International Journal of Diabetes Sciences

ISSN Print: 2664-9101
ISSN Online: 2664-911X
Impact Factor: RJIF 5.42
IJDS 2023; 5(1): 01-05
www.diabeticjournals.net
Received: 03-01-2023
Accepted: 08-02-2023

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Appraisal of once-weekly insulin icodec

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DOI: https://doi.org/10.33545/26649101.2023.5v.1ia.7

Abstract
Insulin icodec is a long-acting basal insulin analog under development that can be administered once weekly. The main purpose of this article is to provide an appraisal on insulin icodec based on available data published in a series of phase 3 clinical trials collectively called the ONWARDS Program. In 3 of the 4 published ONWARDS trials, reductions in glycated hemoglobin (HbA1c) levels were slightly superior with insulin icodec compared with once-daily insulin glargine or degludec with a difference of approximately 0.2 percentage points. In the 4th trial, insulin icodec was not inferior to degludec in decreasing HbA1c values. Data analysis of continuous glucose monitoring (CGM) showed greater or similar time spent in range (TIR) with insulin icodec versus insulin glargine or degludec. Incidence of level 1 hypoglycemia [blood glucose (BG) levels 54-69 mg/dl] was higher with insulin icodec compared with insulin glargine or degludec with estimated rate ratio (ERR) ranging from 1.25 to 1.88. Incidence of combined level 2 hypoglycemia (clinically significant hypoglycemia with BG < 54 mg/dl) and level 3 hypoglycemia (severe hypoglycemia with cognitive impairment requiring external assistance) was approximately 2-3 times higher with insulin icodec versus insulin glargine or degludec. Preliminary data in patients with type 1 diabetes showed approximately doubling rates of combined level 2 or 3 hypoglycemia with insulin icodec [(19.9 hypoglycemic events per person-year-exposure (PYE)] versus insulin degludec (10.3 hypoglycemic events per PYE). Time spent below range (TBR) in CGM was similar between insulin icodec and insulin glargine or degludec. Weight gain was generally similar with use of insulin icodec and insulin glargine or degludec. Yet, in one trial, weight gain was significantly greater with insulin icodec versus degludec, with an estimated treatment difference (ETD) of 1.7 kg. Allergic reactions were not increased with use of insulin icodec compared with glargine or degludec. In conclusion, insulin icodec may be a convenient basal insulin that is administered once weekly. It is at least as effective as insulin glargine or degludec. Yet, it is associated with increased incidence of all levels of hypoglycemia.

Keywords: Insulin, icodec, glargine, degludec, hypoglycemia, glycated hemoglobin

Introduction
The once-weekly insulin icodec was engineered in an attempt to improve adherence to basal insulin intake. The half-life of insulin icodec is 196 hours (8.1 days) making it suitable for once-weekly administration [1]. Insulin icodec reaches a steady state after 3-4 weeks, then exhibits an evenly distributed glucose-lowering activity throughout the week [1]. The long duration of action of insulin icodec is attributed to 2 main factors. First, binding to albumin through addition of a C20 fatty acid-containing side chain to form an albumin-binding depot from which icodec is slowly released in the circulation. Second, 3 amino acid substitutions that decreases affinity of icodec to insulin receptors leading to its decreased rate of clearance. Normally, insulin clearance occurs primarily through internalization following binding of insulin to its receptors at cell surface. Thus, reduced binding of insulin icodec to insulin receptors will lead to its reduced clearance and further prolongation of its action [1]. Importantly, the reduced affinity of icodec to insulin receptor does not compromise its potency but slows its action [1]. The concentration of formulation of insulin icodec is 7 times higher than that of the standard insulin U100 formulation. It follows that the volume of insulin icodec administered once weekly is similar to other basal insulin dosing volumes given once daily [1]. To support its approval, insulin icodec is being evaluated in a program called ONWARDS. The latter consists of 6 phase 3 clinical trials [2]. The idea of this program is to assess efficacy and safety of insulin icodec in different clinical situations in patients with diabetes.

Four of these 6 trials have been recently published and summarized in table 1 [3-6]. The main objective of this article is to review the advantages and limitations of insulin icodec based on results of the ONWARDS program.

Overview of the ONWARDS trials

There are several common features in trials of the ONWARD Program. All included studies were randomized, multinational and treat-to target phase 3a clinical trials [3-6]. All trials were open-label except ONWARDS 3 trial, which was double masked [5]. The primary endpoint was the change in HbA1c levels from baseline to the end of the study. The target of fasting self-measured BG was 80-130 mg/dl. To achieve that target, doses of insulin icodec, glargine and degludec were adjusted weekly based on 3 pre-breakfast BG readings (measured on 2 days prior to and on the day of the weekly titration [3]. Thus, if the mean of the 3 BG values are > 130 mg/dl, insulin icodec dose is increased by 20 units weekly and doses of glargine or degludec are increased by 3 units daily. On the other hand, if the lowest of the 3 fasting BG values is < 80 mg/dl, doses of insulin icodec are decreased by 20 units/week and those of glargine or degludec by 3 units per day [3]. In ONWARDS trials, the initial dose of insulin icodec was equal to 7 times the dose of daily glargine or degludec. Accordingly, in insulin-naïve patients (ONWARDS 1 and 3), insulin icodec was started at 70 units once weekly while glargine or degludec was started at 10 units once daily [3, 5]. In patients already receiving basal insulin such as in ONWARDS 2 and 4 trials, the first insulin icodec dose was increased by 50% to accelerate reaching its steady state [4, 6]. ONWARDS 1 trial is the largest trial of the ONWARDS Program (n=984) and had the longest follow-up duration (78 weeks followed by 5-week follow-up period for safety monitoring) [3]. The latter study compared insulin icodec with insulin glargine in patients with type 2 diabetes who were insulin naïve [3]. ONWARDS 2 trial compared insulin icodec and degludec in patients with type 2 diabetes already treated with a basal insulin [4]. ONWARDS 3 trial compared insulin icodec with insulin degludec in insulin-naïve patients [5]. ONWARDS 4 trial is the only trial that compared insulin icodec with insulin glargine in patients already receiving basal-bolus or meal-time short-acting insulin [6]. Hence, this trial included patients with advanced type 2 diabetes with mean duration of approximately 17 years (table 1) [6]. ONWARDS 5 and 6 have not been published yet. ONWARDS 5 was designed to compare insulin icodec with other basal insulin (glargine U100 or U300, degludec) in insulin-naïve patients with type 2 diabetes under real-practice conditions [2]. Thus, ONWARDS 5 trial includes broader range of baseline HbA1c levels and body mass eligibility criteria with fewer exclusion criteria compared with other ONWARDS trials [2]. Finally, ONWARDS 6 trial is the only trial that compared insulin icodec with degludec in patients with type 1 diabetes [2].

Effects of insulin icodec on glycemic control

In ONWARDS 1, 2, and 3, insulin icodec was shown to be slightly but statistically superior to both glargine glargine and degludec in lowering HbA1c levels, with estimated treatment difference (ETD) of approximately 0.2 percentage points (table 1) [3-5]. In ONWARDS 4, insulin icodec was non-inferior to insulin degludec (table 1) [6]. In the 4 trials, the mean reduction in HbA1c levels by insulin icodec was approximately 1.5 percentage points compared with baseline [3-6]. Inspection of time curves of HbA1c values of insulin icodec revealed that reductions in HbA1c values were evident 10 weeks following its initiation, then reached a trough at week 26 followed by a plateau [3-6]. Similar trajectory was observed with insulin glargine and degludec [3-6]. Data from CGM was used for a duration of 4 weeks in ONWARDS 1 and 2 trials to identify the diurnal pattern of BG [3, 4]. Overall, no significant differences in time spent in range (70-180 mg/dl) was identified between icodec groups and glargine or degludec groups [3, 4]. Yet, in ONWARDS 1 trial, the percentage of time spent with BG levels above the range (ie. > 180 mg/dl) was approximately 1 hour less with insulin icodec than with insulin glargine [3].

Patient satisfaction with insulin icodec

Patient satisfaction with insulin icodec versus degludec was evaluated in ONWARDS 2 trial using the "Diabetes Treatment Satisfaction Questionnaire" (DTSQ) with higher score indicating greater satisfaction [4]. At week 26, the DTSQ was slightly but significantly higher in patients randomized to insulin icodec 4.22 versus insulin degludec 2.96, ETD 1.25 (95% CI, 0.41 to 2.10, P=0.003) (table 1) [4].

Safety of insulin icodec

Hypoglycemia

Given the long duration of action of insulin icodec, there is a major concern about increased risk of prolonged hypoglycemia, slow recovery and recurrence of hypoglycemic episodes. In a short-term (7 weeks) cross-over trial including selected patients with type 2 diabetes (n=43, mean age 56 years) without co-morbidities, Pieber *et al* [7] compared the frequency and severity of hypoglycemia in patients randomized to insulin icodec versus glargine. These authors induced hypoglycemia to a target plasma glucose levels of 54 mg/dl by doubling and tripling the doses of insulin icodec and glargine. Overall, they observed no significant differences between insulin icodec and glargine in the proportions of patients who developed hypoglycemia, hypoglycemic symptoms, time to recovery, and in the extent of rise in insulin counterregulatory hormones in response to hypoglycemia [7]. Despite these preliminary reassuring findings, results of clinical trials including higher number of patients who were followed for longer duration clearly showed increased risk of hypoglycemia with insulin icodec versus either insulin glargine or degludec. Thus, in ONWARDS 1 trial, at week 83, the rates of combined clinically significant (level 2) or severe hypoglycemia (level 3) were significantly greater with insulin icodec compared with glargine, 0.30 and 0.16 hypoglycemic events per PYE, respectively, ERR 1.63 (95% CI, 1.02 to 2.61) [3]. Furthermore, the difference in these rates between insulin icodec and glargine widened with duration of use [3]. Interestingly, the increased rates of hypoglycemia associated with use of insulin icodec was largely attributed to 3 patients who experienced 105 clinically significant hypoglycemic episodes [3]. Unfortunately, the authors did not mention any possible

causes for clustering and recurrent hypoglycemia in these 3 patients such as kidney dysfunction, intermittent sickness with decreased oral intake, medications errors, use of a sulfonylurea, etc) [3]. Rates of level 1 hypoglycemic events were also higher with insulin icodec versus glargine in ONWRDS 1 trial, 3.02 events per PYE versus 1.39 events per PEY at 83 weeks [3]. In ONWARDS 3 trial, combined level 2 and 3 hypoglycemia from baseline to week 26 was approximately 3-fold higher with insulin icodec versus degludec; ERR 3.012 (95% 1.30 to 7.51, P=0.01) [5]. Furthermore, increased risk of hypoglycemia (level 1, and combined level 2 and 3) with insulin icodec was observed compared with insulin degludec in ONWARS 2 and 3 trials (table 1) [4, 5]. As mentioned earlier, ONWARDS 4 trial was the only study that compared insulin icodec with insulin glargine on a background of pre-meal bolus insulin aspart [6]. Again, the latter trial showed increased risk of level 1 hypoglycemia with insulin icodec versus glargine, ERR 1.25 (95% CI, 1.03 to 1.52) P=0.025 (table 1) [6]. In ONWARDS 4 study, combined level 2 and 3 hypoglycemia as well as nocturnal hypoglycemia were not increased in the insulin icodec group compared with the insulin glargine group. However, there was numerical increase in event rate of level 3 hypoglycemia in the insulin icodec group versus glargine group, 0.04 event per PYE vs 0.02 event per PYE, ERR 2.19, 95% CI 0.2 to 24.4, P=0.53) [6]. In type 1 diabetes, preliminary results of ONWARDS 6 trial showed that rates of level 2 and 3 hypoglycemia with insulin icodec were approximately double the rates with degludec at 26 weeks, 19.9 versus 10.3 events per person-year [8]. Meanwhile, the use of CGM for 4 weeks during the ONWARDS 1 and 2 trials revealed similar time spent under BG levels of 54 mg/dl in patients receiving insulin icodec versus glargine or degludec [3, 4].

Weight gain

There was a trend towards more weight gain associated with use of insulin icodec versus glargine or degludec in ONWARDS 1, 3, and 4 trials (table 1). In ONWARDS 2 trial, patients randomized to insulin icodec had a mean weight gain of 1.4 kg, whereas those randomized to insulin degludec had 0.3 kg weight loss, ETD 1.7 kg (95% CI, 0.76 to 2.63, P=0.0004) (table 1) [4].

Advantages of insulin icodec

The major advantage of insulin icodec is the convenience and simplicity of administration once weekly avoiding 6 extra injections per week compared with traditional basal insulins. In addition, if necessary, the day of administration may be changed by up to 3 days ensuring a minimum of 4 days between injections [6]. Moreover, a single dose-study showed that pharmacokinetics and pharmacodynamics of icodec did not change significantly whether injected in the thigh, abdomen or upper arm [9]. In terms of efficacy, insulin icodec proved to be at least as effective, if not slightly more effective, as once-daily insulin glargine and degludec in patients with long duration of type 2 diabetes. However, the mean difference in HbA1c levels of 0.2 percentage points between insulin icodec and glargine or degludec is unlikely to have any major clinical significance. It also reassuring that available evidence do not suggest that insulin icodec is more immunogenic than other basal insulins as reflected by the low number of allergic and injection site reactions that were generally similar to insulin glargine and degludec [3-6].

Limitations of insulin icodec

The main limitation of insulin icodec is the increased incidence of all levels of hypoglycemia as detailed above. When expressed in absolute terms, this high risk of hypoglycemia can be substantial as illustrated by the difference in rates of combined level 2 and 3 hypoglycemia in patients with type 1 diabetes between insulin icodec and insulin degludec, 19.9 events per PYE and 10.4 events per PYE, respectively [8]. In fact, in the latter study, the absolute difference in hypoglycemic episodes between insulin icodec and degludec is sufficiently high to question the safety of use of insulin icodec in patients with type 1 diabetes. Unfortunately, insulin icodec was not studied in patients with end-stage kidney disease and those with baseline HbA1c levels > 11.0% because these patients were excluded from the ONWRDS trials [3-6]. Other limitations of insulin icodec include tendency to cause more weight gain than insulin degludec or glargine and lack of suitability for its use in hospital setting where rapid variations in BG levels are expected. In addition, patients already on insulin icodec before hospital admission should be monitored closely for hypoglycemia for 7 days from the day of last injection. Advantages and limitations of insulin icodec are summarized in table 2.

Conclusions and current needs

Insulin icodec represents a new class of long-acting basal insulin analogs that can be administered once weekly. Available evidence suggest insulin icodec may have similar or slightly higher efficacy than once-daily insulin glargine or degludec. However, the use of insulin icodec is associated with increased risk of hypoglycemia. The latter may be due to its prolonged duration of action and possibly aggressive dose titration. In fact, the titration schedule of the ONWARDS trials was based on an earlier study by Lingvay *et al* [10]. This study showed that insulin icodec dose adjustment by ±20 units weekly to attain the fasting BG target of 80-130 mg/dl achieved the best balance between efficacy and hypoglycemia compared with 2 other more aggressive titration regimens [10]. It is possible that less aggressive titration of insulin icodec might result in less frequency of hypoglycemia, e.g. an increase of its dose by 10 units per week instead of 20 units. The combination of once-weekly icodec with once weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) in one single formulation may be an attractive treatment strategy that potentially lowers icodec doses and therefore incidence of hypoglycemia. In addition, the weight loss-inducing effect of the GLP-1 may help attenuate or even override the weight gain induced by insulin icodec. In fact, multiple phase 3 clinical trials are underway to compare the combination of insulin icodec with semaglutide (called icosema) with each component alone and with glargine in patients with type 2 diabetes [11-13]. Although data derived from the ONWARDS trials was useful in demonstrating the short-term efficacy and safety profile of insulin icodec, well-designed studies are needed to establish its long-term efficacy and safety.

Table 1: *Overview of phase 3a trials of once-weekly insulin icodec

	Onwards 1 [3]	Onwards 2 [4]	Onwards 3 [5]	Onwards 4 [6]
Main purpose	Compare icodec with once-daily glargine in insulin-naïve patients	Compare icodec vs once-daily degludec in basal-insulin treated patients	Compare icodec vs once-daily degludec in insulin naïve-patients	Compare icodec vs once-daily glargine in patients treated with basal-bolus regimen
Design	Randomized, open-label, treat-to-target multi-national	Randomized, open-label, treat-to-target, multi-national	Randomized, double-masked, treat-to-target, multinational	Randomized, open-label, treat-to-target, multi-national
Duration	Main phase: 52 weeks. Extension phase 26 week. Safety monitoring until 83 weeks	26 weeks.	26 weeks. Safety monitoring up to 31 weeks.	26 weeks
Patients	N=984, 60% men in icodec group higher than 53% in the glargine group, 59 year-old, type 2 diabetes of 11 year-duration	N=526, 57% men, 62 year-old, type 2 diabetes of 16 year-duration	N=598, 63% men, 58 year-old, type 2 diabetes of 10 year-duration	N= 582, 52% men, 60 year-old, type 2 diabetes of 17 year-duration
Baseline HbA1c	8.5%	8.1%	8.5%	8.3%
Total insulin doses per week	214 units with icodec vs 222 units with glargine (no significant difference)	268 units with icodec vs 244 units with degludec, ETR 1.10 (95% CI, 1.01 to 1.20) P=0.03	204 units with icodec vs 187 units with degludec (no significant difference)	514 units (73 units/d) with icodec vs 559 units (80 units/d) with glargine. ETR 0.92 (95% CI, 0.85 to 0.99, P=0.034).
Effects on HbA1c	Superior HbA1c reduction with icodec vs glargine at week 52, ETD -0.19%, 95% CI, -0.36 to -0.03, P=0.02	Superior HbA1c reduction with icodec vs degludec, ETD -0.22% (95% CI, -0.37 to -0.08), P=0.003	Superior HbA1c reduction with icodec vs degludec, ETD -0.2% (95% CI, -0.1 to -0.3), P=0.002	Icodec was non-inferior to glargine. ETD 0.02% (95% CI, -0.11 to +0.15), p<0.0001. Icodec was not superior to degludec.
Time of glucose in range (70-180 mg/dl) in CGM	71.9% with icodec vs 66.9% with glargine, ETD 4.27% (95% CI, 1.92 to 6.62), p<0.001	63.1% with icodec vs 59.5% with degludec, ETR 1.10 (95% CI, -0.84 to +5.65) p=0.15	Not evaluated	66.9% with icodec vs 66.4% with glargine
Hypoglycemia level 1 (BG 54-69 mg/dl)	At week 83: 2308 events with icodec (3.02/PYE) vs 1067 events with glargine (1.39/PYE), statistical significance not mentioned)	1209 episodes with icodec vs 589 episodes with degludec. ERR 1.88 (95% CI, 1.4 to 263, p=0.0002)	28% (359 events in 84 patients) with icodec vs 20.1% (159 events in 59 patients) with degludec. At week 31: rates are 2.3/PYE with icodec vs 1.08 with degludec	84% with icodec vs 86% with glargine. Yet, rate of hypoglycemic episodes was higher with icodec than glargine, ERR 1.25 (95% CI, 1.03 to 1.52), P 0.025
Incidence of combined hypoglycemia level 2 (BG <54 mg/dl) and level 3 (cognitive impairment)	At week 83: 226 events in 12.4% of patients receiving icodec vs 114 events in 13.4% receiving glargine. Event rate 0.30 with icodec vs 0.16/PYE with glargine. ERR 1.71 (95% CI, 1.02 to 2.76)	14% with icodec vs 7% with degludec, EOR 1.89 (95% CI, 1.05 to 3.41, p=0.034).	At 26 weeks: 8.2% with icodec vs 4.4% with degludec. ERR, 3.12 (95% CI, 1.30 to 7.51, P=0.01). At 31 weeks difference was not significant.	52% with icodec vs 56% with glargine. 7 events of level 3 hypoglycemia with icodec vs 3 events with glargine. ERR 0.99 (95% CI, 0.73 to 1.33)
Weight changes	+2.2 kg with icodec at week 52 vs +1.83 kg with glargine (no significant difference)	+1.4 kg with icodec vs -0.30 kg with degludec, ETD, 1.7 kg (95% CI, 0.76 to 2.63, P=0.0004)	+2.8 kg with icodec vs 2.3 kg with degludec, ETD 0.46 kg (no significant difference)	+ 2.7 kg with icodec vs 2.2 kg with glargine (no significant difference)
Patient satisfaction score	Not evaluated	+4.22 with icodec vs +2.96 with degludec, ETD 1.25, 95% CI, 0.41 to 2.100, P=0.0035)	Not evaluated	Not evaluated

*The primary outcome in all trials was reduction of HbA1c versus comparator. Values are means.
Abbreviations in the table: ETD: estimated treatment difference, ERR: estimated rate ratio, HbA1c: glycated hemoglobin, CGM: continuous glucose monitoring, PYE: hypoglycemic event per person-year of exposure.

Table 2: Advantages and limitations of insulin icodec

Advantages	Limitations
Once-weekly dosing	Increased risk of hypoglycemia compared with insulin glargine and degludec
Higher patient satisfaction when compared with insulin degludec	Propensity for hypoglycemia in cases of hospital admissions, intermittent sickness, days with severe exercise or variable lifestyle
May be injected in abdomen, thigh or upper arm	Not studied in patients in patients with end-stage kidney disease
No increase in allergic reactions compared with	Not studied in patients with HBA1c > 11.0%

insulin glargine or degludec	
	Unknown long-term effects (safety was studied up to 83 weeks)
	Weight gain is slightly greater than insulin degludec and glargine

Conflict of interest

The author does not have a conflict of interest to declare.

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