin really ready for prime time, meaning, is the data sufficient right now that we will been able to use these agents wisely and safely in the clinic? So I'm going to use the traffic analogy, traffic light analogy to analyze this. Green light will be the data is pretty impressive and will be encouraging to us as clinicians. A yellow light would signify there's some cautions or maybe we need more information. And a red light would mean that perhaps right now we're not ready to use it for whatever reason in the clinic.

So let's start with the green light and hopefully I'll convince you that the efficacy and safety data in type 2 diabetes is rather convincing and also issues around therapeutic inertia, adherence, and treatment satisfaction also will be quite encouraging moving into the future regarding once weekly basal insulins. So let's start with the type 2 diabetes efficacy and safety data. And the Phase 3 program with insulin Icodec has been completed and on this slide you can see the three trials, called ONWARDS 1, 3, and 5, that were done in insulin naive patients with type 2 diabetes. The top line summary of these three trials is that each showed glycemic superiority to a daily comparitor and across the board the rates of level two or three hypoglycemia were incredibly low. So overall in the Phase 3 Program for insulin naive patients, we see superior efficacy and a good safety profile.

So I think once this is available in the clinic, a once weekly option would be great for insulin naive patients with type 2 diabetes. There are also two studies done in patients with type 2 diabetes previously treated with a basal insulin as shown here on the ONWARDS 2 and ONWARDS 4 trials and in these studies you can see either superiority or non-inferiority for glycemic efficacy and again, no statistically significant concern around level two or three hypoglycemia.

We also have CGM metrics for the three studies shown here; ONWARDS 1, ONWARDS 2, AND ONWARDS 4. And you can see compared to the daily basal options, the CGM metrics are quite encouraging, in fact in ONWARDS 1, the time and range was superior compared to the daily basal comparator and across the board you see very low rates of time below range. So overall, insulin Icodec Phase 3 trials in type 2 diabetes really suggest very good efficacy and safety data.

Furthermore, some clinicians may be concerned that with such long duration of action of a basal insulin, would there be the potential for very prolonger hypoglycemia if it occurs and at the American Diabetes Association meeting, we heard that actually there's a similar

duration of hypoglycemia with insulin Icodec compared to daily comparitors. So I don't think we really have to be concerned that the hypoglycemia would linger any longer than a daily basal option.

We have Phase 2 data for insulin Efsitora, shown here is a study in insulin naive patients where there was non-inferiority for glycemia and no concerning signal for hypoglycemia. In the Efsitora basal switch Phase 2 study, again there was non-inferiority to insulin degludec as a comparitor and a suggestion of lower rates of hypoglycemia but that has to be interpreted with caution because the target fasting glucose was actually much higher from a safety point of view in this first trial for the once weekly option. But certainly no safety concern. And so while the Phase 2 data is very encouraging, we will need confirmatory data from Phase 3, but I'm convinced right now that the data in type 2 diabetes for these once weekly insulins looks quite encouraging. The Phase 3 program for Efsitora is ongoing, two trials in insulin naive patients, QWINT 1 and QWINT 2, and two trials with insulin experienced patients, QWINT3 and QWINT 4.

So what about therapeutic inertia? You would think that a once weekly option would make it easier for clinicians to convince individuals with type 2 diabetes to advance to a once weekly injectable option compared to a daily injection. And this issue of therapeutic inertia I think is important because despite poor glycemia initiation of insulin is often delayed, we know that about 30 percent of individuals decline insulin and only 38 percent of decliners eventually start insulin, often with a mean time to insulin initiation for more than two years. Finally, basal insulin up-titration is often very slow and insufficient in the clinic.

Interestingly in the Icodec and Efsitora trials that have been completed in insulin naive patients, the average duration of diabetes was about 11-12 years or so, suggesting that there's a lot of patients out there with long-standing poorly controlled diabetes and I suspect if we offer these individuals a once weekly versus a daily option, that that would encourage them to advance to insulin therapy. Also perhaps the availability of a dosing app may help counteract some of the inertia around appropriate and aggressive insulin titration.

So what about adherence? So we know from the GLP-1 receptor agonist space that patients favor a once weekly injection over a daily injection option. And we now know from the ONWARDS 5 trial, as presented at the ADA meeting, that there was a statistically significantly higher TRIM-D compliance domain score at Week 52, with once weekly Icodec compared to once daily analogues. And TRIM-D is a really validated way to assess compliance in a clinical trial.

So what about treatment satisfaction? We thought patients would like a once weekly option, but this is actually been now presented and that's the treatment satisfaction score with insulin Icodec compared to comparitors in ONWARDS 2 on the left of this slide, and ONWARDS 5 on the right. In the top line summary here is that there is a statistically significant higher change from baseline in total treatment satisfaction score favoring once weekly Icodec over once dale comparitors. So that tells me that our patients in the clinic would be happy with their experience when we prescribe a once weekly insulin.

Now, there are some potential concerns with a once weekly option and they're listed here. So, let's go through some of these issues and one is the fear of very high doses. Because you're given your entire weekly dose in one shot, many patients will end up on very large doses of their once weekly insulin. And so this is the kind of conversation that healthcare providers will have to be aware of. A patient may say something like "I really like this once weekly insulin, doctor, but I'm worried that I'm up to 350 units every week and I'm injecting such a large amount." So, be prepared to address this by answering in the following way. So, you really need to know that 350 units of a weekly insulin such as Icodec is actually equivalent to taking 50 units once a day. So, if you put it in that perspective, that high number is not as scary. Also, because insulin Icodec is seven times the concentration, at 700 units per ml the volume you inject with 350 units is actually the same volume as 50 units of insulin. So this'll take some education to healthcare providers but I think it's something that will be very simple to address.

Well what about complexity? Because the initial dosing and the titration may seem a little bit complex and it actually is a little bit complicated but it can be simplified. So you have to know the insulin initial dose and then the titration algorithm, whether you're insulin naive or whether you're previously on a basal insulin and switching, and as shown on the top of this slide for insulin Icodec, insulin naive patients get 70 units in their first shot and then you titrate by about 20 units upwards if you need to achieve better glycemia. There also has to be a loading dose and in the Icodec trials, when they switched from a daily basal, the initial loading dose was 10.5 times your daily basal, I think I might simplify that and just tell patients to take 10 times their daily basal, so if they're on 40 units, their initial loading dose would be 400 units, for example. And Week 2 they would take seven times their usual daily dose and then they would titrate by 20 units daily. So it's a little bit complicated but like anything new in medicine, education and learning the protocols will be important. I think that dosing guide apps and connected pens, as shown here, will perhaps also reduce some of the complexity for patients.

Finally, there are some special situations that I'll review that might be concerning for such ultra long-acting insulins and we do need further research for situations that increase the risk of hypoglycemia. So for example, what if we suddenly exercise, will hypoglycemia occur? What if there's an acute illness with reduced food intake? Or what if a patient's hospitalized for surgery or undergoing some clinical procedure. So we need answers for all of these questions. Fortunately there is a trial listed on clinicaltrials.gov, with Efsitora insulin looking at the severity of hypoglycemia under conditions of increased hypoglycemia risk. So hopefully this will give some answers

as to what happens if you exercise or if you're suddenly drop your food intake by fasting for example. So we await that study with great interest.

Finally, like any new therapy that comes to the market, cost and access will be a potential concern and that's why I put it in the yellow traffic light analogy here and you know, Dr. Banting would kind of roll over in his grave if he heard about the price of insulins nowadays, because he was quoted as saying insulin does not belong to me, it actually belongs to the world, shortly after he made the discovery, along with his colleagues of insulin over 100 years ago. And so cost and affordability is a big issue, things are improving in the United States and other areas of the world with co-pays and assistant programs, but will once weekly insulins be accessible and affordable is a question that we really will need an answer for.

Finally, I'd like to touch on what I'm giving a red light right now because I think we need more information, and that's the efficacy and safety data that we know so far with type 1 diabetes. So we have top line data from ONWARDS 6, which is the Icodec trial in type 1 diabetes. Was actually similar for A1C lowering compared to the daily comparitor but there was more hypoglycemia. So this hasn't been presented or published yet, and will need a bit of an explanation as to why there was more hypoglycemia. But I think at this point, besides the hypoglycemia from this trial, the other limitations and type 1 diabetes will be the fact that the patient still has to inject their bolus insulin three times daily and I think many patients with type 1 diabetes would like the option to make more frequent adjustments to their basal insulin than only once weekly. So I give that a red light so far, as more information comes to light, maybe that will change. But right now I think the data suggests we need more information in type 1 diabetes.

And while the Phase 2 study with Efsitora and type 1 diabetes looks pretty encouraging from a safety point of view, we really need to await the Phase 3 trials with insulin Efsitora and that's the QWINT 5 trial shown here. So that's the overall summary of "is once weekly insulin ready for prime time" and I think overall if you look at the totality of evidence that for type 2 diabetes patients, once approved a once weekly insulin will be a good go-to for insulin naive patients and also for those that want the convenience of a weekly shot to switch their daily basal to a once weekly option.

So before I finish I'd like to take a brief glimpse into the future and talk about the benefits of combining a weekly basal insulin with a weekly GLP-1 receptor agonist. So this makes a lot of sense from both an efficacy point of view, where the combination would be better than either agent alone, and also from a side effect point of view, where the GLP-1 component of this combination would blunt the weight gain from insulin as well as the hypoglycemia and also because of the slow titration related to the insulin component, you may get less nausea compared to giving a GLP-1 alone. So then it makes perfect sense to maybe study a fixed ratio combination of a once weekly basal with a once weekly GLP-1 and in development is a product called IcoSema, which is a fixed ratio combination of 350 units of Icodec with 1 milligram of Semaglutide. So this molecule is being studied in a Phase 3, a program called the Combined Program, three different studies looking at either patients treated with basal insulin or patients already on a GLP-1, and hopefully in 2023 and into 2024, we'll hear the results of the IcoSema Phase 3 program.

So to take a look at what we've discussed and the future outlook for these ultra long-acting basal insulins, I think we can expect them by 2024 and 20205 and I think as clinicians, we'll likely use them in type 2 diabetes as a basal insulin option or as a switch from a daily basal. We do need some ongoing research to address some issues related to things like exercise or reduced food intake, and we need more data in type 1 diabetes. And moving forward, I think a fixed ratio combination may be a convenient way to give a weekly GLP-1 receptor agonist along with a weekly basal insulin.

And thank you for your attention.

[CHAPTER 5]

Patient:
Hello, my name is Saul, and I live in Aalborg, the fourth largest city in Denmark, Northern Europe, where I have lived for the past 30 years. I've been living alone since my wife died three years ago. I have two children, a girl and a boy, age 43 and 37. My daughter also lives in Aalborg, close by and my son lives in Copenhagen, and I have four grandchildren. I am retired, but during my working life I worked in the finance department of small and middle sized businesses as a financial manager, financial controller, and head of finance. I had therefore always had an inactive life with not much exercise during my daily life and at the cause of an injury to my knee in my early years, I have not been doing much exercise in my spare time either.

I was diagnosed with type 2 diabetes by my general practitioner in 1994 and for the first two years, with no other treatment than changing diet and walking two to three times a week. At that time I was also diagnosed with high blood pressure and high cholesterol, which I was put in treatment for with tablets. Furthermore, there's something wrong with my kidneys for which I receive no treatment right now.

From 1996 and onwards I started treatment for my diabetes with tablets. The amount and brand of the tablets had varied over the years.

After some time, I experienced that I could not tolerate one of the tablets and I had to change to another product. Once I was diagnosed with a heart attack but it proved not to be a heart attack but just that I could not tolerate one of my tablets. When starting treatment with tablets, taking care of my diabetes was transferred from my general practitioner to the endo department of the local hospital with visits every six months.

From approximately 2015 I started treatment of my diabetes with insulin. Before starting to take injection of insulin myself, I was told by a nurse of how to do it, what to be aware of when being on insulin, and what signs that I should pay attention to when measuring my blood sugar levels and what to do if my level of blood sugar became very low. What fruits to have in the kitchen and juice to help low blood sugar. My wife was helping me when learning this and she helped me if I had any questions or worries. My wife was a nurse so it was a big help in the beginning when everything was new. I have been on different types of insulin according to regulations from the authorities from what was the cheapest part of insulin now taking as long-lasting once a day insulin.

Today I'm taking my long-lasting insulin once in the morning and measure my blood sugar three times a day before I eat; morning, noon, and evening. I'm happy with that at the moment and I just have to bring something to eat if I pass my usual eating times of the day. An example, if I'm playing golf from the morning to the afternoon, I have to bring something to eat to avoid too low, low blood sugar. I'm happy with the treatment for my diabetes with long-lasting insulin and I'm glad that I'm not on short-lasting insulin where you have to take injections every time before you eat.

I find it interesting that research is being done trying to improve the treatment of type 2 diabetes with ultra-long-lasting insulin and I'm sure that I will change to that if it becomes available in Denmark. I do see benefits for me as a patient in changing to ultra-long-lasting insulin because I expect that my blood sugar levels would be more stable throughout the period between injections of ultra-long-lasting insulin which possibly require less testing of blood sugar level.

For example, when I think that it might be possible to test three times a day, at the beginning and at the end of the period between injections of ultra-long-lasting insulin, and only once or twice a day in the middle of the period. This will also mean that I do not have to ensure that I have 5-10 minutes every morning to test my blood sugar and inject my insulin. It would also make my everyday life easier. It is not too annoying to inject but it's always a small nuisance to have to inject every morning and shifting to once a week would make my everyday life easier. Less insulin to carry when traveling and it might be easier to find a refrigerator to keep the insulin cold when traveling. I think that traveling will also be easier when I do not have to carry as much insulin needles and test material for my journey and if I'm traveling for less than a week, I do not have to carry anything, which will be a lot improvement of my everyday life. When I visit my son in Copenhagen, I do not have to bring insulin if I'm just staying for a couple of days and it would give me more freedom not to have to think of my diabetes and worrying about the levels of blood sugar at all times. The risk of having to find replacement medication during a visit traveling would also be reduced if I do not have to have so much insulin, needles, and test material with me when traveling. I think I would still have to carry fruit or energy bars during my playing golf and going sailing, but only as a precaution if anything should go wrong and I suddenly have too low blood sugar and not as much as I have today where I always have a sandwich or two with me on the golf course.

While I have never participated in a clinical trial myself, I'm very glad to see that there are researchers thinking about improving us diabetes patients' lives. We need quality of life and that can sometimes be hard when we constantly have to think about our disease. I'm not sure I would have volunteered for a clinical trial should it have been performed in Denmark, but I would really be glad to have spoken to my doctor about it so that we could come up with a plan to test the drug or start it once it had been approved in Europe. I'm looking forward to having the chance to be one of the first patients in Denmark to take ultra-long-acting insulin, mostly so that I can improve the quality of my life. I can't imagine what it would feel like just to be diagnosed with type 2 diabetes and be offered a long-acting insulin right away. I would never had to go through all the ups and downs adjusting my medication and getting used to insulin the way I did many years ago. Life would be simpler from the start and not like in the old days.

I'm very pleased that your clinical trial results listed here today are positive and give a potential new treatment option in the near future. It feels like with the results like this, it is likely to happen soon. It would make me very happy if it is also approved for use for patients in Denmark and Europe. I do not know a lot of patients with diabetes in my network. I do not usually communicate with other diabetes patients, I keep to my nurse and doctors for those conversations. However, if I had a bigger diabetes community connection, I would most certainly tell them that this is potentially coming and the benefits that I see getting insulin through a once a week injection.