Revolutionary change on the horizon for insulin-dependent patients with diabetes

SCIENCE-IN-BRIEF

April 2024

Once-Weekly INSULIN Data Published; It Could Alter Treatment

Key points and synopsis of "Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes: A summary of the ONWARDS 3 Randomized Clinical Trial "published in the Journal of the American Medical Association in June 2023.

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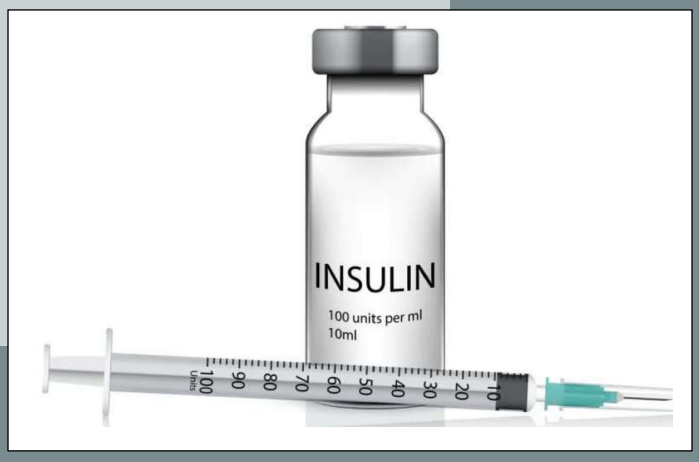

Revolutionary change on the horizon for insulin-dependent patients with diabetes

An investigational form of insulin that only requires once-weekly administration was found to be safe and effective in patients with Type 2 diabetes. This clinical trial established that patients receiving the once-weekly insulin maintained healthy blood glucose levels better than insulin injected daily. The results published in the Journal of the American Medical Association in June 2023 could push this game-changing insulin product one step closer to approval by the Food and Drug Administration.

KEY MESSAGES

- Diabetes is a prevalent disease in the United States affecting over 37 million people.
- Insulin is the most burdensome therapy for people with diabetes, as it requires daily injection(s).
- Nonadherence to insulin is a major issue, significantly increasing morbidity, mortality, and cost to the health care system.
- A new once-weekly insulin could revolutionize how diabetes is treated, dramatically increasing quality of life and the health of people with diabetes.
- Once-weekly insulin can reduce costs associated with treating insulin-dependent diabetes.

BACKGROUND

Diabetes is a prevalent disease in which the body metabolizes and utilizes glucose abnormally, resulting in elevated blood glucose levels.[1] Over 37 million Americans have diabetes, while more than 96 million Americans are living with prediabetes, which could progress to diabetes at any time.[2] The two common forms of diabetes are Type 1 diabetes and Type 2 diabetes. Type 1 diabetes, historically referred to as insulin-dependent or juvenile diabetes, is a disease that can occur at any age. It is a condition in which a person's immune system destroys the cells of the pancreas that make insulin. Approximately 5-10% of people living with diabetes have Type 1 diabetes. Type 2 diabetes is far more common, representing over 90% of people living with diabetes.[2] Type 2 diabetes is characterized by progressive loss of insulin secreted by the pancreas and insulin resistance in the body's cells. Both Type 1 and Type 2 diabetes ultimately result in elevated blood glucose levels. Over time, this elevation in blood glucose is detrimental and causes damage to a person's kidneys, eyes, nervous system, and cardiovascular system.[3] Initial treatment for people diagnosed with Type 1 diabetes requires frequent blood glucose monitoring and daily insulin injection(s). Type 2 diabetes also requires close monitoring of blood glucose but does have many oral options and newer therapies to avoid insulin injections. However, it is often the natural progression of the disease to fail on these therapies and ultimately require insulin as well.[4]

Over the years, progress has been made in developing more user-friendly insulins. Insulin usage in healthcare began with regular bovine insulin, which was first introduced in the 1920's. While it was one of the first effective treatments for people with diabetes, it did require multiple injections a day as its dosing required injections before meals. In the early 1940s, an intermediate-acting insulin called Neutral Protamine Hagedorn (NPH) was introduced. This NPH insulin provided a basal coverage that lasted approximately 12 hours, equating to only two doses daily, but unfortunately required the addition of short-acting insulin around meals. More recently, long-acting insulin glargine was introduced in the early 2000s. This insulin analog mimics a healthy pancreas, creating more stable blood glucose levels and requiring a less frequent, once-daily dosing.[5,6] Since then, ultra-long-acting insulins have been developed but typically don't surpass once-daily dosing. With the frequency, planning, and discomfort required with lancets drawing blood for monitoring and daily insulin injection(s), it is no wonder that patients with diabetes have a lower-than-average adherence rate. This lack of adherence is costly for the patient's health and finances. Financial costs of nonadherence to diabetes treatment are in the billions yearly, and the impact on health is quite significant to patients as it leads to blindness, kidney failure, heart failure, amputations, and death.[7]

ABOUT THE STUDY

The objective of the ONWARDS3 study was to evaluate the efficacy and safety of once-weekly insulin icodec in patients with Type 2 diabetes who had no prior experience with insulin. Participants were randomly assigned to receive either once-weekly insulin icodec and once daily placebo (weekly insulin group) or once-daily insulin degludec and once weekly placebo (daily insulin group). This phase 3, randomized, placebo-controlled trial then followed the 588 patients for six months when they would assess the primary efficacy point of change in Hemoglobin A1C (HbA1C). This simple blood test measures your average blood glucose level over the past three months.[8] Safety assessments during this period included total weekly insulin doses during the last two weeks of treatment, change in body weight, and the number and severity of episodes from low blood glucose.

STUDY RESULTS

ONWARDS3 provided exciting results when comparing the investigational, once-weekly insulin icodec use with the longest-acting daily insulin currently on the market. This study, conducted in patients with Type 2 diabetes, found that weekly insulin icodec was superior to the weekly insulin in controlling blood glucose as the decrease in HbA1C was 1.6% in the weekly insulin icodec arm compared to 1.4% with the daily insulin degludec.
The safety assessments for each group found similar results; however, there were more episodes of low blood glucose with weekly insulin icodec compared to daily insulin degludec (8.9% vs 6.1% of patients by 31 weeks).

IMPLICATIONS OF THESE FINDINGS IN PRACTICE

The pivotal ONWARDS3 trial demonstrated the superiority of weekly insulin icodec compared to once-daily insulin degludec for blood glucose control in patients with Type 2 diabetes who had not previously used insulin. These findings will significantly strengthen the case for approval in the United States through the Food and Drug Administration (FDA). Once approved, this weekly insulin product will revolutionize diabetes care in America in numerous ways, and it will dramatically increase the quality of life for patients with diabetes who require insulin. Currently, patients are required to inject themselves at least daily, and in some cases multiple times a day, to control their blood glucose levels. This once-weekly insulin product will reduce that requirement by a minimum of 365 injections yearly to 52. Another equally important result of this dosing schedule will be better adherence and improved health outcomes. Consequently, better-controlled glucose will reduce secondary complications of diabetes, such as blindness, kidney failure, heart failure, amputations, and even death. Better adherence through easier administration will greatly reduce the number of people who are affected by these consequential life-altering effects of diabetes.

FUTURE DIRECTIONS

This article, along with the other ONWARDS clinical trials investigating weekly insulin icodec, is a landmark trial that will help pave the way for FDA approval of this novel form of insulin. The ONWARDS clinical trials currently include six phase 3a global trials, including a trial with real-world elements involving patients with Type 1 and Type 2 diabetes (table 1).[9] Approval from the FDA is anticipated in April 2024.[10] There may be challenges and delays in implementation and integration into practice post-approval that may include candidate selection for the new therapy, changes in physicians' prescribing habits, financial considerations of affordability for patients, including insurance coverage, co-pay assistance availability, and programs providing low-cost or free medication to patients without insurance. As these programs are established and long-term safety is established with post-marketing surveillance, this ground-breaking therapy will improve the quality of life and health for millions of diabetic patients worldwide.

Table 1. ONWARDS Clinical Development Program[9]

Trial	Population	Primary Endpoint/Results
ONWARDS 1[a]	Once-weekly insulin icodec vs once-daily insulin glargine U100 in people with type 2 diabetes who have not previously been treated with insulin	HbA_{1c} level at 52 weeks was greater with icodec than with glargine U100 (8.50% to 6.93% with icodec (mean change -1.55) and 8.44% to 7.12% with glargine U100 (mean change -1)
ONWARDS 2[b]	Once-weekly insulin icodec vs once-daily insulin degludec in people with type 2 diabetes who have previously been treated with basal insulin	HbA_{1c} was reduced to a greater extent with icodec (8.17% to 7.2%) than degludec (8.10% vs 7·42%) at week 26.
ONWARDS 3[c]	Once-weekly insulin icodec vs once-daily insulin degludec in people with type 2 diabetes who have not previously been treated with insulin	HbA_{1c} level at 26 weeks decreased from 8.6% to 7.0% at 26 weeks in the icodec group and from 8.5% to 7.2%) in the degludec group, confirming noninferiority and superiority of icodec
ONWARDS 4[d]	Once-weekly insulin icodec vs once-daily insulin glargine U100 in people with type 2 diabetes who have previously been treated with basal/bolus insulin	HbA_{1c} at 26 weeks was -1·16 percentage points in the icodec group (baseline 8·29%) and -1·18 percentage points in the glargine U100 group (baseline 8·31%), showing non-inferiority for icodec versus glargine U100
ONWARDS 5[e]	Once-weekly insulin icodec with dosing guide app vs once-daily basal insulin analogs in people with type 2 diabetes who have not previously been treated with insulin	HbA_{1c} reduction baseline to week 52 was greater with icodec with an app than with once daily analogues, establishing noninferiority and superiority.
ONWARDS 6[g]	Once-weekly insulin icodec vs once-daily insulin degludec in combination with insulin aspart in people with type 1 diabetes	HbA_{1c} reductions were -0·47 % icodec and -0·51% degludec, (from baseline values of 7·59% icodec and 7·63% degludec), establishing non-inferiority

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FURTHER ENGAGEMENT/MORE INFORMATION

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CITATION

Larck, C. Revolutionary change on the horizon for insulin-dependent patients with diabetes. 2024.

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