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Mini Review

Icosema: Summary of the Emerging Data for Insulin Icodec and the Study Designs for the Novel GLP-1 Receptor Agonist/Basal Insulin Injection

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Received: June 28, 2022; **Published:** September 13, 2021

Abstract

A novel basal insulin paired with a glucagon-like peptide-1 receptor agonist (GLP-1RA) for the treatment of type 2 diabetes mellitus (T2DM) is currently in phase III studies. The introduction of this combination medication to the population of patients with T2DM offers many benefits spanning effective glucose control, to decreased injection burden. The novel basal insulin is once weekly insulin icodec which is being studied in the ONWARDS clinical study program and has already shown noninferiority in the studies completed to date. The COMBINE studies, evaluating the insulin icodec combination with semaglutide (icosema), are underway with estimated completion dates in late 2023-early 2024. This review serves to present a summary of the emerging data for insulin icodec and introduce the study designs for icosema.

Keywords: *Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs); Type 2 Diabetes Mellitus (T2DM); Icodec; Icosema*

Introduction

Combination medications in the treatment of type 2 diabetes mellitus (T2DM) are commonly used and considered beneficial to the patient for multiple reasons. Increased adherence, decreased pill burden, and increased efficacy are just a few of the benefits of some of the combination medications currently available. The advantage of treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) for patients with T2DM, such as a reductions in weight, the risk of cardiovascular (CV) events, death in patients with established cardiovascular disease (CVD), the risk of hospitalization for heart failure (HHF) and/or the risk of major adverse CV events (MACE) in patients with T2DM and established CVD is widely accepted and established [1]. For patients who continue to require additional therapy, considering an additional agent with a GLP-1 RA such as basal insulin is an option to meet their treatment goals. As basal insulin and injectable GLP-1RAs would require multiple injections for a patient, a combination of GLP-1 analogue semaglutide and insulin icodec intended for once weekly treatment was developed to meet the needs of patients who are concomitantly prescribed an injectable GLP-1RA and basal insulin. This medication, icosema, contains a once weekly basal insulin, insulin icodec, which is currently under investigation and combines it with the widely used once weekly injectable GLP-1RA, semaglutide, developed by Novo Nordisk.

Mechanism of action

Icosema is a combination medication of the once weekly injectable GLP-1RA, semaglutide, and the once weekly injectable basal insulin, insulin icodec, which is currently under investigation. The mechanism of action of semaglutide is widely accepted as part of the GLP-1RA class which lowers blood glucose levels via the incretin pathway [2]. It inhibits glucagon secretion and stimulates insulin secretion in a glucose-dependent manner [2]. Insulin icodec is a basal insulin with increased duration of action due to its reversible binding to albumin and reduced insulin receptor affinity [3,4]. Insulin icodec was designed by adjusting the C-terminal of the B-chain of the HI amino acid

sequence by introducing a 20-carbon atom long icosane fatty diacid [4,5]. This allows it to form a strong yet reversible bond with albumin. Additionally, there are three amino acid substitutions to lower insulin receptor mediated clearance and increase half-life though decreased insulin receptor affinity [4]. The sustained action of insulin icodec is a result of the release of insulin icodec from the albumin-bound depot and results in a half-life of up to 196 hours [5]. The dual mechanism of icosema allows for activation of GLP-1Rs, reducing food intake, increasing insulin secretion, decreasing glucagon secretion, and delaying gastric emptying time with the added activity of a basal insulin.

Clinical studies

Insulin icodec

The ONWARDS program comprises six clinical studies investigating the safety and efficacy of insulin icodec.

ONWARDS 1, a phase III, parallel assignment study randomized 984 subjects to receive either insulin icodec once weekly or insulin glargine once daily for 78 weeks. Subjects were included if they were insulin naive, with a hemoglobin A1c (HbA1c) value of 7.0 - 10.0% [6]. The study demonstrated a reduction in HbA1c of 1.55% for those receiving insulin icodec compared to 1.35% for those receiving insulin glargine. Insulin icodec appeared to be safe and well-tolerated with no statistically significant difference reported in estimated rates of severe or clinically significant hypoglycemia [7].

A phase III, randomized, open-label study, ONWARDS 2, included 526 subjects who were randomized to receive insulin icodec once weekly or insulin degludec once daily for 26 weeks [8]. The study was completed in March 2022 and met the primary endpoint showing non inferiority in reducing HbA1c measured by percent change in HbA1c with a reduction of 0.93% for insulin icodec compared to 0.71% for insulin degludec [9]. Additionally, there were no observed severe hypoglycemia events for subjects with insulin icodec [9].

The ONWARDS 3 study was a phase III, double blinded study which enrolled 574 subjects and randomized them to receive insulin icodec once weekly plus once daily placebo insulin degludec or once weekly placebo insulin icodec and once daily insulin degludec for 26 weeks. Subjects were included if they were insulin naive with HbA1c of 7.0 - 11.0%. Enrollment is complete with an estimated study completion date of June 2022 [10].

A 26-week, phase III study, ONWARDS 4, compared once weekly insulin icodec plus once daily insulin aspart with once daily insulin glargine plus once daily insulin aspart. The primary outcome measured was change in HbA1c for 578 subjects who had T2DM, HbA1c of 7.0-10.0% and BMI below or equal to 40.0 kg/m^2. The study is no longer recruiting with an estimated completion date of June 2022 [11].

ONWARDS 5, is a phase III study comparing insulin icodec with DoseGuide App to guide their titration with once daily basal insulin analogues for 52 weeks. This open label study randomized 1085 subjects to either insulin icodec, insulin glargine 100 U/mL, insulin degludec, or insulin glargine 300 U/mL. The primary outcome measure is assessing percentage point change in HbA1c in subjects who have T2DM, are insulin naive and have HbA1c above 7.0%. The study is expected to be completed in August 2022 [12].

Recently completed, is the ONWARDS 6 study. This phase III, randomized, open label study enrolled and randomized 580 subjects with type 1 diabetes mellitus for at least one year and HbA1c below 10%. The percent point change in HbA1c was the primary outcome assessed for insulin icodec 700 U/mL once weekly with 2 - 4 times daily injections of insulin aspart 100 U/mL at mealtimes compared to insulin degludec 100 U/mL once daily with 2 - 4 times daily injections of insulin aspart 100 U/mL at mealtimes [13]. The study concluded with a statistically significantly higher estimate rate of severe or clinically significant hypoglycemia for those receiving insulin icodec compared to insulin degludec (19.93 events per patient year and 10.37 events per patient year respectively). Insulin icodec did meet its primary endpoint and reached a 0.47% reduction in HbA1c compared to 0.51% for insulin degludec, confirming noninferiority[7].

Icosema

The COMBINE studies are phase III studies currently enrolling subjects to assess the effectiveness and safety of icosema as a treatment for T2DM.

The COMBINE 1 study plans to enroll 1290 subjects with T2DM and a HbA1c value of 7.0 - 10.0%. Subjects will be randomized in an open label, parallel assignment to receive either icosema once weekly or insulin icodec once weekly for 52 weeks. The study will assess the primary outcome of change in HbA1c and secondary outcomes of change in body weight and number of hypoglycemic episodes [14].

A phase III study comparing icosema to semaglutide 1 mg once weekly, COMBINE 2, plans to include 680 subjects with T2DM who are insulin naive and inadequately controlled with a GLP-1RA alone. Subjects must have an HbA1c value between 7.0 and 10.0% and a BMI below or equal to 40.0 kg/m^2. These subjects will be randomized in an open label, parallel assignment to either semaglutide 1 mg once weekly or icosema once weekly for 52 weeks with a primary outcome of change in HbA1c [15].

The study comparing icosema to insulin glargine taken daily with insulin aspart, COMBINE 3, is a phase III, open label, parallel assignment study which plans to include 680 subjects with T2DM, HbA1c value between 7.0 and 10.0%, and BMI below or equal to 40.0 kg/m^2. Subjects will receive either once daily insulin glargine 100 U/mL combined with insulin aspart or icosema for 52 weeks and will be evaluated for change in HbA1c [16].

Conclusion

The results of the ONWARDS studies show promise for insulin icodec in subjects with T2DM for HbA1c reduction. Furthermore, the results of the COMBINE phase III studies will demonstrate if there are additional opportunities to utilize the combination medication of insulin icodec with semaglutide to treat T2DM. The COMBINE studies are expected to be completed between October 2023 and February 2024.

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Volume 6 Issue 2 September 2022
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