TRESIBA® AND XULTOPHY® EQUIP ENDOCRINOLOGISTS WITH TWO POWERFUL DIABETES DRUGS

In Real-World Practice, Endocrinologists Praise Novo Nordisk's Tresiba® and Xultophy®

Although the primary endpoint for the CONCLUDE trial[1,2] was not met—which is superiority of rate of overall symptomatic hypoglycaemia with Tresiba® vs glargine U300 in maintenance period was not significant. However, it was 12% numerically lower in favor of Tresiba®—one of the study's secondary endpoints emerges as a major focus for doctors and patients: lower incidence with Tresiba® of nocturnal hypoglycaemia. Xultophy® (IDegLira) combines degludec and liraglutide in one injection. Findings and observations regarding Tresiba® and Xultophy® presented in this newsletter, supported by Novo Nordisk, are based on interviews with diabetes experts in Saudi Arabia, Europe, and the United States, and presentations at the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD).

Saudi Endocrinologists Comment on CONCLUDE

"The findings for degludec in the CONCLUDE trial were disappointing because the primary endpoint was not achieved. However, the levels for hypoglycaemia were much lower among patients in the degludec arm (Figure 1)," notes Ahmed Haroun, MD, summing up much of what some endocrinologists in Saudi Arabia had to say about the trial. Dr. Haroun is internal medicine and endocrine consultant, and head of the Department of Internal Medicine at Mouwasat Qatif Hospital, Eastern Province, Saudi Arabia. He is also assistant professor at Cairo University in Egypt.

"I have almost three years' experience with Tresiba® in Saudi Arabia," says Dr. Haroun. "I cannot remember us admitting even one patient for severe hypoglycaemia who was being treated with degludec since we started using it in our hospital. With it we have smooth blood sugar control and acceptable fasting blood sugar results. We've also found that because it requires smaller doses, use of Tresiba® reduces our overall insulin cost by 10%. Additionally, lower insulin dosing does not lead to so much weight gain."

For Hussein Elbadawi, MD, in practice at My Clinic Medical Center in Jeddah, Saudi Arabia, the key takeaway from the CONCLUDE trial is the performance of Tresiba® with regard to nocturnal hypoglycaemia. "Nocturnal hypoglycaemia when it occurs takes place from midnight to 6 a.m. Any drop in blood sugar levels during that time is categorized as nocturnal low blood sugar. This can be scary for some patients because they worry about something called dead-in-bed syndrome, where they go to sleep after taking insulin then don't ever wake up because they drop into a hypoglycaemic coma and die," he explains.

"If we use an insulin that creates less risk to patients, or the more we can prevent nocturnal hypoglycaemia, the better that insulin is. Having very good numbers that favor use of Tresiba® in that specific timeframe make it a better drug to prescribe and a safer one overall. Severe hypoglycaemia is really bad hypoglycaemia to such a degree where a patient desperately needs someone to help him administer sugar. That's where Tresiba® proved to be better or less of a risk for pushing a patient into that category."

> "I cannot remember us admitting even one patient for severe hypoglycaemia who was being treated with degludec since we started using it in our hospital."
>
> – Ahmed Haroun, MD

Dr. Elbadawi traces the origins of the CONCLUDE trial to a desire to reconcile data from several previous studies that posed a question researchers wanted to finally settle. "They set out to see if there is a correlation that will prove that when we use a potent—or a little more potent—insulin like degludec, which is less variable and doesn't fluctuate that much throughout the day compared with glargine U300, will that translate into less risk of hypoglycaemia that we saw in other studies such as SWITCH[3], when it was compared with glargine U100? The desire to pull everything together was the backstory that led to the CONCLUDE trial.

"Both degludec and glargine U300 were being compared with what used to be considered the standard of care, glargine U100. The EDITION[4] and BEGIN[5] studies showed degludec and glargine U300 to be better than glargine U100, so the question was, which of the two newer basal insulins is better? The CONCLUDE trial was intended to answer that," adds Dr. Elbadawi.

> "After changing our basal insulin from glargine U100 to degudec, the problem of large fluctuations in blood glucose levels was almost gone."
>
> – Dania Al-Khafaji, MD

Was CONCLUDE a Setback? A Critique

Examining CONCLUDE, Dr. Elbadawi says he had the feeling of watching something where when one thing went wrong several other things also went wrong. "Early in the study there was a problem with inaccurate blood glucose meters, so they had to extend the trial. In the meantime, study patients were asked to use their own meters to document blood sugar levels," a situation that Dr. Elbadawi says depended heavily on the accuracy of and reliability of patients' own meters. "It gave me the feeling that doubts about the accuracy or the credibility of the fine details of every single data point made people a little more skeptical of the study even if there was a positive result."

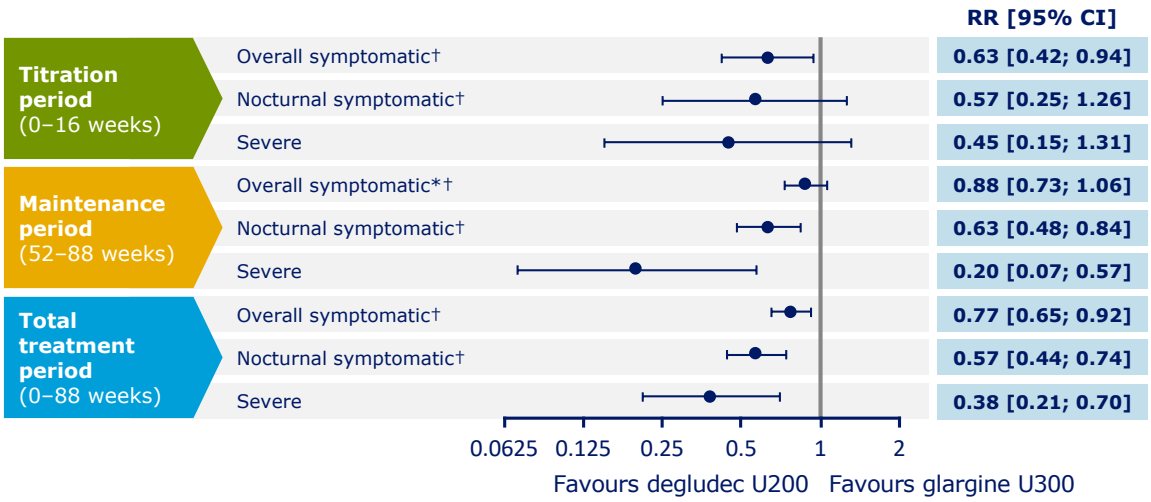
Dr. Elbadawi says he imagines that pharmaceutical manufacturers and researchers will continue to try to answer the question of whether there is clear overall superiority between degludec and glargine U300. "We might see a trial based on the drugs' effects on nocturnal hypoglycaemia as the primary endpoint. Regarding that, we have a signal from CONCLUDE, but we want to make it a fact."

The question of whether CONCLUDE has had any impact on her practice or its good results treating patients with a basal insulin is a question Dania Al-Khafaji, MD, readily answers. Dr. Al-Khafaji is endocrinology consultant, chairwoman of the Diabetes Center, and program director of the Diabetes Fellowship at King Fahad University Hospital, and Imam Abdulrahman Ben Faisal University, Al Khobar, Saudi Arabia. "I am a big fan of Tresiba®, based on what I noticed among our patients here. After changing our basal insulin from glargine U100 to degludec, the problem of large fluctuations in blood glucose levels was almost gone," she says.

FIGURE 1

Degludec performed better than glargine U300 with regard to specific types of hypoglycaemia.[2]

CONCLUDE: rates of hypoglycaemia



*Primary endpoint
†Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms. All nocturnal hypoglycaemia reported between 00:01 and 05:59
CI, confidence interval; glargine U300, insulin glargine 300 units/mL; RR, rate ratio

CONCLUDE
COMPARING THE SAFETY OF DEGLUDEC WITH GLARGINE U300

Thomas Pieber, MD, professor of Medicine, head of the Division of Endocrinology and Metabolism, and chairman of the Department of Internal Medicine at Medical University of Graz, Austria, says Figure 1 shows that one crucial secondary outcome, rates of hypoglycaemia, favors Tresiba®. "If you look at the secondary outcomes, they show us a very clear picture. Although the primary outcome was not achieved, any other secondary outcome is in favor of insulin degludec, or Tresiba®," he says.

The rates of severe hypoglycaemia over the maintenance period of 72 weeks and total treatment period of 88 weeks show a decided advantage to Tresiba®. Dr. Pieber adds: "Because the variability between glargine U300 and Tresiba® favors degludec, diabetes patients can achieve the same glycemic control with less insulin, while also reducing the risk of severe or nocturnal hypoglycaemia."

"It's unfortunate that the primary outcome was not met in CONCLUDE, but in general, Tresiba® met the secondary endpoints, which includes nocturnal hypoglycaemia and severe hypoglycaemia requiring third-party assistance," says Dr. Al-Khafaji.

She adds that she believes the technical problem with the blood glucose meters at the beginning of CONCLUDE affected the result of the study. "I don't think it was totally accurate, especially at the beginning of the study. But in general, Tresiba® met the secondary endpoints, which has made us comfortable using degludec more and more as we wait for further studies to show it meeting other endpoints."

Dr. Al-Khafaji sums up her preference for Tresiba® over glargine U300 by making three observations. "In clinical practice here in Saudi Arabia, I've found that patients achieve much better blood sugar control and targeted hemoglobin A1c levels with degludec than with glargine U300. That's one point.

"Another is the fasting blood glucose levels in our population; they are much more controlled with degludec

than with glargine U300. Third, degludec requires lower doses than does glargine U300. These three points make us much more likely to prefer degludec over glargine U300."

Saudi Endocrinologists Comment on Xultophy®

Xultophy® (IDegLira) balances the best aspects of two powerful diabetes drugs.

- The strength of Xultophy® is that its two component drugs: degludec and liraglutide each counter a common adverse effect of the other drug: possible weight increase from insulin; possible nausea from a glucagon-like peptide 1 (GLP-1).
- Xultophy® seems tailored to the concerns of Saudi endocrinologists' regarding diabetes patients' tendency to be overweight. The medication almost always prevents weight gain even if it does not always bring about actual weight loss.

> "There's the fact that we are using two medications that complement each other and produce less hypoglycaemia for a safer regimen overall."
>
> – Hussein Elbadawi, MD

"Because it was only recently introduced in our hospital here, we have only 10 or 15 patients who are taking it," says Dr. Haroun. "Already it has established a consistent pattern for diabetes patients. We have relatively rapid achievement of glycemic targets and fasting blood sugar levels, only one or two weeks after starting. It also works at a much lower dose than we expected. I usually set a target for my patients, expecting them to need 30 to 40 units of insulin but reached blood sugar control at a much lower dose. Even with just a few patients, we can confirm the efficacy of Xultophy®." Dr. Haroun says patients also experience fewer than expected adverse gastrointestinal effects.

Avoiding Weight Gain and Nausea

The main problem with treating diabetes patients is not fasting blood sugar levels, says Dr. Haroun. "Of course, our diabetes patients have high fasting blood sugar levels, but we can achieve acceptable fasting blood sugar levels in most patients if they will titrate insulin. The main problem is that most patients here maintain a high postprandial blood sugar level because we have a tradition of eating large amounts of rice at lunch and often at dinner as well, in addition to a lot of dates. This makes postprandial hyperglycaemia the main obstacle for getting our patients to their diabetes-related targets. That's why Xultophy®'s fixed-dose combination offers a very good option for our patients in particular, because in addition to targeting fasting blood sugar levels, most users achieve better control over the postprandial component, too. At times I prefer Xultophy® to start with rather than just a basal insulin alone."

Another aspect Dr. Haroun likes about Xultophy® is that it overcomes patients' reluctance to use needles while offering the possibility of some weight loss. "We not only have a big problem with postprandial hypoglycaemia, we also have a big problem with compliance, especially with injectable therapy. So, if we have a combination drug that offers a solution to the unmet need of patients to control their blood sugar levels—fasting and postprandial—with a lower risk of hypoglycaemia, has a good effect on weight—either adds no weight or reduces it—and does all this with just one injection, you can see why we like Xultophy®"

Dr. Haroun says that a big contributing factor to diabetes patients' weight problems is that aside from a moderate to high carbohydrate at most meals, they often don't exercise regularly. "Even patients taking a GLP-1 alone have a moderate to high carbohydrate load in most of their meals and don't exercise regularly. So while I am not expecting to see much weight loss by patients taking Xultophy®, at least patients will not gain weight. I tell patients that while it's good to have weight loss if you don't lose weight at least you can achieve your blood sugar target without gaining weight as we see with basal insulin alone."

Dr. Elbadawi says that being able to avoid the side effect of nausea with GLP-1s "is huge. We've been using degludec and liraglutide separately for two years here in Saudi Arabia. When they are administered together, we start very low and then build up the dose slowly. That sort of slow titration helps patients adjust better and not complain about the nausea we used to see when we gave liraglutide as a starting dose.

"I was fortunate to be the first prescriber of Xultophy® in Saudi Arabia. We have a good number of Xultophy® users now since December 2018. Since then, I've only had one patient complain of nausea. Nausea definitely has been much diminished with this co-formulation."

Dr. Elbadawi adds that being able to promise patients that their basal insulin/GLP-1 combination therapy can be reduced to one injection "is enough to overcome patients' reluctance to start on the new therapy.

"There's also the cost savings for both patients and payers. And then there's the fact we are using two medications that complement each other and produce less hypoglycaemia for a safer regimen overall."

Another element of Xultophy® that Dr. Elbadawi praises is its degludec backbone. "That gives it a lot of flexibility. Tresiba®'s long half-life offers an 8-hour window of delay that gives patients a grace period that's a third of the day, with extended action of up to a day and a half, so if a dose is missed, patients can safely take it and still maintain control. With Xultophy®, patients are not restricted to taking it before a meal or after a meal."

Another benefit Dr. Elbadawi sees is that some of his patients have been able to reduce the amount of insulin they are taking. "The GLP-1 component increases insulin sensitivity while helping patients experience a greater sense of satiety from the food they've eaten. Some were taking Tresiba® only, but when they moved to Xultophy® where they had been taking 30 units of insulin they were able to drop down to 24 units. That gave them a sense of improvement in their lives. It made them happy. They felt that they were achieving some progress in controlling their disease."

A1c Levels: Achieving Goal

One effect of Xultophy® is its dramatic influence on lowering hemoglobin A1c levels. For Dr. Elbadawi and thousands of other endocrinologists worldwide, the A1c goal for long-time diabetes patients is below 7%. "That's when you can tell your patients, 'you're now at goal and you're in control.' That's why it was amazing that in all the Xultophy® trials patients were easily able to achieve an A1c level below 7%. It's a number we thought was kind of scary because once we saw patients hitting 6%, we'd say "maybe they're actually dropping their blood sugar levels because of hypoglycaemia for them to go that low. But they were below 7% without an increase in hypoglycaemia. Patients from different groups were able to achieve very good control, which gives us hope that in the future that we can lower A1c levels consistently once we start to offer Xultophy® to a larger patient population."

One measure of the success of a diabetes drug is how patients accept it and stick with it. "We saw patients refilling their medications and sticking to them long after where we would expect many patients to stop asking for refills," says Dr. Elbadawi. "And we were seeing that after six or 12 months patients were still feeling good about Xultophy® and a high proportion of them were ordering refills. There just wasn't much of a drop in patients using the drug, just 10%."

The ideal candidate for Xultophy®, says Dr. Elbadawi, is someone with type 2 diabetes who is probably overweight and requires insulin. "Once patients with type 2 diabetes need insulin, then you probably want to prescribe a GLP-1 with it because insulin tends to be obesogenic. It can push someone from overweight into obesity. But if you have a medication that's weight-neutral or can slow that progression, then it's a better drug."

Dr. Al-Khafaji often recommends that patients taking Tresiba® but who are experiencing weight gain or are at a point where more insulin can invite hypoglycaemia should shift to Xultophy®. "In our private practice I have to complete a full medical report in order to convince the patient's insurance plan that this medication is needed. It's not just for cosmetic purposes or only for weight loss, it's a medical necessity for a patient."

She acknowledges that Xultophy®, for all its benefits, cannot work alone to provide weight loss or glycemic control. "Talking to patients about weight loss, we have to convince them first to adopt a more healthy lifestyle. They have to be following a healthy diet and engage in more physical exercise."

Even so, Dr. Al-Khafaji is able to give her diabetes patients a reassuring message. "I tell them, number one, that their insulin dose requirement will be much less, so their weight gain, if any, will be less. Number two, Xultophy®'s GLP-1 component reduces appetite and slows gastric emptying. By this mechanism, it causes weight loss. This is a very powerful thing to be able to tell patients."

Patients with type 2 diabetes uncontrolled on glargine U100

Once-daily Xultophy®, independent of meals at any time of day:*

vs basal-bolus therapy

Comparable HbA_{1c} reduction with 44 fewer insulin units
1.5% reduction for both[1]

Weight loss
Superior 3.6 kg difference[1]

Significant reduction of overall hypoglycaemia
89% lower rate[1]

* Preferably at the same time each day.

A simple intensification treatment combining degludec and liraglutide in 1 pen[1]

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Reference:
1. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin; The Dual VII randomized clinical trial. Diabetes Care. 2018;41(5):1009-1016. https://doi.org/10.2337/dc17-1114.

Xultophy®
insulin degludec/liraglutide [rDNA origin] injection

Diabetes Experts Offer Views on Degludec and IDegLira

What the CONCLUDE Study Says–and Doesn't Say

Endocrinologists practicing real-world diabetes medicine have a much more positive view of Tresiba® versus glargine U300 than might be expected from the CONCLUDE study's results.

Summary of CONCLUDE's findings:

CONCLUDE was a two-year study involving 1,609 type 2 diabetes patients in Europe and North America. The trial's aim was to compare the efficacy and safety of insulin degludec versus insulin glargine 300 units/mL in type 2 subjects whose diabetes was inadequately treated with basal insulin—with or without oral antidiabetic drugs. The trial was completed in March 2019.

The most important endpoint did not clearly establish Tresiba®'s superiority over glargine U300 with regard to overall hypoglycemic events in the maintenance period. However, experts familiar with both insulins who have worked with them in real-world practice, say that there is more to the CONCLUDE trial than that one endpoint.

Experts Comment

Athena Philis-Tsimikas, MD, is corporate vice president of Scripps Whittier Diabetes Institute at Scripps Health, San Diego, California, USA, and associate clinical professor, Division of Endocrinology and Metabolism, at the University of San Diego. She says that one of the notable aspects of CONCLUDE was that, "when you look at the absolute number of hypoglycaemia events that occurred, there were fewer events in the Tresiba® group compared with the group being treated with glargine U300 (Figure 2)." Dr. Philis-Tsimikas gave an oral presentation on CONCLUDE at the EASD meeting in Barcelona, Spain.

While she does not claim that this result obviates CONCLUDE's primary finding, and that it can best be characterized as "directional" and not a trend, she does note that five of the study's six endpoints were met by Tresiba®. "Not only was there no difference for us to be able to say we can use one over the other, but only through subsequent studies can we determine if superiority will be seen for nocturnal outcomes."

Degludec or Glargine U300?

While the CONCLUDE trial did not provide definitive confirmation of insulin degludec's superiority over glargine U300 with regard to hypoglycaemic episodes, diabetes experts operating under real-world conditions did not hesitate to favor degludec over glargine U300.

"I have used both," says Dr. Philis-Tsimikas. "They're both better than older insulins in terms of fewer hypoglycemic episodes. But a somewhat higher dose of glargine U300 is needed in order to achieve the same lowering of blood glucose level than with Tresiba®."

Giorgio Sesti, MD, professor of internal medicine, Department of Clinical and Molecular Medicine at Sapienza University of Rome, Italy, agrees that glargine U300 requires higher dosages compared with Tresiba®. "With glargine U300, we have to increase the dose, so, more units of insulin are required to obtain the target whereas we can use less with Tresiba®. "I think most clinicians who are knowledgeable about insulin look at degludec the way it has been designed," he continues. "The chemistry, biochemistry and everything behind it has been really clever and new, whereas glargine U300 is made more concentrated to reduce the volume of insulin. So I think for most diabetes specialists, the degludec story looks much more convincing than the glargine U300 story." Dr. Sesti gave an oral presentation at the EASD meeting in Barcelona, Spain.

The Trouble With Meters

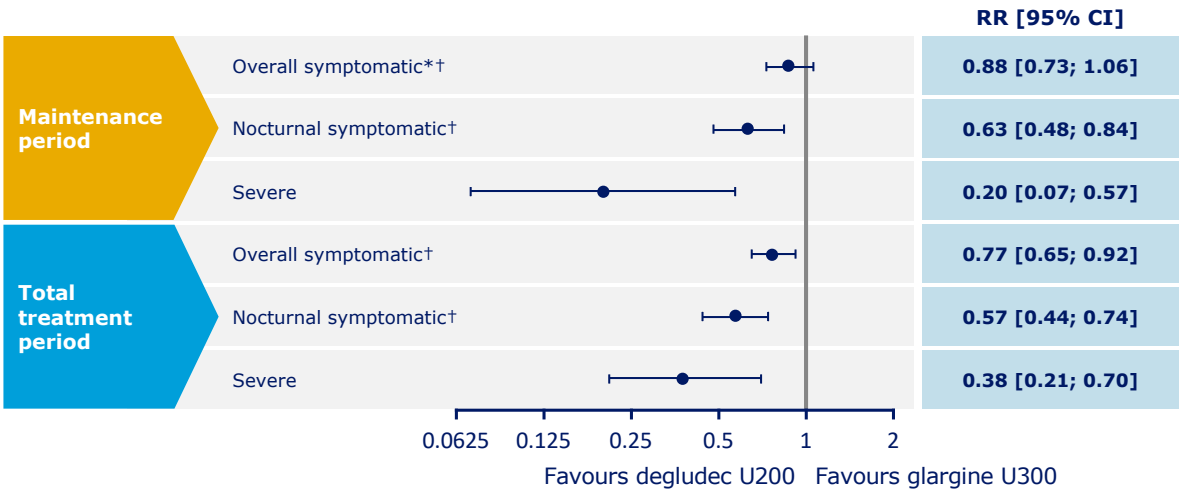
Diabetes experts specifically mentioned CONCLUDE's problems with faulty blood glucose meters as an important consideration. While none disputed CONCLUDE's findings, they did question whether the meter problem cast an unfortunate shadow on the study's findings.

"The problem with CONCLUDE was that this was an unfortunate trial due to the problems with the glucose monitoring devices, and possibly also the study design," says Dr. Sesti.

FIGURE 2

Severe or nocturnal cases of hypoglycaemia were less likely using Tresiba® versus glargine U300.[2]

Conclusion: main hypoglycaemia endpoints



*Primary endpoint
†Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms. All nocturnal hypoglycaemia reported between 00:01 and 05:59
Glargine U300, insulin glargine 300 units/mL

CONCLUDE
COMPARING THE SAFETY OF DEGLUDEC WITH GLARGINE U300

Athena Philis-Tsimikas, MD, of Scripps Whittier Diabetes Institute, San Diego, California, notes that 5 of the 6 measures of different categories of hypoglycaemia had point estimates that favored degludec and confidence intervals that did not cross the line of unity. She adds: "This does not indicate "superiority" but is directional and encouraging for development of protocols for future studies."

"Overall, I think the trial design may have not been ideal," says Professor Steve Bain, assistant medical director for Research & Development for ABM University Health Board and clinical director for the Diabetes Research Unit, Cymru, Wales, UK. "The meter issues within the trial definitely created problems which led to the complete rejigging of the trial," which, ultimately, he says, affected the study's publication. "I think these things are just unfortunate. But for those clinicians who feel that degludec certainly has an advantage over glargine U100, which is shown clearly in the SWITCH trials, it was very much a similar trend seen in the CONCLUDE study with glargine U300.

"The trouble with the meters," he continues, highlighted flaws in the regulatory environment around blood glucose monitoring "that show how it needs to be tightened up and how doing things purely in a clinical trial setting versus the real-world environment highlights that there are issues with these testing systems."

Thomas Pieber, MD, of Medical University of Graz in Austria, calls the meter malfunctions "mishaps and unfortunate events. The glucose meters didn't work properly, especially in the hypoglycaemic range. This was discovered by patients and by the steering community that we had very severe hypoglycaemic events in this trial that were highly unlikely to occur, and which led us eventually to discover that the meters were not accurate."

The effects, says Dr. Pieber, were distressing. "The meters were measuring correctly for blood glucose values above 100 mg or 110 mg per deciliter, but gave falsely high blood glucose values in the hypoglycemic range,

FIGURE 3

Previous studies pointed the way to CONCLUDE.[2]

Rationale for the CONCLUDE trial

PK/PD profiles

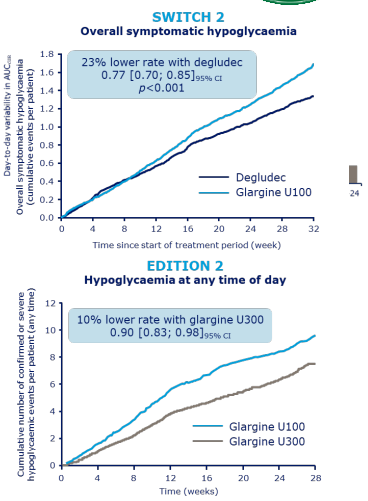
- Degludec U200: 4 times lower day-to day variability versus glargine U300[1]
- Glargine U300: 30% lower potency versus degludec U200[1]

Hypoglycaemia

- SWITCH 2: Degludec U100 has 23% lower risk of severe or BG-confirmed (<3.1 mmol/L) symptomatic hypoglycaemia versus glargine U100[2]
- EDITION 2: Glargine U300 has 10% lower risk of severe or BG-confirmed (≤3.9 mmol/L) hypoglycaemia versus glargine U100[3]

Insulin dose

- SWITCH 2: Degludec U100 has 4% lower dose requirement versus glargine U100[2]
- EDITION 2: Glargine U300 has 10% higher dose requirement versus glargine U100[3]



BG, blood glucose; glargine U100/U300, insulin glargine 100/300 units/mL; PD, pharmacodynamic; PK, pharmacokinetic
1. Heise *et al. Diabetes Obes Metab* 2017;19:1032–9; 2. Wysham *et al. JAMA* 2017;318:45–56; 3. Yki-Järvinen *et al. Diabetes Care* 2014;37:3235–43

Dr. Pieber says that the rationale for the CONCLUDE trial came from several studies (Figure 3). "One is the group of pharmacokinetic/pharmacodynamic (PK/PD) studies that were done comparing insulin degludec vs glargine U300. There were chemistry studies that had showed the same variability for glargine U300 and for glargine U100, which was four times higher than the day-to-day variability compared with insulin degludec.

"These chemistry trials also showed lower potency for glargine U300. We also saw in the CONCLUDE trial that 12% less insulin was needed when using degludec." It confirmed, he says, what had already been seen in the PK/PD studies.

"Also in the SWITCH trial, we saw already that less insulin is needed when degludec is used in the comparison between glargine U100 versus glargine U300. We always need more insulin when we switch to glargine U300. It was 10% less in the EDITION 2 trial and 12% less in the CONCLUDE trial. The difference in potency definitely is there."

so patients and physicians were over titrating insulin. That was a problem in the early phase of the trial." Dr. Pieber presented on CONCLUDE at the EASD meeting in Barcelona, Spain.

The Biggest Fear: Nocturnal Hypoglycaemia

It became apparent throughout the CONCLUDE trial and in the comments that followed it that nocturnal hypoglycaemia remains perhaps the greatest fear among diabetes patients who use insulin. Addressing those fears is one area where expert commentators say that degludec demonstrates superiority.

Professor Bain also sounds a cautionary note about prescribing a basal insulin to insulin-naive patients. "Diabetes patients who are insulin-naive have never experienced hypoglycaemia. But starting insulin might induce it. And once patients have experienced

a hypoglycaemic event, it's definitely something that influences how they engage their therapy. The up-titration therapy is a major downer, and in the aftermath of hypoglycaemic events, they're not going to happily continue to up-titrate."

Some Conclusions About CONCLUDE

Dr. Philis-Tsimikas advises endocrinologists "to look at the overall study outcomes combined with their personal experiences to determine the best basal insulin to use for their patients. We are fortunate to have newer, safer basal insulins that will provide greater benefit for our patients with diabetes."

Dr. Pieber notes: "We cannot say that Tresiba® is superior based on this trial. But if we compare the magnitude of differences between Tresiba® and glargine U100, and also compare the magnitude of differences between Tresiba® and glargine U300, we see little difference between glargine U100 and glargine U300.

"It is unfortunate that the primary outcome of CONCLUDE was not achieved, but the overall picture is quite clear if you look at the differences for the secondary outcomes: nocturnal hypoglycaemia, and severe hypoglycaemia."

Dr. Pieber also notes that diabetes patients enrolled in the CONCLUDE trial achieved the same level of glycemic control with less degludec than with glargine U300. "Where cost is an issue, this is of relevance because degludec was as effective as insulin glargine U300 at a 12% lower dose. Both glargine U100 and glargine U300 have a little bit less bioavailability."

He says that one inspiration for CONCLUDE came from previous studies comparing degludec's variability with glargine U100 and glargine U300. "One is the group of pharmacokinetic/pharmacodynamic studies that were conducted comparing insulin degludec versus glargine U300 (Figure 3). There were chemistry studies that showed the same variability for both glargine U300 and glargine U100, which was always four times higher in day-to-day variability compared with insulin degludec."

Xultophy®: Fewer Injections, Weight Reduction Are Persuasive Points With Patients

"Xultophy® (IDegLira) accomplishes two things," says John B. Buse, MD, PhD, chief, Division of Endocrinology, Verne S. Caviness Distinguished Professor, director of the Diabetes Center, and director of the University of North Carolina Translational and Clinical Sciences Institute at the UNC School of Medicine. "First, insulin degludec is arguably the most powerful fasting blood sugar lowering drug, while insulin and liraglutide also have beneficial post-prandial effects—effects that keep the blood sugar level down during the day. And liraglutide is arguably among the most powerful GLP-1 receptor agonists.

"The second thing is the consideration that insulin is associated with weight gain and an increased risk of hypoglycaemia, while a GLP-1 receptor agonist is associated with weight loss and a decreased risk of hypoglycaemia."

Dr. Buse cites a major side effect of GLP-1s, nausea, as a third consideration. "The way IDegLira is titrated going up by two dose steps which is .072 milligrams at a time, there is a much lower titration rate and probably a lower risk of GI-related adverse events. It turns out that the two drugs together mitigate the potential for adverse events of each and provide for better efficacy in blood glucose lowering than with either component part."

There are two circumstances under which where Dr. Buse is most likely to prescribe Xultophy®. "Let's say a patient on basal insulin is taking increasing doses of insulin but still has not reached the blood sugar level we want and we are starting to have problems with hypoglycaemia. That's when we'd consider using IDegLira instead. Or if we have a patient on a GLP-1 receptor agonist who has reached the maximum dose that he can tolerate but still hasn't achieved his A1c target, we may want to use Xultophy® instead.

"This provides a better shot on tolerability and, therefore, a better possibility that two months from now, the patient will on an effective dose of IDegLira with good blood glucose control and an acceptable adverse event profile."

Dr. Buse acknowledges that while some patients will be reluctant to take Xultophy® either because they don't like needles or don't like the idea of GLP-1-associated

nausea. "However, the majority of patients we've worked with who were on one drug or the other—insulin or a GLP-1—transitioned nicely to a fixed dose Xultophy® combination for the additional efficacy it provided."

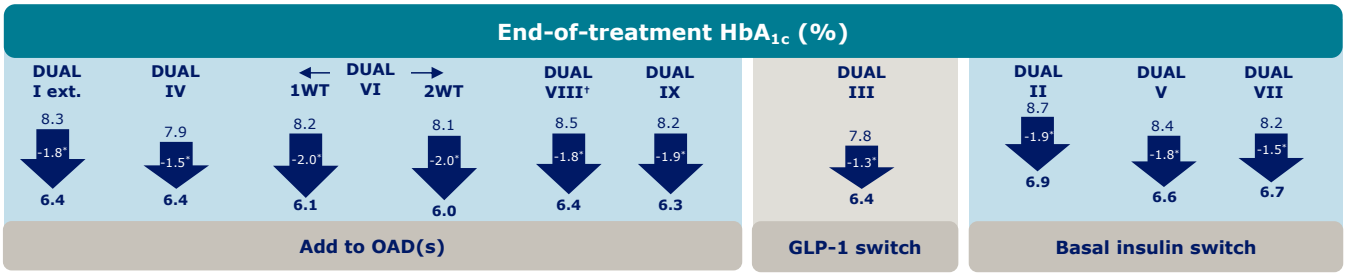
Regarding titration, Dr. Buse says that if he is more worried about hypoglycaemia and weight gain, he might at the start say to a patient, "Let's just keep going up until most of your blood sugar levels are less than 130 mg/dL and then on your next visit, we can decide whether to go with an even lower target." He reminds patients that when they start on insulin, "it's not a commitment to take it for the rest of your life.

"I think glycemic control is really important for preventing poor outcomes, particularly in patients with very high A1c levels above 9% and Xultophy® is a great tool for addressing them," concludes Dr. Buse.

FIGURE 4

The DUAL trials consistently showed Xultophy®'s ability to lower patients' A1c levels below 7%.[7]

IDegLira demonstrated significant improvements in HbA_{1c} across the DUAL programme



Across all nine studies, IDegLira decreased mean HbA_{1c} to below 7.0% (6.0–6.9%)

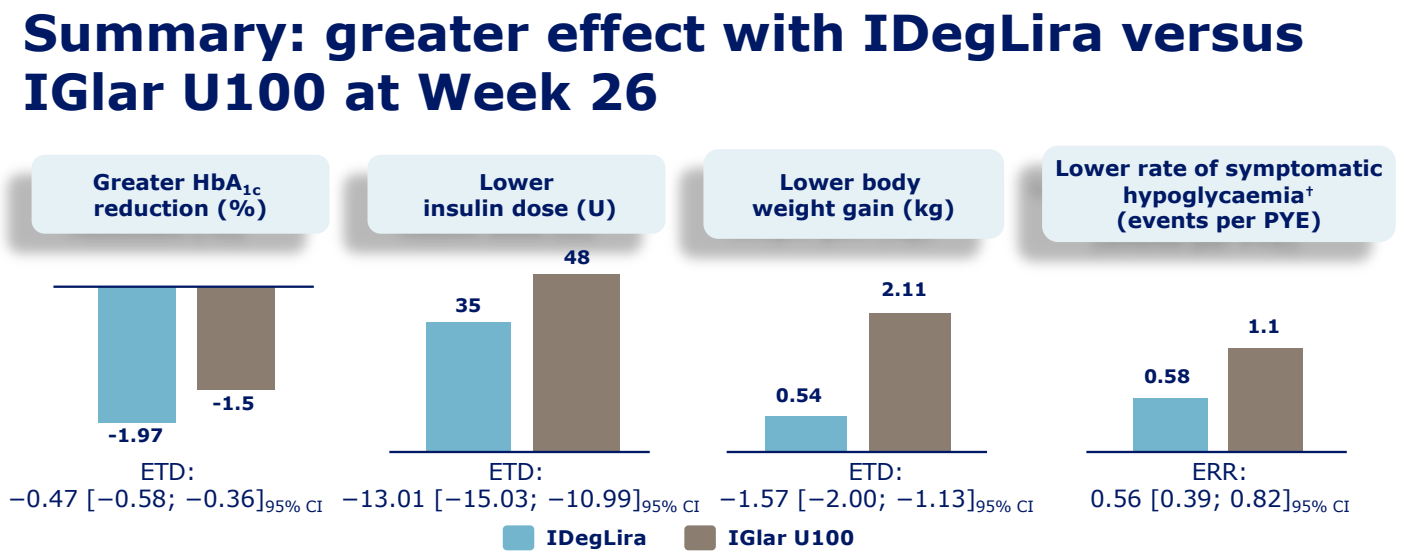
Looking across the various DUAL trials, Dr. Sesti points to DUAL VIII, the trial comparing the IDegLira combination versus IGlar U100 (Figure 4).[7] "It was a two-year trial designed to assess the durability of the fixed dose combination of IDegLira versus IGlar U100 in patients with classic type 2 diabetes, insulin naive, 18 years and older, treated with oral agents, and with hemoglobin A1c levels ranging between 7% and 11%. For people treated with oral agents there comes a need to initiate injectable medications to obtain the optimized blood glucose control. DUAL VIII was designed to mirror what happens in current clinical practice when shifting to injectables and to test the time needed for intensification after starting XULTOPHY vs IGlar U100.

"Obviously, this was an open-label study because of the impossibility of having a masked injectable while trying to treat to target. It was suggested to doctors to treat patient with baseline characteristics typical of people with type 2 diabetes. The mean age was 56 years. The percentage of male and female was almost the same. The body mass index averaged 32; patients were mostly overweight. The A1c level at baseline was between 8.4% and 8.6%, and the average duration of diabetes was more than 10 years.

"The main result in terms of reduction of A1c levels was obtained by more patients treated with the fixed-ratio dose combination with IDegLira. The percentage of patients achieving the target of an A1c level of less than 7% with this fixed dose combination was 78% compared with 55% in the group treated with IGlar U100. This included a reduction in A1c level without hypoglycaemia and weight gain. A greater proportion of subjects treated with the IDegLira obtained this target, 35% versus 15% in the arm treated with IGlar U100."

FIGURE 5

Overall performance statistics show clear superiority of IDegLira over Glar U100.[8]



A higher proportion of patients reached the composite target of HbA_{1c} <7.0% without hypoglycaemia and no weight gain with IDegLira (35.2%) than IGlar U100 (13.6%)*

*OR: 3.32 [2.40;4.58]95% CI
†Severe or BG-confirmed symptomatic: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/L) with symptoms consistent with hypoglycaemia. PYE, patient-year of exposure

Dr. Sesti offered four conclusions regarding IDegLira's performance in the DUAL VIII trial[8]:

1. In the first 26 weeks of the trial, more patients met hemoglobin A1c goals using IDegLira than patients using glargine U100 (Figure 5).
2. The trial was designed to mirror actual clinical practice with fewer scheduled clinic visits and telephone calls compared with standard treat-to-target trials.
3. Due to broad inclusion criteria, the study population reflected patients with type 2 diabetes eligible for basal insulin initiation.
4. Data support the potential role of IDegLira as an effective and well-tolerated first injectable therapy.

Proof From the DUAL VIII Trial

One of the first tests of IDegLira's utility was the DUAL VIII trial,[6] a 104-week study that compared the effects of IDegLira versus insulin glargine U100. It was selected as a comparator because of its marketplace status as one of the most widely prescribed basal insulins.

One of the study's co-authors was Giorgio Sesti, MD, of Sapienza University of Rome, Italy. He says that by the end of the study, DUAL VIII showed several results favoring IDegLira, thus, the superiority of a combination insulin-GLP-1 medication versus basal insulin alone:

- Over the study's two-year span, fewer patients using IDegLira required intensification of their treatment—37.2% of IDegLira users versus 66.2% of IGlar U100 users.
- It took IDegLira users a longer time—a median of two years to require intensification versus one year for IGlar U100 users.
- A greater percentage of IDegLira patients, 55.7%, achieved A1c levels of <7% versus 28.5% for IGlar U100 patients.
- IDegLira users had a lower average rate of hypoglycaemia, lower estimated mean insulin dose, and no weight gain: 20.9% IDegLira patients versus 6.3% IGlar U100 patients (Figure 4).

Another aspect that Dr. Sesti points out is that with regard to diabetes management, the types of questions researchers asked patients included: "Does your treatment help you to prevent tiredness or lack of energy, avoid both high and low blood sugar levels, manage your weight, and control your diabetes? "Answers to these questions favored the IDegLira treatment.

"DUAL VIII's data supported the potential role of the IDegLira combination as an effective and well-tolerated first injectable therapy after all the agents have failed. So, this medication could be a strategy for patients to be better controlled with more satisfaction and using less of a dose of insulin. In terms of safety, add the reduced risk of hypoglycaemia and weight gain."

Dr. Sesti says that a primary reason for undertaking DUAL VIII was to find what would be a most suitable treatment for patients whose oral agent therapy has failed. "We didn't know whether treatment with a fixed dose combination of GLP-1 with insulin would have a greater durability over a study span in terms of glycemic control." He adds that DUAL VIII was designed and started before EASD issued guidelines indicating that probably the best injectable to initiate after oral therapy was a GLP-1, followed later with insulin.

"Ours was not a strategy of comparison among three approaches. Otherwise, the design would have been a GLP-1 versus IGlar U300 versus the fixed-dose combination. But what do we do in clinical practice? We start with insulin. The question was whether we can start with the combination instead of just insulin alone."

Dr. Sesti says that because IDegLira's fixed-dose combination was classified as insulin and not as a GLP-1, "We could start with a reduced dose of the fixed combination, minimizing potential adverse effects due to insulin alone, and then increase the dose over time. This means being able to start with an injectable that was more favorable for patients. We could reassure them that there were no associated physical adverse effects due to initiation of insulin therapy.

"Because this was a durability therapy that was associated with fewer adverse effects, patients were more in favor of the treatment because they experienced less hypoglycemia incidence and just a modest weight gain despite being treated with insulin.

"We have a smart combination, a potent insulin associated with very low risk of hypoglycemia together with a potent GLP-1, which is associated with cardiovascular protection. I can observe less weight gain and I can observe more people reaching the target hemoglobin A1c level. Most important, all this was obtained in a real-world trial. This was real life. So, it works in real life." ■

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NEW ADA/EASD 2018
TYPE 2 DIABETES CONSENSUS REPORT:
When it is time for insulin, choose a basal insulin with a lower risk of hypoglycaemia[1]*

REDUCE YOUR PATIENTS' RISK OF SEVERE HYPOGLYCAEMIA BY 40% WITH TRESIBA®

VS GLARGINE U100[2¶]

* In patients without established ASCVD or CKD, when there is a need to minimise hypoglycaemia[1]

¶ Patients with type 2 diabetes at high risk of CV events[2]

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* Establishing a routine is important; Tresiba® should be dosed once daily, with a minimum of 8 hours between doses.[1]
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