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Review

# Efficacy and safety of the second generation basal insulin analogs in type 2 diabetes mellitus: A critical appraisal

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ABSTRACT

Type 2 diabetes mellitus is a progressive disease, which requires insulin treatment when other management is no longer effective. Although, insulin plays a vital role in the treatment of diabetes, conventional basal insulins have certain limitations, which have led to the development of more stable and peak less analogues.

*Objectives:* To analyze the efficacy and safety of second generation vs. first generation basal insulins, and the efficacy and safety of second generation vs. second generation basal insulins, in patients with type 2 diabetes mellitus, from the evidence provided by head-to-head randomized controlled trials.

*Methods:* The following electronic databases were searched: PubMed and MEDLINE, Scopus, BIOSIS, Embase, ClinicalTrials.gov, Google Scholar, and Springer Online Archives Collection, from January 1966 to October 2018. Articles resulting from these searches and relevant references cited in those articles were examined.

*Results:* The efficacy among insulins evaluated was similar, however, second generation insulins cause a lower risk of hypoglycemia compared to first generation insulins. A single study showed similar metabolic control with subtle differences in the risk of hypoglycemia among second generation insulins.

*Conclusions:* The second-generation basal insulins result in metabolic control similar to first generation insulins, with lower risk of hypoglycemia. Second-generation insulins have comparable efficacy, with some differences in the risk of hypoglycemia.



## 1. Background

Diabetes mellitus (DM) describes a group of metabolic disorders characterized by increased blood glucose (BG) concentration. The specific complications associated with DM include microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary artery, cerebrovascular and peripheral artery disease). People living with DM have a greater risk of morbidity and mortality than the general population, and it is one of the leading causes of premature morbidity and mortality worldwide [1,2]. The global prevalence of DM in adults has been increasing over recent decades. In 2014, the World Health Organization reported that 1 in 10 adults worldwide had type 2 DM (T2DM). The International Diabetes Federation (2017) has estimated the worldwide prevalence of DM in adults (20–79 years) at 8.8%, with the estimated number of people with DM increasing to 451 million if the age range is expanded to 18–99 years. If these trends continue, it is estimated that by 2045, 693 million people (adults 18–99 years) and 629 million of people (adults of 20–79 years), will have DM [3,4]. Whereas cardiovascular disease (CVD) is responsible for the majority of mortality in people with T2DM, the microvascular complications, such as retinopathy and nephropathy, have the greatest impact on patient's quality of life and the economic cost of patients' management. Good glycemic control can potentially prevent complications and premature death in DM. Although benefits of good glycemic control have been well established, action is needed to increase the proportion of individuals achieving recommended glycemic goals [5,6]. Given the progressive nature of T2DM (with progressive β-cell dysfunction), the majority of patients require intensification of initial oral antihyperglycemic drugs (OADs) treatment with the addition of

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second-line OADs, a non-insulin injectable, and/or insulin. Despite very effective agents such as sodium-glucose co-transporter 2 inhibitors (SGLT2 inh) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), which have been shown to reduce major cardiovascular events (MACEs) in patients with T2DM and established CVD [empagliflozin, canagliflozin (and probably, dapagliflozin), liraglutide and semaglutide] [7,8], insulin therapy remains a critical therapeutic in the treatment of T2DM. In this patient population, basal insulin (BI) is generally first used in combination with OADs, and its use has been shown to be effective in improving glycemic control, with between 40% and 70% of patients reaching a target HbA1c of <7% in randomized controlled trials (RCTs) [9,10]. A number of insulin formulations have been used in this setting, including neutral protamine Hagedorn (NPH) and ultralente insulin (administered at bedtime or twice daily), or long-acting human insulin analogs [i.e., insulin Detemir (Det); insulin Glargine (Glar) in its two preparations Glar-100 (100 U/mL) and Glar-300 (300 U/mL); insulin Degludec (IDeg) in its two preparations IDeg-100 (100 U/mL) and IDeg-200 (200 U/mL)]. In the last decade, significant advances have been made in BI formulations; the "second generation" BI analogues (Glar-300 and IDeg) offer compelling therapeutic benefits over first-generation basal insulin therapies (Det and Glar-100) which can be explained by their ability to more closely mimic the peakless and continuous pharmacokinetic (PK) profile of endogenous BI secretion. These benefits include reduced risk of hypoglycemia which can benefit both healthcare providers and patients by overcoming this critical barrier to the initiation and intensification of insulin therapy [11,12].

## 2. Data selection

The following electronic databases were searched: PubMed and MEDLINE, Scopus, BIOSIS, Embase, ClinicalTrials.gov, Google Scholar, and Springer Online Archives Collection, from January 1966 to October 2018, using the terms "insulin," "glargine," "glargine 300," "glargine 100," "degludec", "detemir" and "basal insulin" in combination with the term "diabetes." Articles resulting from these searches and relevant references cited in those articles were examined. International conference proceedings on diabetes mellitus (2016–2018) were also reviewed. In addition, a manual search of references from relevant reviews and trials was performed. Only articles published in English were included.

## 3. Basic concepts about the efficacy of basal insulins (comparisons Glar-100 vs. NPH; det vs. NPH; det vs. Glar-100)

Compared with NPH insulin, BI analogs aim to provide a PK and pharmacodynamic (PD) profile that more closely mimics the normal physiologic pattern of BI secretion. This type of profile provides a more evenly distributed, predictable and prolonged time-action profile likely to reduce the risk of hypoglycemia and facilitate more flexible dose regimens [13,14]. Consequently, in RCTs assessing Glar-100 vs. NPH in patients with T2DM, similar metabolic control in terms of HbA1c and fasting plasma glucose (FPG) lowering was demonstrated, but with lower rates of overall and nocturnal hypoglycemia (incidences and rates) in the Glar-100-treated patients [15,16]. Similarly, RCTs comparing Det vs. NPH in T2DM failed to recognize any differences in the HbA1c level (in individuals receiving combined therapy with OADs or rapid-acting insulin). Additionally, the individuals managed with Det also experienced less weight gain compared to patients receiving NPH [17,18]. As with studies comparing the first-generation BI analogues to NPH, trials that compared Det vs. Glar-100 in T2DM also demonstrated similar reductions in HbA1c and FPG as well as the proportion of patients achieving the HbA1c targets without symptomatic hypoglycemia. At the end of treatment, however, the results showed that Det-treated subjects required a higher daily insulin dose and had a higher probability of needing to split the daily dose (twice a day) as compared to Glar-100-treated subjects [19,20].

## 4. Efficacy and safety of IDeg vs. Glar-100 (BEGIN program)

### 4.1. General characteristics of the BEGIN program

The efficacy and safety of IDeg was assessed in a large-scale clinical development program, which included nine 26- or 52-week trials. For individuals with T2DM, each of the trials were randomized, treat-to-target, parallel-group, open-label, non-inferiority trials comparing IDeg once daily (QD) with Glar-100 QD. The key study objectives included: change in HbA1c from baseline (BL) (the primary endpoint in all trials), change in FPG; and episodes of confirmed hypoglycemia and nocturnal confirmed hypoglycemia. Each of the trials were non-inferiority trials and the primary endpoint was confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the estimated treatment difference (ETD) (IDeg minus comparator) was below or equal to the non-inferiority margin of 0.4%. Confirmed hypoglycemia was defined as a value of <56 mg/dL (3.1 mmol/l), regardless of symptoms, with nocturnal hypoglycemia being defined as an episode occurring between midnight and 6 a.m. [21,22]. In the BEGIN program, studies comparing IDeg vs. Glar-100 in individuals with T2DM were: BEGIN Basal-Bolus Type 2, BEGIN Once Long, The BEGIN LOW VOLUME, BEGIN FLEX and BEGIN once Asia (Table 1**).** In this program, the patients were excluded if they had taken GLP-1RAs or rosiglitazone within the previous 3 months [additionally, in the BEGIN Flex trial, participants were excluded if they were using DPP-4 inhibitor (DPP-4 inh), or alpha-glucosidase inhibitors (AGI) within 3 months of screening], or if they had impaired renal function, recurrent severe hypoglycemia or hypoglycemic unawareness, among others.

### 4.2. BEGIN Basal-Bolus Type 2

This 52-week RCT compared the efficacy and safety of IDeg-100 QD with Glar-100 QD in a basal-bolus regimen with mealtime insulin aspart, with or without metformin, pioglitazone, or both in participants with T2DM (n = 1006 adults) age ≥18 years, across 123 sites in 12 countries (Bulgaria, Germany, Hong Kong, Ireland, Italy, Romania, Russia, Slovakia, South Africa, Spain, Turkey, and the United States), with body mass index (BMI) ≤40 kg/m$^2$, and HbA1c between 7.0 and 10.0% (53–86 mmol/mol, both inclusive) after using any insulin regimen (premix, self-mix, basal only, basal-bolus) with or without OADs, for 3 months or longer. Basal and bolus insulin were titrated to aim for self-measured plasma glucose (SMPG) levels of between 70 mg/dL (3.9 mmol/L) and less than 90 mg/dL (5.0 mmol/L) before breakfast for BI, and pre-prandially and at bedtime for bolus insulin. The primary endpoint was non-inferiority of IDeg to Glar-100, assessed as a reduction in HbA1c from BL to week 52. Secondary endpoints included change from BL in FPG, mean SMPG, prandial plasma glucose increment, time to reach the pre-breakfast SMPG target of 70-<90 mg/dL from 4-point and 9-point SMPG profiles, and health-related quality of life (HRQoL). After 52 weeks of treatment, IDeg and Glar-100 decreased mean HbA1c concentrations from BL by 1.10 and 1.18%, respectively. An ETD of 0.08% (95% CI: −0.05–0.21%) indicated that IDeg was non-inferior to Glar-100. The rates of overall hypoglycemia were lower in IDeg group [11.09 vs. 13.63 episodes/patient-year of exposure (PYE), p = 0.0359]. Additionally, the rates of diurnal (9.28 vs. 11.39 episodes/PYE, p = 0.044) and nocturnal (1.39 vs. 1.84 episodes/PYE, p = 0.0399) hypoglycemia were significantly lower in

**Table 1**
Trials characteristics, inclusión criteria and adverse events in the BEGIN program (T2DM).

| Trial characteristics | BEGIN Basal-Bolus | | BEGIN Once Long | | BEGIN LOW VOLUME | | BEGIN Flex | | | BEGIN once Asia | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NCT number (year) | NCT00972283 (2012) | | NCT00982644 (2012) | | NCT01068665 (2013) | | NCT01006291 (2013) | | | NCT01059799 (2013) | |
| Duration (weeks) | 52 | | 52 | | 26 | | 26 | | | 26 | |
| Number of patients | 1006 | | 1030 | | 457 | | 458 | | | 435 | |
| Female (%) | 46 | | 38 | | 47 | | 50 | | | 46 | |
| Predominant ethnic group | White | | White | | White | | White | | | White | |
| Duration of Diabetes (years) | IDeg | Glar-100 | IDeg | Glar-100 | *IDeg | Glar-100 | IDeg | Glar-100 | | IDeg | Glar-100 |
| | 13.6 ± 7.5 | 13.4 ± 6.9 | 9.4 ± 6.3 | 8.6 ± 5.7 | 8.6 ± 6.7 | 8.0 ± 5.6 | 10.8 ± 6.9 | 10.8 ± 6.4 | | 11.8 ± 6.5 | 11.1 ± 6.5 |
| Inclusion criteria | | | | | | | | | | | |
| Age (years) | ≥18 | | ≥18 | | ≥18 | | ≥18 | | | ≥18 | |
| HbA1c (%) | ≥7-≤10 | | ≥7-≤10 | | ≥7-≤10 | | ≥7-≤11 or ≤10 | | | ≥7-≤10 | |
| Fasting SMPG target (mg/dL) | 70-<90 | | 70–88 | | <90 | | 70-<90 | | | 70-<90 | |
| BMI (Kg/m$^2$) | ≤40 | | ≤40 | | ≤45 | | ≤40 | | | ≤35 | |
| Glucose-lowering therapy at BL | Basal ± mealtime Insulin ± OADs | | Insulin-naïve + OADs | | Insulin-naïve + OADs | | Insuline-naïve + OADs or basal Insulin + OADs | | | Insulin naïve + OADs | |
| Rate of Aes | IDeg | Glar-100 | IDeg | Glar-100 | IDeg | Glar-100 | IDeg OD Flex | IDeg OD | Glar-100 OD | IDeg | Glar-100 |
| Total, serious AEs (%) | 18.46 | 21.12 | 15.14 | 15.95 | 6.58 | 4.39 | 2.61 | 3.54 | 1.75 | 2.82 | 5.48 |
| Patients with AE (%) | 59.36 | 58.17 | 60.44 | 59.53 | 22.37 | 26.32 | 25.22 | 25.22 | 23.14 | 20.42 | 26.71 |
| **Deaths (%) | 8 | 2 | 1 | 1 | 0 | 2 | 1 | | 1 | †1 | 0 |

Abbreviations: AEs: adverse events; BL: baseline; BMI: Body mass index; Glar-100: Insulin Glargine-100 (100 units/mL); IDeg: Insulin Degludec (100 units/mL); OADs: Oral antihyperglycemic drugs; OD: Once-day; SMPG: Self-measured plasma glucose; T2DM: Type 2 Diabetes Mellitus; *IDeg: Insulin Degludec (200 units/mL); **Deaths considered unrelated to treatment by investigators; †Death considered possibly related to the trial product by the investigator.

the IDeg group. Rates of severe hypoglycemia were similar between groups (0.06 and 0.05 episodes/PYE, respectively, p = NS). Rates of other adverse events (AEs) did not differ between groups [23].

### 4.3. BEGIN Once Long

This 52-week RCT compared the efficacy and safety of IDeg-100 QD with those of Glar-100 QD in 1030 insulin-naïve adults with T2DM (n = 1030) with a mean age of 59 years, across 166 sites in 12 countries (Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Norway, Serbia and Montenegro, Spain, and the United States). Eligibility criteria included HbA1c between 7.0 and 10.0% after taking OADs (metformin monotherapy or metformin in any combination with a sulphonylurea –SU-, a glinide, a gliptin or acarbose for 3 months or longer) and BMI ≤40 kg/m$^2$. The primary endpoint was non-inferiority of IDeg to Glar-100, with the intention-to-treat analysis. The secondary endpoints included change from BL in FPG and frequency of "responders" for HbA1c less than 7.0%, functional health status, and HRQoL. After 52 weeks of treatment, IDeg and Glar-100 decreased mean HbA1c concentrations from BL by 1.06 and 1.19%, respectively. An ETD of 0.09% (95% CI: −0.04–0.22%) indicated that IDeg was non-inferior to Glar-100. The rates of overall hypoglycemia were similar (1.52 vs. 1.85 events/PYE, respectively, p = 0.106), but nocturnal hypoglycemia was significantly less frequent with IDeg (0.25 vs. 0.39 events/PYE, respectively, p = 0.038), particularly during the maintenance period (weeks 16–52). Rates of severe hypoglycemia were low and occurred significantly less frequently with IDeg (0.003 vs. 0.023 episodes/PYE, respectively, p = 0.017), although few events were reported for either group. Finally, AEs were similar in both groups [24].

### 4.4. BEGIN Low Volume

This 26-week RCT compared efficacy and safety between IDeg-200 and Glar-100, both administered QD in combination with metformin with or without a DPP-4 inh in participants with T2DM (n = 457) previously treated with OADs, who qualified for intensification of treatment. The study was conducted at 106 sites in 8 countries (Canada, France, Ireland, the Russian Federation, South Africa, Ukraine, the United Kingdom, and the United States). Participants were insulin-naïve adults with T2DM for ≥6 months, HbA1c 7–10%, BMI ≤45 kg/m$^2$, and previous treatment with metformin with or without additional OADs for ≥3 months. The primary endpoint was the change from BL in HbA1c after 26 weeks of treatment, and secondary outcomes included change from BL in FPG, the number of treatment-emergent confirmed hypoglycemic episodes, and frequency of participants achieving HbA1c <7% without confirmed hypoglycemic episodes. The supportive secondary endpoints included 9-point SMPG profiles, frequency of participants achieving HbA1c <7%, and HRQoL. After 26 weeks, the primary outcome was −1.3% from a BL of 8.3% (67 mmol/mol); and −1.3% from a BL of 8.2% (66 mmol/mol) for IDeg-200 and Glar-100, respectively [ETD: 0.04% (95% CI: −0.11 to 0.19)], confirming non-inferiority. Central laboratory-measured FPG decreased by 3.7 mmol/L (66.7 mg/dL) to 5.9 mmol/L (105.7 mg/dL) with IDeg-200 and by 3.4 mmol/L (60.9 mg/dL) to 6.3 mmol/L (113.1 mg/dL) with Glar-100 [ETD: −0.42 (95% CI: −0.78 to −0.06)]. The event rate of confirmed hypoglycemia at any time during the day was 1.22 vs. 1.42 episodes/PYE, for IDeg-200 and Glar-100, respectively [estimated rate ratio 0.86 (95% CI: 0.58 to 1.28)]. The rate of nocturnal confirmed hypoglycemia was 0.18 vs. 0.28 episodes/PYE, for IDeg-200 and Glar-100, respectively [estimated rate ratio 0.64 (95% CI: 0.30 to 1.37)] [25].

### 4.5. BEGIN flex

This 26-week RCT (three-arm) compared the efficacy and safety of QD IDeg-100 given in a prespecified, "forced," rotating morning and evening dosing regimen to create 8–40-h intervals between injections, with that of Glar-100 dosed QD at the same time each day. The trial was conducted at 69 sites in 14 countries (Argentina, Finland, Hungary, India, Israel, Malaysia, Mexico, Norway, Republic of Macedonia, Russian Federation, Serbia and Montenegro, South Africa, Taiwan, and United Kingdom), in adults ≥18 years of age (n = 458), diagnosed with T2DM for at least 6 months, a BMI of ≤40 kg/m$^2$, and previously treated with either OADs (metformin, SU or glinides, pioglitazone with a stable dose for at least 3 months), BL HbA1c: 7.0–11.0% (inclusive) or any with BI ± OADs (BL HbA1c: 7.0–10.0%, inclusive). The primary endpoint was the change from BL in HbA1c level after 26 weeks of treatment. Secondary efficacy endpoints included patients

achieving an HbA1c concentration of <7%, changes in FPG, insulin dose, and 9-point SMPG profiles. After 26 weeks, variable QD dosing of IDeg was non-inferior to Glar-100 for glycemic control. Primary outcome (mean change in HbA1c from BL to week 26) was −1.28% from a BL of 8.5% (69 mmol/mol); −1.07% from a BL of 8.4% (68 mmol/mol); and −1.26% points from a BL of 8.4%, for IDeg variable QD, IDeg QD, and Glar-100 QD, respectively [ETD between IDeg flexible dosing and Glar-100: 0.04% points (95% CI: −0.12 to 0.20)], confirms non-inferiority. Participants with overall confirmed hypoglycemia was 3.6, 3.6 and 3.5 episodes/PYE, for IDeg variable QD dosing, IDeg QD, and Glar-100 QD, respectively [estimated rate ratio between IDeg flexible dosing and Glar-100: 1.03 (95% CI: 0.75 to 1.40)]. Participants with nocturnal confirmed hypoglycemia was 0.6, 0.6, and 0.8 episodes/PYE for IDeg variable QD dosing, IDeg QD, and Glar-100 QD, respectively [estimated rate ratio between IDeg variable QD dosing and Glar-100: 0.77 (95% CI: 0.44 to 1.35)] [26].

### 4.6. BEGIN Once Asia

This 26-week RCT compared the efficacy and safety of IDeg-100 QD with Glar-100 QD in insulin-naïve Asian patients with T2DM (n = 435), at 52 sites in six countries (Hong Kong, Japan, Malaysia, South Korea, Taiwan and Thailand), in adults (aged ≥18 years; ≥20 years for Japan) diagnosed with T2DM for at least 6 months, with a BMI ≤35 kg/m$^2$, BL HbA1c 7.0–10.0%, and currently being treated with monotherapy or a combination of an insulin secretagogue (SU or glinide) and metformin, with or without addition of AGI or a DPP-4 inh, with unchanged dosing for at least 3 months. The primary endpoint was the change from BL in HbA1c concentration after 26 weeks of treatment. The secondary efficacy endpoints included the proportion of patients achieving an HbA1c concentration of <7% and ≤6.5% (48 mmol/mol) −and proportion of patients achieving these targets in the absence of confirmed hypoglycemia during the final 12 weeks of treatment-, changes in the FPG and nine-point SMPG profiles, and HRQoL. After 26 weeks of treatment, the mean HbA1c concentration was similar for IDeg [7.2% (55 mmol/mol)] and Glar-100 [7.1% (54 mmol/mol)], as were mean decreases from BL (−1.24 and −1.35%, respectively); ETD between IDeg and Glar-100 was 0.11% (95% CI: −0.03 to 0.24), showing that IDeg was non-inferior to Glar-100 in lowering HbA1c. At end-of-trial, mean FPG levels were similar for IDeg [99 mg/dL (5.5 mmol/L)] and Glar-100 [103 mg/dL (5.7 mmol/L)]; mean glucose concentrations from the 9-point profiles were reduced from BL by 2.88 and 2.97 mmol/L, respectively [estimated mean treatment difference between IDeg and Glar-100: −0.09 mmol/L (95% CI: −0.41 to 0.23, p = 0.59)]. The overall rate of confirmed hypoglycemia did not differ significantly between IDeg and Glar-100 [3.0 vs. 3.7 episodes/PYE; rate ratio: 0.82 (95% CI: 0.60 to 1.11, p = 0.20)]. The rates of nocturnal confirmed hypoglycemia for the full trial period between IDeg and Glar-100 were 0.8 vs. 1.2 episodes/PYE; rate ratio: 0.62 (95% CI: 0.38 to 1.04, p = 0.07). However, for the maintenance period of the trial (from week 16 to end-of-trial) the rate of overall confirmed hypoglycemia was significantly lower with IDeg [rate ratio: 0.63 (95% CI: 0.42 to 0.94, p = 0.0242)] [27].

## 5. Clinical trials that are not part of the BEGIN program and that compared the use of IDeg vs. Glar-100 in individuals with T2DM (Table 2)

### 5.1. SWITCH 2 trial

This randomized, double blind, 2-period crossover, multicenter, treat-to-target trial was conducted in patients with T2DM (n = 721) treated with BI with or without OADs, across 152 sites in the United States. The total trial duration was 65 weeks; this included 32 weeks of treatment with QD IDeg or Glar-100 followed by crossover to Glar-100 or IDeg, respectively, for a further 32 weeks. There was then a 1 week of follow-up. The inclusion criteria specified adults (aged ≥18 years) with T2DM for at least 26 weeks, an HbA1c level ≤9.5% (80 mmol/mol), BMI ≤45 kg/m$^2$, and treatment with any BI with or without OADs for at least 26 weeks. Patients treated with bolus or premixed insulin or with SU or meglitinide within 26 weeks before the first visit were not included. The primary outcome measure was the rate of severe or confirmed symptomatic hypoglycemic episodes during the maintenance period (weeks 16–32 and 48–64). Severe hypoglycemia was defined as an episode requiring third party assistance, and confirmed symptomatic hypoglycemic was defined as BG values of <56 mg/dL, with symptoms consistent with hypoglycemia. The secondary outcome measures included the number of severe or BG confirmed symptomatic nocturnal hypoglycemic episode (between 00:01 and 05.59 a.m., inclusive) during the maintenance period, incidence of AEs, change from BL in HbA1c, and FPG (glucose values at week 32 and week 64). The observed mean HbA1c level at the end of treatment period 1 was 7.06% (54 mmol/mol) with IDeg vs. 6.98% (53 mmol/mol) with Glar-100 [ETD: 0.09% (95% CI: −0.04% to 0.23%, p < 0.001 for non-inferiority)] and at the end of treatment period 2 was 7.08% (54 mmol/mol) with IDeg vs. 7.11% (54 mmol/mol) with Glar-100 [ETD: 0.06% (95% CI: −0.07% to 0.18%, p < 0.001 for non-inferiority)]. During the maintenance period, the rates of overall symptomatic hypoglycemia for IDeg vs. Glar-100 were 185.6 vs. 265.4 episodes/100 PYE [rate ratio: 0.70 (95% CI: 0.61 to 0.80, p < 0.001); difference: −23.66 episodes/100 PYE (95% CI: −33.98 to −13.33)], and the proportions of patients with hypoglycemic episodes were 22.5% vs. 31.6% [difference: −9.1% (95% CI: −13.1% to −5.0%)]. The rates of nocturnal symptomatic hypoglycemia with IDeg vs. Glar-100 were 55.2 vs. 93.6 episodes/100 PYE [rate ratio: 0.58 (95% CI: 0.46 to 0.74, p < 0.001); difference: −7.41 episodes/100 PYE (95% CI: −11.98 to −2.85); and the proportions of patients with hypoglycemic episodes were 9.7% vs. 14.7% [difference: −5.1%; (95% CI: −8.1% to −2.0%)]. The proportions of patients experiencing severe hypoglycemia during the maintenance period were 1.6% (95% CI: 0.6% to 2.7%, for IDeg) vs. 2.4% (95% CI: 1.1% to 3.7% for Glar-100), risk difference: −0.8% (95% CI: −2.2% to 0.5%, p = 0.35). Statistically significant reductions in overallTable 2 and nocturnal symptomatic hypoglycemia for IDeg vs. Glar-100 were also seen for the full treatment period [28].

### 5.2. A multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naïve patients with T2DM

This was a 26-week, randomized, open-label, parallel group, treat-to-target trial conducted at 68 centers in six countries (Brazil, Canada, China, South Africa, Ukraine, and United States). The trial included insulin-naïve subjects with T2DM (n = 833), who were inadequately controlled on OADs and qualified for intensified treatment. Participants were eligible to participate if they were ≥18 years of age, T2DM diagnosed for ≥6 months, HbA1c levels between 7.0 and 10%, BMI ≤40 kg/m$^2$, and treated with stable doses of OADs (metformin monotherapy or in combination with an insulin secretagogue, DPP-4 inh, or acarbose for ≥3 months prior to randomization). Exclusion criteria included treatment with glitazones or GLP-1RAs within the previous 3 months prior to screening. The primary endpoint was the change from BL in HbA1c (%) after 26 weeks of treatment. Secondary endpoints included percent of subjects achieving HbA1c targets of <7.0% and ≤6.5%), HbA1c target achievement without confirmed hypoglycemic episodes during the

**Table 2**
Trials characteristics, inclusion criteria and adverse events of clinical trials (different to the BEGIN and EDITION program), comparing IDeg Vs. Glar-100, or Glar-100 vs. Standard care (T2DM).

| Trial characteristics | DEVOTE (IDeg vs. Glar-100) | | SWITCH 2 (IDeg vs. Glar-100) | | Pan C et al. (IDeg vs. Glar-100) | | ORIGIN (Glar-100 vs. SC) | |
|---|---|---|---|---|---|---|---|---|
| NCT number (year) | NCT01959529 (2017) | | NCT02030600 (2017) | | NCT01849289 | | NCT00069784 | |
| Duration | 24 months | | 65 weeks | | 26 weeks | | 6.2 years | |
| Number of patients | 7637 | | 721 | | 833 | | 12,537 | |
| Female (%) | 37 | | 47 | | 48 | | 35 | |
| Predominant ethnic group | White | | White | | Asian non-Indian | | South American | |
| Duration of Diabetes (years) | IDeg | Glar-100 | IDeg | Glar-100 | IDeg | Glar-100 | Glar-100 | SC |
| | 16.6 ± 8.8 | 16.2 ± 8.9 | 14.2 ± 8.3 | 13.9 ± 8.0 | 7.55 ± 5.28 | 8.26 ± 5.45 | 5.5 ± 6.1 | 5.3 ± 5.9 |
| Inclusion criteria | | | | | | | | |
| Age (years) | ≥50 | | ≥18 | | ≥18 | | ≥50 | |
| HbA1c (%) | ≥7 | | ≤9.5 | | ≥7-≤10 | | <9.0 or <8.0 | |
| Fasting SMPG target (mg/dL) | N/A | | N/A | | 70–90 | | N/A | |
| BMI (Kg/m$^2$) | N/A | | ≤45 | | ≤40 | | ** | |
| Glucose-lowering therapy at baseline | ≥1 OADs ± GLP-1Ra, or insulin therapy | | Basal Insulin + OADs | | Insulin-naïve + OADs | | ±OADs | |
| Rate of adverse events | IDeg | Glar-100 | IDeg | Glar-100 | IDeg | Glar-100 | Glar-100 | SC |
| Total, serious AEs (%) | 38.6 | 39.7 | 9.5 | 9.8 | 2.9 | 3.6 | ¥ | ¥ |
| % of patients with AEs | 39 | 40 | 57.2 | 61.1 | 53 | 57.9 | ¥ | ¥ |
| Deaths (%) | 5.3† | 5.8† | 0.55 | 1.38 | 0 | 1 | 9.3† | 9.2† |

Abbreviations: AEs: adverse events BMI: Body mass index; Glar-100: Insulin Glargine-100 (100 units/mL); IDeg: Insulin Degludec (100 units/mL); N/A: Not applicable; OADs: Oral antihyperglycemic drugs; SC: standard care; SMPG: Self-measured plasma glucose; T2DM: Type 2 Diabetes Mellitus; *The HbA1C level of people with prior diabetes had to be <9% if on no ADOs and <8% if on half maximum or a greater dose of such agents; **It was not an inclusion criterion; †Cardiovascular deaths; ¥No previously unrecognized AEs of basal insulin were identified during follow-up; hypoglycemia rates were low and weight gain modest.

last 12 weeks of treatment, change in central laboratory-measured FPG, nine-point SMPG profiles, within-subject variability in pre-breakfast SMPG, and HRQoL. The groups showed similar mean (SD) changes from BL in HbA1c: −1.3% (1.1) for IDeg and −1.2% (1.0) for Glar-100 (ETD: −0.05% (95% CI: −0.18 to 0.08) confirming the non-inferiority of IDeg to Glar-100 in HbA1c reduction. The ETD in change from BL in FPG was 4.7 mg/dL [−0.26 mmol/L (95% CI: −0.53 to 0.02, p = NS)]. The rate of confirmed hypoglycemia was 85 and 97 episodes/100 PYE with IDeg and Glar-100, respectively. IDeg was associated with a 20% lower rate of confirmed hypoglycemia [estimated rate ratio: 0.80 (95% CI: 0.59 to 1.10)]. The rate of nocturnal confirmed hypoglycemia was 22 and 24 episodes/100 PYE in the IDeg and Glar-100 groups, respectively [estimated rate ratio: 0.77 (95% CI: 0.43 to 1.37)]. Across the entire 26-week trial period, IDeg had a constant rate of overall and nocturnal confirmed hypoglycemic episodes, while Glar-100 had a low rate in the initial part of the trial and an increasing rate as the trial progressed [29].

### *5.3. Clinical trials comparing cardiovascular safety of IDeg vs. Glar-100 in patients with*

T2DM at high risk of cardiovascular events:

#### *5.3.1. DEVOTE trial*

This trial was a multicenter, international, active comparator-controlled cardiovascular outcomes RCT, designed as an event-driven trial that would continue until at least 633 positively adjudicated, primary cardiovascular outcome events were accrued. The study was conducted at 438 sites in 20 countries (Algeria, Argentina, Brazil, Canada, Croatia, Greece, India, Italy, Japan, Malaysia, Mexico, Poland, Romania, Russia, Spain, South Africa, South Korea, Thailand, United Kingdom, and United States). The primary endpoint was the time from randomization to the first event of a composite MACEs outcome consisting of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The multiplicity-adjusted confirmatory secondary outcomes were the number and incidence of adjudicated events of severe hypoglycemia. Other secondary outcomes included an expanded composite cardiovascular outcome (the primary composite outcome or unstable angina leading to hospitalization) and the time from randomization to death from any cause, along with serious AEs or AEs leading to discontinuation of the intervention, levels of HbA1c, FPG, blood pressure, pulse, lipid measurements, weight, BMI, estimated glomerular filtration rate (eGFR), nocturnal severe hypoglycemia (occurring between 12:01 a.m. and 5:59 a.m.), and basal and bolus insulin dose. Eligible patients included individuals with T2DM (n = 7637) treated with ≥1 OADs or injectable antihyperglycemic therapy, HbA1c ≥ 7.0% (or <7.0%, if treated with ≥20 units/day of BI). Two cohorts were eligible for recruitment into the trial: Prior CVD or history of moderate chronic kidney disease (CKD) cohort, and no prior CVD cohort. The exclusion criteria were: An acute coronary or cerebrovascular event in the previous 60 days, planned coronary, carotid or peripheral artery revascularization, chronic heart failure (NYHA class IV) current hemodialysis or peritoneal dialysis or eGFR <30 mL/min per 1.73 m$^2$, end-stage liver disease, female of child-bearing potential who is pregnant, breastfeeding or intends to become pregnant, current or past (within the last 5 years) malignant neoplasms. IDeg met the primary endpoint of non-inferiority compared with Glar-100 for MACEs, the primary outcome occurred in 8.5% in the IDeg group and 9.3% in the Glar-100 group [Hazard ratio (HR): 0.91 (95% CI: 0.78 to 1.06, p < 0.001 for non-inferiority)]. Additionally, the findings for each component of MACEs were consistent with the primary endpoint, including first occurrence of cardiovascular death [HR: 0.96 (95% CI: 0.76 to 1.21, p = 0.714)], non-fatal myocardial infarction [HR: 0.85 (95% CI: 0.68 to 1.06, p = 0.150)] or non-fatal stroke [HR: 0.90 (95% CI: 0.65 to 1.23, p = 0.502)]. At 24 months, the mean HbA1c was 7.5 ± 1.2% in each group, whereas the mean FPG was significantly lower in the IDeg group than in the Glar-100 group (128 ± 56 vs. 136 ± 57 mg/dL, p < 0.001). Results from the secondary endpoints of the trial showed a significant reduction in the rate of severe hypoglycemia [40%; 3.70 episodes/100 PYE with IDeg vs. 6.25 episodes/100 PYE with Glar-100, equivalent to 4.9% in the IDeg group and 6.6% in the Glar-100 group, for an absolute difference of 1.7 percentage points, rate ratio: 0.60, p < 0.001 for superiority; odds ratio (OR): 0.73, p < 0.001 for superiority]; and nocturnal severe hypoglycemia [53%; 0.65 vs. 1.40 episodes/100 PYE, with IDeg vs. Glar-100 (p < 0.001)]. The rates of AEs did not

differ between the two groups [30].

The main results of the studies that compared IDeg vs. Glar-100 are summarized in figures 1 to 4.

## 6. Efficacy and safety of Glar-300 vs. Glar-100 (EDITION program)

### 6.1. General characteristics of the EDITION program

The EDITION program was a worldwide and extensive series of phase III studies evaluating the efficacy and safety of Glar-300 in different populations of people with DM. In T2DM, Glar-300 was assessed in several multinational, treat-to-target, open-label, parallel-group RCTs (all studies included a 6-month treatment period and a 6-month extension period). The trials utilized a common core protocol that standardized most aspects of the study design, including the comparator (Glar-100), 1:1 randomization, stratification by screening HbA1c, targets for fasting pre-breakfast SMPG, recommendations for dosing of Glar-300 and Glar-100, primary and secondary efficacy and safety variables, such as the definitions used for the hypoglycemia categories and analyses. The primary outcome in all EDITION studies was change of HbA1C over 6 months. Non-inferiority was assessed for the primary endpoint; the upper bound of the two-sided 95% CI, was compared to the predefined non-inferiority HbA1c margin of <0.4% [31,32]. To gain a greater understanding of the effect of Glar-300 vs. Glar-100 on hypoglycemia, categories of hypoglycemia were evaluated, including "confirmed hypoglycemia" (cut-offs ≤70 mg/dL, and <54 mg/dL) and the combination of "confirmed and/or severe events." In the EDITION program, studies comparing Glar-300 vs. Glar-100 in individuals with T2DM were: EDITION 1, 2, 3 and JP2 (Table 3). In the EDITION program, the study inclusion and exclusion criteria for selecting the patient population were as unrestrictive as possible across the studies to reflect the general population of patients with DM. Exclusion criteria included age <18 years, HbA1c <7.0% for all 4 studies, HbA1c >10.0% (86 mmol/mol) for EDITION 1, EDITION 2, and EDITION JP2; and >11.0% (97 mmol/mol) for EDITION 3. Additionally, only patients with concomitant illnesses or medications that could limit the ability of patients to safely complete the study periods, confound the evaluation of study findings, or that conformed to potential contraindications of insulin therapy, were excluded.

### 6.2. EDITION 1 trial

This study was a multicenter, open label, parallel-group study conducted in 13 countries (three in North America, nine in Europe, and in South Africa), and compared the efficacy and safety of daily Glar-300 vs. Glar-100 while maintaining mealtime insulin. The inclusion criteria were a diagnosis of T2DM (n = 807), use of BI therapy, including current basal therapy with ≥42 units/day of either Glar-100 or NPH, together with mealtime therapy with insulin lispro, aspart or glulisine, with or without metformin, for at least 1 year. The exclusion criteria were as follows: less than 1 year on basal plus mealtime insulin and SMPG; use of human regular insulin as mealtime insulin in the last 3 months before the screening visit; use of an insulin pump in the last 6 months before the screening visit; initiation of new glucose-lowering agents and/or weight loss drugs in the last 3 months before the screening visit. The following efficacy outcomes were assessed: change from BL in glycemic control (HbA1c, FPG and 8-point SMPG profiles); mean insulin dose (basal and meal-time); and score on the Diabetes Treatment Satisfaction Questionnaire (DTSQ), as well as change from BL in body weight, percentage of participants experiencing ≥ 1 hypoglycemic event, annualized rates of hypoglycemic events, and the occurrence of other AEs. In the EDITION 1 trial, the mean HbA1c decreased in the two treatment groups; at the end of treatment, HbA1c was 7.25% (56 mmol/mol) with Glar-300 vs. 7.28% (56 mmol/mol) with Glar-100 [least squares (LS) mean change was −0.83% for both groups; the difference was −0.00%


**Fig. 1.** Estimated LS mean difference (95% CI) in HbA1c and FPG reduction in the BEGIN and EDITION clinical trials in participants with T2DM. Abbreviations: CI: confidence interval: FPG: fasting plasma glucose; Glar-100: insulin glargine 100 U/mL; Glar-300: insulin glargine 300 U/mL; IDeg: insulin degludec; LS: least squares: OD: once daily; T2DM: type 2 diabetes mellitus. See text for more details.

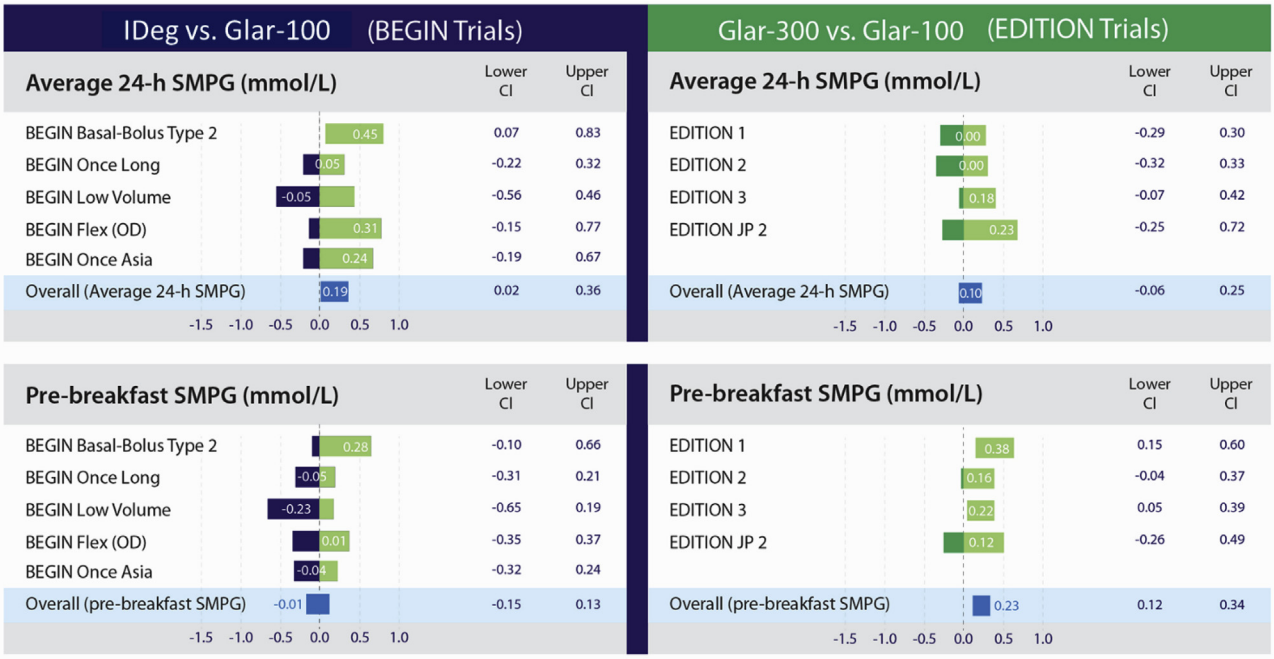


**Fig. 2.** Estimated LS mean difference (95% CI) in average 24 h SMPG and pre-breakfast SMPG reduction in the BEGIN and EDITION clinical trials in participants with T2DM. Abbreviations: CI: confidence interval; Glar-100: insulin glargine 100 U/mL; Glar-300: insulin glargine 300 U/mL; IDeg: insulin degludec; LS: least squares; OD: once daily; SMPG: self-measured plasma glucose; T2DM: type 2 diabetes mellitus. See text for more details.

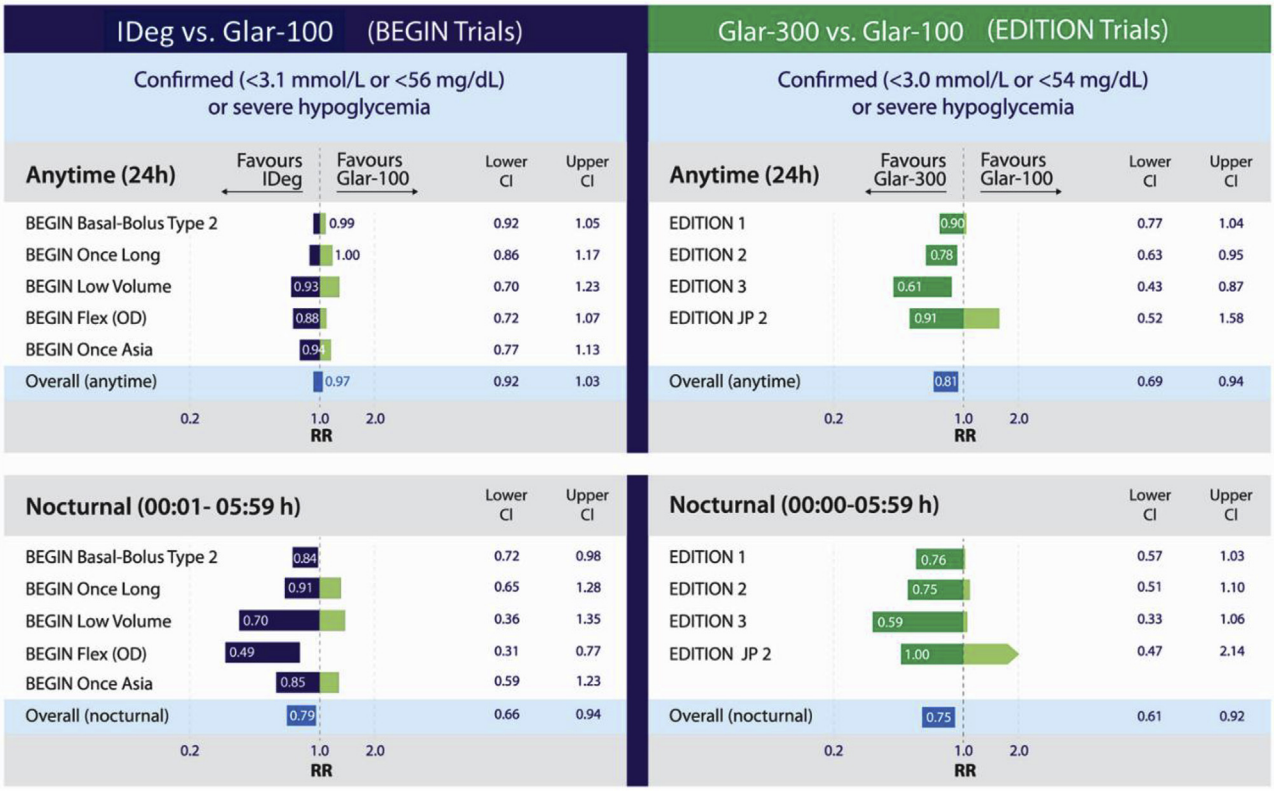


**Fig. 3.** Relative risk (RR) of 21 confirmed [<3.1 mmol/L (<56 mg/dL) or <3.0 mmol/L (<54 mg/dL)] or severe hypoglycemic event (anytime and nocturnal) in the BEGIN and EDITION clinical trials in participants with T2DM. Abbreviations: CI: confidence interval; Glar-100; insulin glargine 100 U/mL; Glar-300: insulin glargine 300 U/mL; IDeg: insulin degludec; OD: once daily; T2DM: type 2 diabetes mellitus. See text for more details.


**Fig. 4.** Relative risk {RR) of >1 documented symptomatic [<3.9 mmol/L {<70 mg/dL)] hypoglycemic event (anytime and nocturnal) in the BEGIN and EDITION clinical trials in participants with T2DM, Abbreviations: CI: confidence interval: Glar-100: insulin glargine 100 U/mL; Glar-300: insulin glargine 300 U/mL; IDeg: insulin degludec; OD: once daily: T2DM: type 2 diabetes mellitus. See text for more details.

**Table 3**
Trials characteristics, inclusion criteria and adverse events in the EDITION program (T2DM).

| Trials characteristics | EDITION 1 | | EDITION 2 | | EDITION 3 | | EDITION JP2 | |
|---|---|---|---|---|---|---|---|---|
| **NCT number (year)** | NCT01499082 (2014) | | NCT01499095 (2014) | | NCT01676220 (2015) | | NCT01689142 (2016) | |
| **Duration (weeks)** | 26* | | 26* | | 26* | | 26* | |
| **Number of patients** | 804 | | 808 | | 862 | | 240 | |
| **Female (%)** | 47 | | 54 | | 42 | | 44 | |
| **Predominant ethnic group** | Caucasian | | Caucasian | | Caucasian | | Asian (Japanese) | |
| **Duration of Diabetes (years)** | Glar-300 | Glar-100 | Glar-300 | Glar-100 | Glar-300 | Glar-100 | Glar-300 | Glar-100 |
| | 15.6 | 16.1 | 12.7 | 12.5 | 10.1 | 9.6 | 14.0 | 13.9 |
| Inclusion criteria | | | | | | | | |
| **Age (years)** | ≥18 | | ≥18 | | ≥18 | | ≥18 | |
| **HbA1c (%)** | ≥7.0, ≤10.0 | | ≥7.0, ≤10.0 | | ≥7.0, ≤11.0 | | ≥7.0, ≤10.0 | |
| **Fasting SMPG target,** | 80–100 | | – | | – | | – | |
| **BMI (Kg/m$^2$)** | N/A | | N/A | | N/A | | N/A | |
| **Glucose-lowering therapy at baseline** | Basal + mealtime insulin ± MET | | Basal insulin + OADs | | Insulin-naïve + OADs | | Basal insulin + OADs | |
| Rate of adverse events | Glar-300 | Glar-100 | Glar-300 | Glar-100 | Glar-300 | Glar-100 | Glar-300 | Glar-100 |
| **TEAEs** | 56.4 | 54.2 | 58.8 | 50.7 | 56.8 | 55.9 | 58.3 | 56.7 |
| **Serious TEAEs** | 6.4 | 5.2 | 3.7 | 3.7 | 5.5 | 5.9 | 4.2 | 3.3 |
| ***Deaths, number** | 1 | 2 | 2 | 0 | 1 | 0 | 0 | 0 |

Abbreviations: BMI: Body mass index; Glar-100: Insulin Glargine-100 (100 units/mL); Glar-300: Insulin Glargine-300 (300 units/mL); IDeg: Insulin Degludec (100 units/mL); N/A: not applicable; OADs: Oral antihyperglycemic drugs; OD: Once-day; SMPG: Self-measured plasma glucose; T2DM: Type 2 Diabetes Mellitus; TEAEs: Treatment-emergent adverse events; *None of the deaths were considered to be related to the study drug; in the EDITION 1 and 3 trials, additional deaths occurred after treatment discontinuation.

(95% CI: −0.11 to 0.11)]. At month 12, the mean HbA1c with Glar-300 was 7.24% (56 mmol/mol) and with Glar-100 was 7.42% (58 mmol/mol) [LS mean difference between reductions with Glar-300 and Glar-100 was −0.17% (95% CI: −0.30 to −0.05, p = 0.007)]. Reductions in FPG from BL were observed in both treatment groups, from 157 mg/dL (8.7 mmol/L) to 130 mg/dL (7.21 mmol/L) with Glar-300; and 160 mg/dL (8.9 mmol/L) to 129.8 mg/dL (7.2 mmol/L) with Glar-100. The reduction in risk of nocturnal hypoglycemia (≤70 mg/dL) with Glar-300 vs. Glar-100 was 21% (and 16% at month 12). In terms of hypoglycemia at any time during the day (≤70 mg/dL), the reduction was 14%, 7% and 6% for the BL to week 8, BL to month 6 and BL to month 12 periods, respectively. With the exception of severe nocturnal hypoglycemic events, the percentage of participants within each category of nocturnal events [any hypoglycemia, documented (≤70 and < 54 mg/dL)] symptomatic hypoglycemia, and confirmed (≤70 and < 54 mg/dL) or severe hypoglycemia, was lower for Glar-300 than for Glar-100 [relative risk (RR): 0.72 to 0.78] throughout the course of treatment. Over 12

months, the cumulative number of confirmed (≤70 mg/dL) or severe hypoglycemic events per participant increased at similar rates for Glar-300 and for Glar-100 throughout the period of observation; however, the event rates did not differ between treatments [rate ratio: 1.06 (95% CI: 0.89 to 1.27)] [33,34].

### 6.3. EDITION 2 trial

This study compared the efficacy and safety of daily Glar-300 vs. Glar-100 plus OADs in patients with T2DM (n = 811). The study comprised a 2-week screening phase, followed by a 6-month treatment period and a 6-month safety extension period. Patients were recruited in 213 centers across 13 countries (Canada, Chile, Finland, France, Germany, Hungary, Mexico, Portugal, Romania, Russia, South Africa, Spain, and the United States). High-dose BI use was an eligibility criterion in EDITION 2, with participants required to use ≥42 units/day; exclusion criteria included use of premixed insulin, Det, or new glucose-lowering agents; recent (within the past 2 months) use of SU; recent (>10 days in the past 3 months) use of human regular insulin or mealtime insulin. After the main 6 months treatment period, participants in this trial continued in a 6 months safety extension to examine the longer-term outcomes of treatment with Glar-300 and Glar-100. The authors evaluated the changes in glycemic control (HbA1c, FPG and SMPG), BI dose from BL to the end of 12 months of treatment, changes in body weight, status, title and cross-reactivity with human insulin of anti-insulin antibodies (AIAs), and AEs. Hypoglycemic events at any time (24 h) and during the night, scores from DTSQ, and a more stringent plasma glucose threshold of <54 mg/dL was also used. In this study, the mean HbA1c at month 6 was 7.57% (59 mmol/mol) in the Glar-300 group and 7.56% (59 mmol/mol) in the Glar-100 group [mean difference of −0.01% (95% CI: −0.14 to 0.12)]. In both treatment groups, FPG declined mostly in the first 12 weeks of therapy with a treatment mean difference of Glar-300 vs. Glar-100 of 0.19 mmol/L [3.38 mg/dL (95% CI: −2.670 to 9.435)]. Despite decrease in FPG in both groups, there was a larger adjusted decrease for Glar-100 [−21.9 mg/dL (−1.21 mmol/L)] compared to Glar-300 [−18.5 mg/dL (−1.02 mmol/L)]. At month 12, the glycemic control achieved with Glar-300 and Glar-100 was similar [the LS mean difference in HbA1C between treatment groups was 0.06% (95% CI: −0.22 to 0.10%)]. FPG was similarly improved in both groups (LS mean difference in change from BL in FPG between groups at month 12 was 3.6 mg/dL). Moreover, the risk reduction in the at-any-time risk of hypoglycemia with Glar-300 was statistically significant for the BL to week 8 and BL to month 6 periods (with a risk reduction identified of 22% and 10%, respectively). At month 12, there was a 37% relative reduction in annualized rate with Glar-300 compared with Glar-100 [1.74 vs. 2.77; rate ratio: 0.63 (95% CI: 0.42 to 0.96, p = 0.0308)]. Considering all hypoglycemia, there were fewer nocturnal hypoglycemic events reported with Glar-300 [(1.8 events/PYE) vs. Glar-100 (2.9 events/PYE), rate ratio: 0.61 (95% CI: 0.41 to 0.92)]. During the 12 months study period, severe hypoglycemia at any time was reported by 7 (1.7%) participants (10 events) in the Glar-300 group and 6 (1.5%) participants (13 events) in the Glar-100 group, corresponding to a rate of 0.03 events/PYE in both treatment groups [35,36].

### 6.4. EDITION 3 trial

This study compared the efficacy and safety of daily Glar-300 and Glar-100 in insulin-naïve patients with T2DM (n = 878) not adequately controlled with non-insulin antihyperglycemic drugs. The study comprised a 2-week screening phase and a 6-month treatment period, followed by a 6-month safety extension period. Patients were recruited in 197 centers across 15 countries (2 in North America, 12 in Europe, and Japan). The inclusion criteria were adults with T2DM, inadequately controlled with non-insulin antihyperglycemic drugs. The exclusion criteria were as follows: history of T2DM for <1 year before screening; <6 months before screening with OADs treatment; change in dose of OADs treatment in the last 3 months before screening; initiation of new glucose-lowering medications and/or weight loss drug in the last 3 months before the screening visit and/or initiation of GLP-1RAs in the last 6 months before the screening visit; current or previous insulin use, except for a maximum of 8 consecutive d (i.e., acute illness, surgery) during the last year prior to screening. Participants who completed the 6 months treatment period continued to receive either Glar-300 or Glar-100, according to initial randomization, for a further predefined 6 months extension phase. The authors evaluated the change from BL to month 12 in HbA1c, FPG, pre-breakfast SMPG, 8-point SMPG profiles and basal insulin dose. Safety/tolerability outcomes included risk of hypoglycemia, change from BL to month 12 in body weight, and the occurrence of other AEs. The EDITION 3 trial showed a decrease in HbA1c in Glar-300 from a BL (mean) of 8.49% (69 mmol/mol) to 7.08% (54 mmol/mol). In the Glar-100 group, the HbA1c decreased from a BL (mean) of 8.58% (70 mmol/mol) to 7.05% (54 mmol/mol). The LS mean difference in change of HbA1c was 0.04% (95% CI: −0.09 to 0.17). Both, Glar-300 and Glar-100 decreased the FPG throughout the 6 months treatment period [the adjusted between group difference was +6.99 mg/dL (95% CI: 1.8 to 12.2)]. At month 12, the LS mean difference in FPG change for Glar-300 versus Glar-100 was 1.32 mg/dL (95% CI: −4.62 to 7.26). Mean HbA1c was 7.13% (54 mmol/mol) with Glar-300 and 7.24% (56 mmol/mol) with Glar-100 [LS mean difference in HbA1c change for Glar-300 vs. Glar-100 was −0.08% (95% CI: −0.23 to 0.07)]. The annualized event rates of nocturnal confirmed or severe hypoglycemia were similar in the two treatment groups during the 6-mo study period. The annualized event rate of hypoglycemia at any time was significantly lower with Glar-300 vs. Glar-100 over 6-mo [6.4 vs. 8.5 events/PYE, RR: 0.75 (95% CI: 0.57 to 0.99, p = 0.042)]. A lower risk was observed for confirmed (<54 mg/dL) or severe hypoglycemia [RR: 0.61 (95% CI: 0.43 to 0.87)] and for documented (<54 mg/dL) symptomatic hypoglycemia [RR: 0.55 (95% CI: 0.37 to 0.82)] over the 6-mo period in the Glar-300 group vs. Glar-100. At month 12, a benefit in risk reduction of documented symptomatic hypoglycemia <54 mg/dL (at any time) was documented for Glar-300. The annualized rates of the any time of day events (documented symptomatic hypoglycemia ≤70 mg/dL) showed a statistically significant reduction with Glar-300 vs. Glar-100 [RR: 0.73 (95% CI: 0.54 to 0.99)] [37,38].

### 6.5. EDITION JP2 trial

This study compared the efficacy and safety of daily Glar-300 and Glar-100 both in combination with OADs in Japanese patients with T2DM (n = 241). The study comprised a screening phase, 6-month treatment period, a pre-planned 6-month safety extension and follow-up. Patients were recruited at 22 centers in Japan. The inclusion criteria were diagnosis of T2DM for at least 1 year at the time of the screening visit treated with basal insulin in combination with OADs for at least 6 months before the screening visit. The exclusion criteria were as follows: BMI ≥35 kg/m$^2$ at the screening visit; patients on SMPG <6 months before the screening visit; use of pre-mix insulin, insulin detemir (2 times or more a day), or GLP-1RAs in the last 3 months before the screening visit; use of mealtime insulin (rapid-acting insulin analogue and short-acting insulin) for more than 10 days in the last 3 months before the screening visit; use of insulin pump in the last 6 months before the screening visit; initiation of new glucose-lowering medications and/or weight loss drugs in the last 3 months before the screening visit; severe

hypoglycemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months before the screening visit. Following a 6 months treatment period, participants continued receiving previously assigned QD Glar-300 or Glar-100 plus OADs, in a 6 months extension period. The authors evaluated the changes from BL to month 12 in HbA1c, FPG, average pre-injection SMPG and average 7-point SMPG, as well as daily BI dose, mean 7-point SMPG profiles at BL and month 12, hypoglycemic events, body weight and AEs during the 12 months period. In this trial, Glar-300 met the primary endpoint of non-inferiority for change in HbA1C over 6 month compared with Glar-100 [LS mean difference: 0.10% (95% CI: −0.08 to 0.27)]. No between-treatment differences were observed in change from BL to month 6 in FPG [LS mean difference between groups: 0.8 mg/dL (95% CI: −7.3–8.8 mg/dL)]. At month 12, the reductions in HbA1c levels from BL were similar in the two treatment groups [LS mean difference: 0.0% (95% CI: −0.2 to 0.2)]. The mean change in HbA1c from BL to month 12 was −0.3% with Glar-300 and −0.3% with Glar-100. The mean FPG also decreased from BL to month 12, to 126.5 mg/dL (7.02 mmol/L) in the Glar-300 group and 115.3 mg/dL (6.4 mmol/L) in the Glar-100 group; the mean change in FPG from BL was −12.1 mg/dL (−0.67 mmol/L) with Glar-300 and −18.6 mg/dL (−1.03 mmol/L) with Glar-100. Finally, this study showed a reduction in the risk of nocturnal hypoglycemia (≤70 mg/dL) with Glar-300 over the week 9 to month 6, BL to month 6, and BL to month 12 periods (42%, 38%, and 27% drop, respectively), as well as in the risk of any-time hypoglycemia (≤70 mg/dL) over the BL to week 8 period (31% reduction). Confirmed (≤70 mg/dL) or severe hypoglycemia (nocturnal) over the 6 month study period (annualized rates, events per participant-year) was lower with Glar-300 [rate ratio: 0.45 (95% CI: 0.21 to 0.96, p = 0.040)] and for any time of day [rate ratio: 0.64 (95% CI: 0.43 to 0.96, p = 0.030)]. At month 12, the annualized rate of confirmed (≤70 mg/dL) or severe hypoglycemia was lower with Glar-300 [rate ratio: 0.41 (95% CI: 0.18 to 0.92) for nocturnal hypoglycemia, and rate ratio: 0.64 (95% CI: 0.44 to 0.94) for hypoglycemia at any time] [39,40].

The main results of the studies that compared Glar-300 vs. Glar-100 are summarized in Tables 3, 4; and in figures 1 to 4.

## 7. Clinical trials comparing cardiovascular safety of Glar-100 vs. standard care in patients with T2DM at high cardiovascular risk (Table 2)

### 7.1. ORIGIN trial

The ORIGIN study is not part of the EDITION program. This trial tested the effect of titrated basal Glar-100 vs. Standard care and of n−3 fatty acid supplements vs. Placebo on cardiovascular outcomes. Participants were enrolled from 573 cardiology, diabetes, or other clinical sites in 40 countries. The inclusion criteria were individuals with impaired fasting glycaemia (IFG) and/or impaired glucose tolerance (IGT), or early T2DM (on no pharmacological treatment) for at least 10 weeks prior to screening, or taking one OADs from among SU, biguanides, glitazones, AGI, and meglitinides at a stable dose while ambulatory for at least 10 weeks at the time of screening, adults ≥50 years, and with cardiovascular risk factors, microalbuminuria or clinical albuminuria, left ventricular hypertrophy, significant stenosis on angiography of coronary, carotid, or lower extremity arteries. The exclusion criteria were: Type 1 DM (T1DM), requiring ambulatory insulin treatment or uncontrolled or symptomatic hyperglycemia or a new antidiabetic agent, known *anti*-glutamic acid decarboxylase antibody positivity in the past, serum creatinine >2.0 mg/dL at screening, active liver disease, chronic or recurrent treatment with systemic corticosteroids, or niacin treatment for hyperlipidemia, and heart failure. Participants assigned to Glar-100, targeting a SMPG level of 95 mg/dL (5.27 mmol/L) or less. Participants assigned to standard care were treated on the basis of the investigator's best judgment and local guidelines. There were two coprimary composite cardiovascular outcomes. The first was death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke, and the second was a composite of any of these events, a revascularization procedure, or hospitalization for heart failure. Other adjudicated outcomes were a composite microvascular outcome, incident cases of DM in participants without BL diabetes, all-cause mortality, and new or recurrent cancers. Hypoglycemic episodes since the previous visit were recorded at each visit. In this Study, the rates of incident cardiovascular outcomes were similar in the Glar-100 and standard-care groups [2.94 and 2.85 per 100 PYE, respectively, for the first coprimary outcome, HR: 1.02 (95% CI: 0.94 to 1.11, p = 0.63); and 5.52 and 5.28 per 100 PYE, respectively, for the second coprimary outcome, HR: 1.04 (95% CI: 0.97 to 1.11, p = 0.27)]. New-onset DM was diagnosed approximately 3 months after therapy was stopped among 30% vs. 35% of 1456 participants without baseline DM [OR: 0.80 (95% CI: 0.64 to 1.00, p = 0.05)]. Rates of severe hypoglycemia were 1.00 vs. 0.31 per 100/PYE. Median weight increased by 1.6 kg in the Glar-100 group and fell by 0.5 kg in the standard-care group. There was no significant difference in cancers [HR: 1.00 (95% CI: 0.88 to 1.13, p = 0.97)] [41].

## 8. Head-to-head comparisons between Glar-300 and IDeg

### 8.1. The BRIGHT study

This was a phase IV, 24-week, multinational, multicentre, open-

**Table 4**
Weight change and basal insulin dose at the end of studies in BEGIN and EDITION trials in T2DM.

| BEGIN trials | Weight Change (Kg) IDeg | Weight change (Kg) Glar-100 | IDeg−Glar100 Difference (p value) | Final BID, U/kg (IDeg) | Final BID, U/kg (Glar-100) | P value |
|---|---|---|---|---|---|---|
| Weight change and IDeg−Glar difference | | | | Basal insulin dose at the end of studies | | |
| BEGIN Basal-Bolus | +3.6 | +4.0 | −0.4 Kg (NS) | 0.75 | 0.69 | <0.05 |
| BEGIN Once Long | +2.4 | +2.1 | +0.3 Kg (NS) | 0.59 | 0.60 | NS |
| BEGIN LOW VOLUME* | +1.9 | +1.5 | +0.4 Kg (NS) | 0.53 | 0.60 | <0.05 |
| BEGIN Flex | +1.6 | +1.3 | +0.3 Kg (NR) | 0.5 | 0.5 | NS |
| BEGIN once Asia | +1.3 | +1.4 | −0.17 Kg (NS) | 0.28 | 0.35 | <0.05 |
| EDITION trials (6 months) | Weight change (Kg) Glar-300 | Weight change (Kg) Glar-100 | Glar-300−Glar100 Difference (p value) | Final BID, U/kg Glar-300 | Final BID, U/kg Glar-100 | P value |
| EDITION 1 | +0.93 | +0.90 | +0.03 Kg (NS) | 0.97 | 0.88 | <0.05 |
| EDITION 2 | +0.08 | +0.66 | −0.58 Kg (0.015) | 0.92 | 0.84 | <0.05 |
| EDITION 3 | +0.49 | +0.71 | −0.22 Kg (NS) | 0.62 | 0.53 | <0.05 |
| EDITION JP2 | −0.6 | +0.4 | −1.0 Kg (0.0003) | 0.35 | 0.30 | <0.05 |

Abbreviations: BID: basal insulin dose; Glar-100: Insulin Glargine-100; Glar-300: Insulin Glargine-300; IDeg: Insulin Degludec; NR: not reported; NS: non-significant; T2DM: Type 2 Diabetes Mellitus, *IDeg-200 vs. Glar-100.

label, two-arm, parallel-group trial, including insulin-naïve adults with T2DM [(n = 929), 155 centers from 16 countries] inadequately controlled with OADs, with or without a GLP-1RAs. Participants were randomized 1:1 to receive Glar-300 (0.2 U/kg) or IDeg (10 U), administered QD between 18:00 and 20:00 h Using similar treat-to target titration protocols. The primary endpoint was HbA1c change from BL to week 24; both the non-inferiority and then superiority of Glar-300 vs. IDeg were assessed. Secondary endpoints included the incidence and event rates of hypoglycemia, BG level changes, variability of prebreakfast glucose and AEs. The study also included patient-reported outcomes as assessed by the DTSQ and the Hypoglycemia Attitudes and Behavior Scale (HABS). Others secondary endpoints were: percentage of patients reaching HbA1c targets <7% or ≤6.5%; percentage of patients reaching HbA1c targets <7% or ≤6.5% without severe and/or confirmed hypoglycemia; percentage of patients requiring rescue therapy; to assess the frequency of occurrence and diurnal distribution of hypoglycemia by American Diabetes Association (ADA) category of hypoglycemia; to assess the safety in each treatment group. In this study, the glycemic control was similar in both treatment arms, the non-inferiority of Glar-300 vs. IDeg was demonstrated for the primary endpoint [HbA1c change from BL to week 24: LS mean difference −0.05% (95% CI: −0.15 to 0.05) or −0.6 mmol/mol (95% CI: −1.7 to 0.6), non-inferiority p-value <0.0001]. The superiority of Gla-300 vs. IDeg-100 was not demonstrated. Mean (±SD) HbA1c at baseline was 8.7 ± 0.8% (72 ± 9 mmol/mol) and 8.6 ± 0.8% (70 ± 9 mmol/mol) in the Glar-300 and Deg-100 groups, respectively, decreasing to 7.0 ± 0.8% (53 ± 9 mmol/mol) and 7.0 ± 0.8% (53 ± 8 mmol/mol) by week 24. The proportions of individuals who reached HbA1c target <7.0%, or HbA1c target <7.0% without confirmed hypoglycemia (<70 mg/dL or <54 mg/dL) at any time of day (24 h), at week 24 were comparable between treatment arms. The LS mean difference in FPG change from BL to week 24 was 7.7 mg/dL (95% CI 2.7−12.7) for Glar-300 vs. Deg-100. The LS mean difference in fasting SMPG change from BL to week 24 was 1.1 mg/dL (95% CI: 21.9-4.1) for Glar-300 vs. Deg-100. The eight-point fasting SMPG profiles appeared similar with Gla-300 and IDeg-100 by week 24. Mean coefficient of variation for eight-point profiles (24-h SMPG), expressing within-day plasma glucose variability, was comparable for Glar-300 and Deg-100 at BL (22.5% and 23.4%, respectively) and at week 24 (27.6% and 28.0%, respectively). The incidence of confirmed hypoglycemia at any time of day (24h) was comparable for both BI treatment groups, irrespective of background OADs/GLP-1RA therapy; the incidence of hypoglycemia (≤70 mg/dL and <54 mg/dL) at any time of day (24h) were lower with Glar-300 in the 0−12 week titration period [OR: 0.74 (95%, CI: 0.57 to 0.97, p = 0.03); and OR: 0.63 (0.40−0.99, p = 0.044), respectively]. The event rates of hypoglycemia (≤70 mg/dL and <54 mg/dL) at any time of day (24h) were lower with Glar-300 in the 0−12 week titration period [RR: 0.77 (95%CI: 0.62 to 0.96, p = 0.023); and RR: 0.57 (0.34−0.97, p = 0.038), respectively]. The rate of nocturnal confirmed hypoglycemia (≤70 mg/dL) was lower with Glar-300 in the 0−12 week titration period (00:00-06:00 h and 00:00-08:00 h) [RR: 0.65 (95%CI: 0.43 to 0.98), p = 0.040] (Table 5). The mean daily insulin dose (±SD) on day 1 was 16.9 ± 4.4 units (0.19 ± 0.04 units/kg) for Glar-300 and 10.2 ± 1.9 units (0.12 ± 0.04 units/kg) for IDeg-100. At week 24, the mean daily dose was 50.5 ± 25.6 units (0.54 ± 0.26 units/kg) for Glar-300 and 39.2 ± 23.3 units (0.43 ± 0.24 units/kg) for IDeg-100. The mean dose increases from BL to week 24 were 33.6 ± 24.4 units (0.36 ± 0.25 units/kg) for Glar-300, and 29.1 ± 23.3 units (0.31 ± 0.24 units/kg) for IDeg-100. The mean (±SD) body weight increased from BL (90.6 ± 16.1 kg and 88.7 ± 15.9 kg in the Glar-300 and IDeg-100 groups, respectively) to week 24 (92.5 ± 16.6 and 91.4 ± 16.7 kg), an absolute mean increase of 2.0 ± 3.8 kg with Glar-300 and 2.3 ± 3.6 kg with IDeg-100. LS mean difference in body weight change for Glar-300 vs. IDeg-100 was 20.33 kg (95% CI 20.81 to 0.15). The percentage of AEs between both treatment arms was similar (no specific safety concerns were reported) [42,43].

## 9. Other results

### 9.1. Quality-of-life assessments, and treatment satisfaction scores

In the BEGIN Program, the Quality-of-life assessments was evaluated using validated short form SF-36 questionnaires to assess HRQoL outcomes. The SF-36 questions are grouped into eight domains, including a physical component summary score and a mental component summary score. The benefits in favor of IDeg were small (less than two points on 100 point scales with five to 10 point differences considered clinically significant), particularly in improvements in bodily pain, physical health, vitality and quality of life. In general, significant differences were found in favor of IDeg in: BEGIN Basal Bolus, BEGIN Once Long, BEGIN Low Volume trials; no statistically significant differences were observed in the BEGIN Once Asia, and also in the study by Pan C et al.; however, in this last study, the total score for the Treatment Related Impact Measures-Diabetes Device (TRIM-D Device) questionnaire at the end of treatment showed a statistically significant difference between treatments in favor of IDeg. This aspect was not evaluated in the BEGIN Flex, in the DEVOTE and the SWITCH2 trials. Moreover, in the EDITION program, the treatment satisfaction scores were measured by the DTSQ, this questionnaire addresses the participant's satisfaction with treatment (satisfaction with current treatment; convenience of the treatment; flexibility; satisfaction with own understanding of their diabetes; how likely to recommend their present treatment; and how satisfied to continue with their present treatment). In general, the treatment satisfaction scores were similar between treatment groups in EDITION 1, EDITION 2, and EDITION 3. This aspect was not evaluated in the EDITION JP2 [44,45].

### 9.2. Injection site reactions and hypersensitivity reactions

This parameters were reported at a similar rate with IDeg, Glar-100, and Glar-300 (in BEGIN program, EDITION program, DEVOTE, SWITCH, ORIGIN, and Pan C et al. Trials). None of the injection site reactions was serious. No safety signal was detected for hypersensitivity reactions among IDeg vs. Glar-100 and Glar-300 vs. Glar-100, most events were reported as mild or moderate in intensity. The majority of patients recovered or improved while treatment was ongoing [46].

### 9.3. Malignancy

No safety signal was detected for malignancy in the T2DM pools for patients receiving IDeg vs. Glar-100, and Glar-300 vs. Glar-100. The number of cases was comparable between the treatment groups. Finally, in the ORIGIN trial, showed no significant difference in the incidence of any cancer, death from cancer, or cancer at specific sites [47].

### 9.4. Cardiovascular safety

No cardiovascular safety signal was detected in the T2DM pools for patients receiving IDeg, Glar-300 or Glar-100 in BEGIN and EDITION trials, it must be taken into account that the BEGIN and EDITION trials has not been designed to specifically assess the cardiovascular risk. MACEs including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke were low and comparable for participants receiving IDeg vs. Glar-100 and Glar-300 vs. Glar-100. Moreover, in the ORIGIN study, Glar-100 had a

**Table 5**
BRIGHT Study (key efficacy and safety results for Glar-300 vs. IDeg in different treatment periods).

| Efficacy parameters (ITT population) | Glar-300 (n = 462) | IDeg (n = 462) |
|---|---|---|
| | HbA1c% | |
| BL | 8.72 ± 0.83 | 8.57 ± 0.80 |
| Week 24 | 7.03 ± 0.79 | 7.03 ± 0.77 |
| LS mean change From BL to week 24 ± SE | −1.64 ± 0.04 | −1.59 ± 0.04 |
| LS mean difference (95%CI) | −0.05 (−0.15 to 0.05), noninferiority confirmed (p < 0.0001) | |
| | FPG (mg/dL) | |
| BL | 190.60 ± 49.36 | 182.12 ± 51.68 |
| Week 24 | 123.76 ± 40.60 | 114.54 ± 33.23 |
| LS mean change from BL to week 24 ± SE | −63.47 ± 1.956 | −71.16 ± 1.977 |
| LS mean difference (95%CI) | **7.68 (2.71–12.65)** | |
| | **Participants who reached HbA1c target <7.0%** | |
| N (%) | 225 (48.7) | 206 (44.9) |
| OR (95% CI) | 1.19 (0.91–1.54) | |
| | **Participants who reached HbA1c target without confirmed (≤70 mg/dL) hypoglycemia** | |
| N (%) | 62 (13.4) | 60 (13.0) |
| OR (95% CI) | 1.05 (0.71–1.55) | |
| | **Participants who reached HbA1c target without confirmed (≤54 mg/dL) hypoglycemia** | |
| N (%) | 194 (42.0) | 175 (37.9) |
| OR (95% CI) | 1.20 (0.92–1.57) | |
| | **Fasting SMPG (mg/dL)** | |
| BL | 177.85 ± 40.49 | 171.65 ± 38.16 |
| Week 24 | 115.21 ± 23.66 | 113.29 ± 20.65 |
| LS mean change from BL to week 24 ± SE | −58.11 ± 1.21 | −59.18 ± 1.22 |
| LS mean difference (95%CI) | 1.08 (−1.94 to 4.10) | |
| Safety parameters (safety population) | **Incidence (%) of confirmed hypoglycemia at any time of day (24 h) (0–12 weeks)** | |
| ≤70 mg/dL | 47.4 | 54.3 |
| OR (95% CI) | **0.74 (0.57 to 0.97), p = 0.030** | |
| ≤54 mg/dL | 7.8 | 11.7 |
| OR (95% CI) | **0.63 (0.40 to 0.99), p = 0.04** | |
| | **Event rate (E/PYE) of confirmed hypoglycemia at any time of day (24 h) (0–12 weeks)** | |
| ≤70 mg/dL | 8.08 | 10.47 |
| RR (95% CI) | **0.77 (0.62 to 0.96), p = 0.023** | |
| ≤54 mg/dL | 0.49 | 0.86 |
| RR (95% CI) | **0.57 (0.34 to 0.97), 0.038** | |
| | **Event rate (E/PYE) of confirmed nocturnal (00:00–to 05:59 h) hypoglycemia (0–12 weeks)** | |
| ≤70 mg/dL | 1.42 | 2.20 |
| RR (95% CI) | **0.65 (0.43 to 0.98), p = 0.040** | |

Abbreviations: BL: baseline, CI: confidence interval; E/PYE: event/participant-year exposure; FPG: fasting plasma glucose; Glar-300: Insulin Glargine-300 (300 units/mL); IDeg: Insulin Degludec (100 units/mL); ITT: intention-to-treat; LS: least squares; OR: odds ratio; RR: rate ratio; SE: standard error; SMPG: self-measured plasma glucose.

neutral effect on cardiovascular outcomes, and on the other hand, in the DEVOTE trial, among patients with T2DM at high risk for cardiovascular events, IDeg was non-inferior to Glar-100 with respect to the incidence of major cardiovascular events [48].

### 9.5. Immunogenicity

In the BEGIN Once Long, the immunogenicity of IDeg was negligible; in the BEGIN LOW VOLUME, the cross-reacting insulin antibodies remained low in both treatment groups, in the BEGIN Flex and BEGIN Once Asia, the levels of IDeg and Glar-100 specific antibodies remained close to zero during the trial. Moreover, in the EDITION program (EDITION 2 and EDITION 3) showed that at BL 41.6% in the Glar-300 group and 37.7% in the Glar-100 group were positive for AIAs. The percentage of patients showing a conversion of the antibodies status from negative at BL to positive slightly increased from 10% at week 4 to about 20% in both groups at month 6. The percentage of patients who converted from BL positive to negative AIAs was about 20% [49].

### 9.6. Adverse events

The total number of all AEs was similar for patients receiving IDeg vs. Glar-100 and Glar-300 vs. Glar-100. The most common AEs were headache, upper respiratory infections, and pharyngitis, and they were similar between the treatment groups [45,46] **(**Table 1**).**

### 9.7. Average 24h SMPG, and pre-breakfast SMPG

The average 24h SMPG reduction from BL to study end was significantly better for Glar-100 only for BEGIN Basal-Bolus Type 2 (in the BEGIN trials); in the EDITION trials there were no significant differences in this parameter **(**Fig. 1**).** Moreover, there were no significant differences in the pre-breakfast SMPG with IDeg and Glar-100 (for BEGIN trials). While in EDITION 1 and 3, reduction in pre-breakfast SMPG was significantly better for Glar-100 vs. Glar-300 [44,50].

### 9.8. Changes in weight, and basal insulin dose at the end of the study

No significant weight differences were observed In the BEGIN trials; in the BEGIN Flex, the difference in weight between IDeg and Glar-100 was 0.3 kg, but statistical significance was not reported. On the other hand, there were weight differences between the patients receiving Glar-300 and Glar-100 in the EDITION trials. The weight gain was statistically lower (in favor of Glar-300) in the EDITION 2 (at month 6 and month 12), no significant weight differences were observed in the EDITION 1 (at month-6 and month-12), and EDITION 3 (at month-6 and month-12). Furthermore, in the EDITION JP2 (BL to month-6 and BL to month-12), the participants receiving Glar-300 lost weight compared to those receiving Glar-100, who experienced weight gain; the differences in both

groups, over both follow-up periods, were statistically significant. In general, the basal insulin dose was raised at the end of the follow-up period, both in the BEGIN studies and in the EDITION trials (Table 4). In the case of BEGIN, specifically in the BEGIN Basal-Bolus study, the basal insulin dose was significantly lower with Glar-100; in contrast in the BEGIN Low trial and in the BEGIN Once Asia, the insulin dose was significantly lower with IDeg. However, in the EDITION 1, 2, 3 and JP2 trials, the basal insulin dose was significantly increased in the group receiving Glar-300 [51].

## 10. Discussion

The advent of the second-generation basal insulins has changed the overall idea of insulin therapy (both in individuals requiring a basal regimen ± OADs, and in those requiring multiple daily injection therapy with basal and mealtime insulin). The current evidence shows that when comparing IDeg and Glar-300 vs. Glar-100, the metabolic control achieved is similar (as determined by the HbA1c levels, FPG, average 24-h SMPG and Pre-breakfast SMPG); however, there are some minor differences in those results. For instance, when evaluating the average 24-h SMPG in the BEGIN trials, the results were significantly in favor of Glar-100 (in the BEGIN Basal-Bolus Type 2 trial); moreover, the FPG value was better in individuals receiving IDeg (in the BEGIN Once Long trial). In contrast, in the EDITION program there were differences in the FPG levels (in favor of Glar-100, only in the EDITION 3 trial) and in the pre-breakfast SMPG values (in favor of Glar-100, in the EDITION 1 and 3 trials). Meanwhile, the DEVOTE, SWITCH 2, and the Pan C et al. studies could not show any significant differences in the HbA1c levels either, and of these three studies, only DEVOTE documented a significant reduction in the FPG level in the group receiving IDeg. The fact that no differences were identified in the HbA1c level in IDeg vs. Glar-100 and in Glar-300 vs. Glar-100, and that only small differences were shown in the metabolic control, can be explained because all the RTCs evaluated had a treat-to-target design, and hence the insulin doses administered had to be adjusted so that every participating patient in the various trials reached a specific and validated fasting glucose concentration. This means that the decrease in HbA1c should (at least *a priori)* be similar among the various treatment groups and consequently, no differences were anticipated in efficacy, as measured by the change in HbA1c, as was demonstrated in these trials. Therefore, the treat-to-target RCTs such as those previously described, by evaluating the efficacy and safety of the different insulins, further enable the evaluation of other secondary outcomes (i.e., risk of hypoglycemia, tolerance, AEs, safety, compliance, among others, for a similar HbA1c level among groups of individuals receiving insulin therapy). In view of the above, an important and relevant aspect when comparing the second generation insulins vs. Glar-100, is the evaluation of the risk of hypoglycemia; for instance, in the BEGIN program, the risk of confirmed hypoglycemia or severe hypoglycemia [<56 mg/dL (3.1 mmol/L)] anytime (24h) was similar between both groups, and the risk of nocturnal hypoglycemia (00:01-05:59 h) was significantly lower with IDeg [in the BEGIN Basal-Bolus, and BEGIN Flex (OD) trials]. In contrast, in the EDITION trials, the risk of documented symptomatic hypoglycemia ([≤70 mg/dL (3.9 mmol/L)] anytime (24h) was significantly decreased (in the group receiving Glar-300) in EDITION 1 and 2. Moreover, the risk of nocturnal hypoglycemia [≤70 mg/dL (00:01-05:59h)] was reduced in the EDITION 1, 2 and JP2 studies (in favour of Glar-300). When trying to explain the results with respect to the risk of hypoglycemia with the second generation insulins (vs. Glar-100), keep in mind that IDeg has differences in its protraction mechanism vs. Other basal insulins, since in the presence of phenol and zinc, (as in a pharmaceutical formulation) it forms a soluble and stable dihexamer, but after injection, as phenol diffuses away, this re-organizes to form multi-hexamer chains that will have a long residence time at the injection depot [52,53]. The pharmacological consequence of this protraction mechanism is that IDeg reaches steady-state with daily dosing to produce a flat and stable PK/PD profile, with a lower risk of hypoglycemia [54]. In contrast, Glar-300 offers a more even and prolonged PK/PD profile, and the size of the SC depot is dependent upon the concentration of the injection solution, so that Glar-300 forms a smaller precipitate than Glar-100, consequently, Glar-300 provides more stable BG levels throughout the day, with low diurnal fluctuation, low intrasubject glucose variability, and high level of between-day reproducibility compared with Glar-100. Additionally, it has been documented that the peak-trough ratio of Glar-300 is low (approximately 1.7) vs. 2.3 for Glar-100, and this could help to minimize glycemic variability (since, the less pronounced peak of action could result in a more gradual drop in BG, with a reduced risk of hypoglycemia) [55,56]. Consequently, the lower risk of hypoglycemia identified with IDeg and Glar-300 vs. Glar-100 may be at least partly explained by the smoother, more even PK and PD profiles and the low within-day variability of these insulins [57]. Furthermore, no significant differences were identified in the rate of other AEs and in mortality, indicating that the use of second generation insulins is at least as safe as the use of Glar-100. No differences were identified with regards to weight with second generation insulins in the BEGIN trials, whilst in the EDITION 2 and JP2 trials, a significant difference was documented in favor of the group receiving Glar-300 (in the JP2 study, there was even a significant weight loss in patients receiving Glar-300 as compared with those receiving Glar-100). This fact of the EDITION trials may be explained (at least partially) by the higher risk of hypoglycemia in the group receiving Glar-100 (that may have increased the caloric intake —defensive snacking- hypothetically increasing the weight gain in individuals receiving Glar-100). Similarly, the BI dose was generally increased at the end of the follow-up period, with some differences among the various studies. For instance, in the BEGIN Basal-Bolus study, the BI dose was significantly lower with Glar-100, while in the BEGIN Low Volume and the BEGIN Once Asia studies, the BI dose was significantly lower with IDeg. However, in all the EDITION studies, the BI dose was significantly increased in patients receiving Glar-300. Such increase in the Glar-300 dose in the EDITION studies can be accounted for by the development of a more compact SC insulin deposit and prolonged residence time in the subcutaneous tissue, leading to a more pronounced enzyme inactivation by the tissue peptidases (with lower Glar-300 bioavailability, that results in the need to increase the dose) [58].

From the cardiovascular safety point of view, the ORIGIN study showed that Glar-100 exhibited a neutral cardiovascular result (neutral effect) on outcomes such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and these events plus revascularization or hospitalization for heart failure; in the DEVOTE trial, the established cardiovascular safety of IDeg relative to Glar-100 was reflected in the individual components of the primary composite outcome, and was consistent across multiple pre-specified subgroups (IDeg has a cardiovascular safety profile at least not worse than Glar-100). This at least indicates the cardiovascular neutral effect of Glar-100 and IDeg (assuming that the Glar-100 results could also be extrapolated to Glar-300, since Glar-300 is the same Glar molecule, but is simply more concentrated) [59,60]. The Quality-of-life assessments, and treatment satisfaction scores showed that in general, the second-generation insulins either improve or have a neutral effect on quality of life compared with Glar-100 (with significant differences in favor of IDeg in the BEGIN program, with no significant differences in the EDITION program).

Finally, BRIGHT trial was the first direct comparison of the safety and efficacy of Glar-300 vs. IDeg-100, and showed a similar glycemic control with both insulins (for HbA1c and fasting SMPG reduction, with similar variability in 24-h SMPG and fasting SMPG), and a modest and comparable weight gain with both treatments despite a slightly higher mean daily insulin dose for Glar-300 at study-end. Additionally, during the full study and maintenance periods, the incidence and rates of anytime (24 h) and nocturnal (0:00–06:00 h) confirmed hypoglycemia (≤70 and < 54 mg/dL) were comparable between both insulins, but, during the titration period (0–12 weeks), the incidence and rates of anytime (24 h) confirmed hypoglycemia (≤70 and < 54 mg/dL) and the rate of nocturnal (00:00–06:00 h) confirmed hypoglycemia (≤70 mg/dL) were lower with Glar-300. This is clinically relevant, as it has been shown that when an HbA1c target of ≤7.0% is achieved in the insulin titration phase (first approximately 12 weeks), good metabolic control can be predicted in the medium- and long-term; however, failure to achieve a target of ≤7.0% by 12 weeks (post BI initiation) was associated consistently with suboptimal long-term blood glucose control. Similarly, the treatment response and hypoglycemia incidence during the insulin titration phase are associated with longer-term glycemic control and hypoglycemic risk, respectively [61-63]. Given this, the differences in hypoglycemia seen with Glar-300 in the Bright Study during this critical period could play a role in deciding which second generation basal insulin to use in selected insulin-naïve patients with T2DM.

## 11. Conclusions

The second-generation basal insulins (IDeg and Glar-300) result in metabolic control similar to that of Glar-100, with lower risk of hypoglycemia and less body weight impact (specifically with Glar-300), despite the need for a higher absolute dose of Glar-300 vs. Glar-100. A head-to-head comparison of Glar-300 vs. IDeg in insulin-naïve patients with T2DM shows similar metabolic control but Glar-300 lowers the risk of hypoglycemia, specifically during the titration phase. Further head-to-head RCTs comparing the efficacy and safety of Glar-300 and IDeg in other patient populations (e.g., insulin-treated patients with T2DM, patients with chronic kidney disease) are needed to further understand similarities and potential differences between these two insulin formulations.

## 12. Authors' contributors

H V-U and JPF designed the paper, planned the analyses, did the data mining and wrote the manuscript. The authors reviewed and approved the final manuscript.

## 12. Abbreviations:

**ADA** American Diabetes Association
**AEs** Adverse events
**AGI** Alpha-glucosidase inhibitors
**AIAs** Anti-insulin antibodies
**BG** Blood glucose
**BI** Basal insulin
**BL** Baseline.
**BMI** Body mass index
**CI** Confidence interval
**CKD** Chronic kidney disease
**CVD** cardiovascular disease
**Det** Detemir
**DM** Diabetes mellitus
**DPP-4 inh** DPP-4 inhibitor
**DTSQ** Diabetes treatment satisfaction questionnaire.
**eGFR** Estimated glomerular filtration rate
**ETD** Estimated treatment difference
**FPG** Fasting plasma glucose
**Glar** Glargine
**GLP-1RAs** Glucagon-like peptide-1 receptor agonists
**HABS** Hypoglycemia Attitudes and Behavior Scale
**HbA1c** Hemoglobin A1c
**HR** Hazard ratio
**HRQoL** Health-related quality of life.
**IDeg** Degludec
**IFG** Impaired fasting glycaemia
**IGT** Impaired glucose tolerance
**LS** Least squares
**MACEs** Major cardiovascular events
**NPH** Neutral protamine Hagedorn
**OADs** Oral antihyperglycemic drugs
**PD** Pharmacodynamic
**PK** Pharmacokinetic
**PYE** Patient-year of exposure
**QD** Once daily
**RCTs** Randomized controlled trials
**RR** Relative risk
**SGLT2 inh** Sodium-glucose co-transporter 2 inhibitors. T2DM: Type 2 diabetes mellitus
**SMPG** Self-measured plasma glucose
**SU** Sulphonylurea
**T1DM** Type 1 diabetes mellitus
**T2DM** Type 2 diabetes mellitus
**TRIM-D Device** Treatment Related Impact Measures-Diabetes Device.

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