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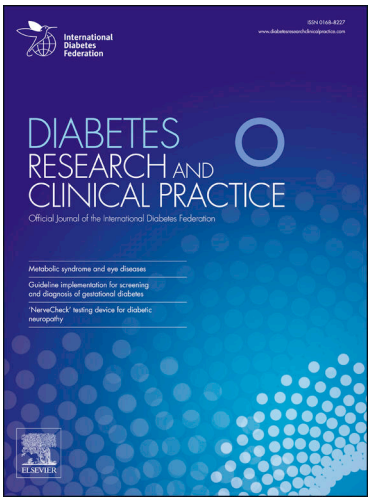

Efficacy and safety of basal insulin Degludec 100 IU/mL versus Glargine 300 IU/mL for type 1 diabetes: the single-center INEOX Randomized Controlled Trial

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TITLE PAGE

Title: Efficacy and safety of basal insulin Degludec 100 IU/mL versus Glargine 300 IU/mL for type 1 diabetes: the single-center INEOX Randomized Controlled Trial.

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Short running title: Deg-100 versus Gla-300 for type 1 diabetes.

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STRUCTURED ABSTRACT

Aims: To compare efficacy and safety of degludec 100 IU/mL (Deg-100) and glargine 300 IU/mL (Gla-300) in adults with type 1 diabetes.

Methods: Open-label, single-center, randomized, parallel-group, 24-week trial in adults with type 1 diabetes, on basal-bolus insulin therapy, HbA1c ≤10%, using self-monitoring blood glucose. Participants were randomized 1:1 to a basal-bolus insulin regimen with Deg-100 (N=129) or Gla-300 (N=131). Primary efficacy endpoint: mean change in HbA1c from baseline to week-24. Main safety outcome: incidence rate of hypoglycemia during the study. Quality of life (DQoL) and satisfaction with diabetes treatment (DTSQ) were assessed.

Results: At week 24, after adjusting for baseline HbA1c, the decrease in HbA1c did not differ between groups: Deg-100 (-0.07±0.7%) and Gla-300 (-0.16±0.77%) (*P*=0.320). There were no significant differences between groups in HbA1c, nocturnal hypoglycemia, severe hypoglycemia, DQoL, or DTSQ scores. The incidence rates of hypoglycemia <3.9 mmol/L (Deg-100: 115.24 events/person-year vs. Gla-300: 99.01 events/person-year, p<0.001); and <3.0 mmol/L (Deg-100: 41.17 events/person-year vs. Gla-300: 34.29 events/person-year, p<0.001) were different between groups.

Conclusions: Deg-100 and Gla-300 have similar metabolic efficacy, incidence ratio of nocturnal and severe hypoglycemia, DQoL and DTSQ scores. Differences in the incidence rate of hypoglycemia < 3.9 mmol/L and < 3 mmol/L should be confirmed.

KEYWORDS:

Type 1 diabetes; Glargine U-300; Degludec U-100; Clinical trial.

1. INTRODUCTION

Insulin degludec 100 IU/mL (Deg-100) and insulin glargine 300 IU/mL (Gla-300) are two second-generation long-acting basal insulin analogs indicated for both type 1 and type 2 diabetes. They were developed to achieve more stable and prolonged pharmacokinetic and pharmacodynamic profiles than their predecessor insulin glargine 100 IU/ml (Gla-100).[1–3] The results from the BEGIN and EDITION clinical trial programs for Deg-100 and Gla-300, respectively, proved their efficacy and safety compared with Gla-100 in subjects with type 1[4–8] and type 2 diabetes.[9–16] These clinical trials confirmed the 24-hour activity of Deg-100 and Gla-300 after their

once-daily administration, providing a glucose-lowering efficacy similar to Gla-100 with a flatter effect that reduced the risk of hypoglycemia.

Head-to-head clinical trials comparing Deg-100 and Gla-300 in subjects with type 2 diabetes showed a comparable efficacy in glycemic control in insulin-naïve or previously insulin-treated patients.[17–19]

In subjects with type 1 diabetes, evidence for the efficacy of these second-generation long-acting basal insulin analogs is scarce. Most direct comparisons between Deg-100 and Gla-300 are limited to pharmacodynamic and pharmacokinetic studies, with contradictory results: less within-day variability and more evenly distributed pharmacokinetics when using Gla-300,[20] lower day-to-day and within-day variability in pharmacodynamic response with Deg-100,[21] and similar pharmacodynamic response during euglycemic clamps.[22] A recent systematic review[23] analyzed the clinical trials evaluating insulin Deg-100 or Gla-300 for more than 12 weeks in type 1 diabetes. However, it is noteworthy that none of the nine clinical trials included in the analysis directly compared both insulin analogs. In 2021, Conget I, et al. published an observational multicenter study (OneCARE), [24] aimed to compare the efficacy of Deg-100 and Gla-300 in adult subjects with type 1 diabetes mellitus in routine clinical practice. In this study, the choosing of the insulin analog Deg-100 or Gla-300 was made according to the physician discretion.

In light of the above, we designed a randomized clinical trial aimed to compare the efficacy and safety of the second-generation basal insulin analogs Deg-100 and Gla-300 in type 1 diabetes.

2. MATERIALS AND METHODS

2.1. Study Design and Participants

This was an open-label, single-center, randomized, parallel-group, phase IV clinical trial conducted according to the World Medical Association Declaration of Helsinki, all its amendments, and national regulations. This clinical trial was designed to resemble routine clinical practice.

This clinical study formed part of a larger project that aims to evaluate differences in oxidative stress and inflammation in people with type 1 diabetes treated with second-generation basal insulin analogs (ClinicalTrials.gov Identifier, NCT03328845), the results of which are currently being analyzed.

This clinical trial was approved by the ethics committee of the Regional University Hospital of Malaga (Malaga, Spain), and all patients gave their written informed consent before the start of any study-related procedures.

The study included subjects who met the selection criteria and agreed to participate between January 2017 and June 2018. Eligible subjects were adults aged 18-64 years, with type 1 diabetes for more than 2 years before

screening and undergoing routine follow-up in the Diabetes Unit of the Endocrinology and Nutrition Department at the Regional University Hospital of Malaga (Malaga, Spain). Patients also had to have received multiple daily injections of basal-bolus insulin therapy with either insulin detemir or Gla-100 for >12 months before enrolment and had to have glycosylated hemoglobin (HbA1c) levels ≤10% (85.8 mmol/mol). Subjects with type 2 diabetes were excluded, as were those with liver or chronic kidney disease, thyroid dysfunction except for hypothyroidism under control with appropriate treatment, hyperuricemia (i.e., uric acid level ≥7 mg/dL or allopurinol treatment), and those who were pregnant or planning to become pregnant.

2.2. Intervention/Assessments

Eligible subjects attended an initial face-to-face study visit in which informed consent was obtained, eligibility confirmed, and baseline data collected (Supplemental Figure S1). Included subjects were randomized 1:1 to basal-bolus insulin therapy with Deg-100 or Gla-300. The rapid-acting insulin analog received before randomization remained unchanged during the study follow-up. The randomization list was generated using the Statistical Package for the Social Sciences (SPSS) Random Number Generator.

Due to previous evidence that supported a lower bioavailability of Gla-300 versus Deg-100[1,20], the study protocol determined a reduction of the basal insulin dose in participants allocated to Deg-100 as follows: 25% reduction when HbA1c was ≤7% (53 mmol/mol), 15% reduction when HbA1c was 7-8% (53-64 mmol/mol), and the same dose when HbA1c was ≥8% (64 mmol/mol); participants allocated to Gla-300 received the same basal insulin dose that they used before randomization. Although Deg-100 and Gla-300 could be administered at any time of the day, patients were instructed to inject them at 3:00 p.m. to maintain uniformity throughout the study.

All participants were provided with a glucometer (Accu-Chek®, Roche Diabetes Care Spain S.L., San Cugat del Vallès, Spain) to self-monitor blood glucose and access to the Emminens eConecta® platform (Roche Diabetes Care Spain S.L., San Cugat del Vallès, Spain) to download the glucometer data and communicate with the healthcare professional at week 4 (±2 weeks). Patients were instructed in the use of this tool and were given basic education on managing their diabetes. They were also instructed in self-monitoring their blood glucose four times per day (before each meal and at bedtime), and any time if they had symptoms of hypoglycemia. Additionally, they were required to perform a complete profile with pre- and 2-hour post-meal measurements once weekly, and modify the insulin dose following this algorithm:

A) Titrate basal insulin doses according to fasting capillary blood glucose levels, targeting 4.4 to 7.2 mmol/L.[25] When capillary blood glucose was ≤3.9 mmol/L in more than three measurements within the previous week, the

basal insulin dose was reduced by 1 IU. When it reached ≥7.2 mmol/L in more than three measurements within the previous week, the basal insulin dose was increased by 1 IU.

B) Titrate rapid insulin according to 2-hour post-meal capillary blood glucose levels, targeting less than 8.32 mmol/L.

Two follow-up visits were then performed at weeks 4 (±2 weeks) and 24 (±2 weeks) (Supplemental Figure S1). The week 4 visit was an online visit conducted through the Emminens eConecta® platform. Its primary aim was to titrate basal insulin doses according to fasting capillary blood glucose levels, targeting 4.4 to 7.2 mmol/L.[25] When capillary blood glucose was ≤3.9 mmol/L in more than three measurements within the previous week, the basal insulin dose was reduced by 1 IU. When it reached ≥7.2 mmol/L in more than three measurements within the previous week, the basal insulin dose was increased by 1 IU. The last study visit was conducted at week 24, which was a face-to-face visit aimed at collecting data on the study outcome measures.

2.3. Outcome Measures

The primary efficacy outcome measure was the mean change in HbA1c levels from baseline to week 24: ($HbA1c_{Baseline} - HbA1c_{Week\ 24}$). Secondary efficacy outcomes included differences in the proportion of patients achieving HbA1c levels ≤7% (53 mmol/mol), mean blood glucose levels, coefficients of glucose variation, and body mass index. Mean blood glucose levels and coefficients of glucose variation were identified from the capillary blood glucose levels downloaded from the Accu-Chek® glucometer within the 2-weeks previous to baseline and at week 24.

The main safety outcome measure was the incidence rate of symptomatic hypoglycemia <3.9 mmol/L (grade I), <3.0 mmol/L (grade II)[26], symptomatic nocturnal hypoglycemic episodes (hypoglycemia occurring between 00:00 and 5:59 h) and severe hypoglycemia (altered mental and/or physical functioning requiring assistance from another person[26]) throughout the 24-week treatment hypoglycemia. They were identified from the 6-month capillary blood glucose levels downloaded from the Accu-Chek® glucometer at week 24. The episodes of hypoglycemia that were not confirmed by capillary blood glucose measurement were not recorded. Hypoglycemia awareness was assessed using the Clarke test [27] at baseline and at week 24. The Clarke test consists of 8 questions related to the perception of hypoglycemia, to the frequency of severe and non-severe episodes, as well as to the blood glucose thresholds at which the patient experiences symptoms. This test is scored from 1-2 points (normal perception), 3 points (perception of undetermined category) and >3 points (abnormal perception of hypoglycemia).[27,28]

Other secondary outcome measures included differences in insulin doses and scores on patient-reported outcome measures of treatment satisfaction and quality of life throughout the study. They were obtained using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Diabetes Quality of Life (DQOL) instrument, respectively. The DTSQ includes 6 items assessing treatment satisfaction and 2 items assessing the perceived frequency of hyperglycemia and hypoglycemia. The status version (DTSQs) was used at baseline, and the change version (DTSQc) was used at week 24 to assess changes over the study period.[29–32] The satisfaction items of the DTSQs were scored from 6 (very satisfied) to 0 (very dissatisfied), providing an overall score from 36 (very satisfied) to 0 (very dissatisfied), and the perceived frequency of hyperglycemia/hypoglycemia items from 6 (most of the time) to 0 (none of the time). The satisfaction items of the DTSQc were scored from 3 (much more satisfied now) to -3 (much less satisfied now), providing an overall score from -18 (much less satisfied now) to 18 (much more satisfied now), and the perceived frequency of hyperglycemia/hypoglycemia items from -3 (much more frequent now) to 3 (much less frequent now). The DQOL is a 43-item questionnaire that assesses health-related quality of life according to four subscale scores: treatment satisfaction (15 items), treatment impact (17 items), social/vocational worry (7 items), and diabetes worry (4 items).[33,34] Satisfaction items were rated from 1 (very satisfied) to 5 (very dissatisfied), while the impact and worry scales were rated from 1 (no impact and never worried) to 5 (always impacted and always worried). Subscale scores resulted from the addition of individual item scores within each subscale. The total DQOL score ranges from 43 to 215, with lower scores indicating better quality of life.

2.4. Statistical Analysis

2.4.1. Sample size calculation

For the clinical study of the project, we calculated a sample size of 130 in each study group, which would give the study a 90% power to detect a 0.3 difference in the primary endpoint between the two groups, assuming a standard deviation of 0.7%[35] with a two-sided significance level of 5% and a 12% drop-out rate.

2.4.2. Statistical analysis

The primary efficacy endpoint analysis was assessed in the intention-to-treat population, including all randomized patients allocated to each treatment group. The secondary endpoint analyses were based on all valid data from randomized patients who completed the study according to the per-protocol analysis. Frequency distributions were used to describe qualitative outcome measures, while quantitative measures were described using means and standard deviations. The incidence rate of hypoglycemia and 95% confidence intervals (CI) were calculated for each treatment group. The normal distribution of quantitative measures was confirmed using the Shapiro-Wilk

test. An analysis of covariance (ANCOVA) was used to assess differences in the HbA1c levels from baseline to week 24 between treatment groups while controlling for baseline HbA1c levels. Other comparisons between treatment groups were performed using Chi-square or t-tests. The statistical analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

3. RESULTS

3.1. Patient Characteristics

A total of 300 subjects were screened, 40 of whom were screening failures, and 260 were finally randomized to the study treatments: 129 subjects to Deg-100 and 131 to Gla-300 (Supplemental Figure S2). All randomized subjects received the allocated treatment, and a total of 232 completed the 24-week study treatment: 118 subjects in the Deg-100 group and 114 in the Gla-300 group. There were no significant differences in the main characteristics of the subjects who completed the study versus those who discontinued early (Supplementary Table S1).

Baseline participant characteristics in each treatment group are summarized in Table 1. They were balanced between groups except for HbA1c, which required correcting the HbA1c outcome analysis for baseline HbA1c levels.

3.2. Insulin Treatment

At week 24, the total doses of insulin did not differ significantly between Deg-100 and Gla-300 (Supplemental Table S2). However, patients receiving Deg-100 versus Gla-300 showed 18.6% lower doses of basal insulin, lower mean percentages of basal insulin analog in the total daily dose, and lower basal insulin analog doses per kg (Supplemental Table S2). Patients switching from insulin detemir showed a decrease in basal insulin doses per kg of 30.9% in the Deg-100 group and 16.4% in the Gla-300 group at week 24 (Supplemental Figure S3). In patients switching from Gla-100, the basal insulin doses per kg at week 24 decreased by 17.1% in the Deg-100 group and increased by 7.3% in the Gla-300 group (Supplemental Figure S3).

3.3. Metabolic Control

After adjusting for baseline HbA1c levels, the decrease in HbA1c from baseline to week 24 did not differ significantly between treatment groups, with mean values of 0.07±0.76% (0.72±8.33 mmol/mol) in the Deg-100 group and 0.16±0.77% (1.77±8.54 mmol/mol) in the Gla-300 group (P=0.320) (Table 2). Similarly, there were no significant differences between treatment groups in mean HbA1c levels (7.6±1.1% [60±12 mmol/mol] versus

7.8±1.1% [62±12 mmol/mol], *P*=0.315) or the proportion of patients achieving HbA1c levels <7% (53 mmol/mol) at week 24 (36.3% versus 29.4%, *P*=0.244) (Table 2).

In the Deg-100 group, HbA1c levels decreased from baseline to week 24, but this reduction was not statistically significant (Figure 1, Supplemental Table S3). There were no significant changes in other efficacy outcomes in the Deg-100 group (Supplemental Table S3). However, HbA1c levels decreased significantly from baseline to week 24 in the Gla-300 group (Figure 1, Supplemental Table S3), and the percentage of patients with HbA1c levels ≤7% (53 mmol/mol) increased from 19.1% to 29.4% (Supplemental Table S3).

The mean blood glucose levels at week 24 were comparable, as was the mean number of blood glucose measurements per day, coefficient of glucose variation, and body mass index (Table 2).

3.4. Hypoglycemia

The incidence rate of hypoglycemia <3.9 mmol/L was higher in the Deg-100 group compared with the Gla-300 group (table 3), and the incidence rate ratio was 1.16 (CI95% 1.12-1.21, p<0.001). Similarly, the incidence rate of hypoglycemia <3.0 mmol/L was higher in the Deg-100 group vs. Glarg-300 group, with an incidence rate ratio of 1.20 (CI95% 1.13-1.27, p<0.001). We found no significant differences in the incidence rate of nocturnal hypoglycemia and severe hypoglycemia between the study groups (table 3).

The mean number of mild hypoglycemic episodes at any time during the 24-week study treatment did not differ significantly between the Deg-100 and Gla-300 groups, considering both blood glucose levels <3.9 mmol/L and <3.0 mmol/L (Table 3). The mean number of symptomatic nocturnal hypoglycemic episodes during the 24-week study was also comparable in both treatment groups, as was the mean number of severe hypoglycemic episodes.

With regard to hypoglycemia awareness, results of the Clarke test are shown in supplemental table S5. There were no significant differences in the Clarke test score between groups at baseline or at week 24.

3.5. Patient-reported outcomes

Patients in the Deg-100 group showed an improvement from baseline to week 24 in the DQOL total score (Supplemental Table S4) and those in the Gla-300 group in the DQOL treatment satisfaction score (Supplemental Table S4). However, there were no significant differences between the Deg-100 and Gla-300 groups in quality of life reported according to total and subscale DQOL scores at week 24 (Table 4).

Concerning the DTSQ questionnaire, although patients in the Deg-100 group perceived a higher frequency of hypoglycemia at baseline, no significant difference between the Deg-100 and Gla-300 groups was found in treatment satisfaction according to the total DTSQ score or perceived frequency of hyperglycemia/hypoglycemia at week 24 (Table 4).

4. DISCUSSION

The results of this randomized phase IV clinical trial, performed under conditions similar to those of routine clinical practice, suggest that both Deg-100 and Gla-300 provide similar metabolic control in adults with type 1 diabetes. Subjects in the Gla-300 group had slightly higher baseline HbA1c levels and showed a modest but statistically significant decrease that led to an increased percentage of patients with HbA1c levels ≤7% (53 mmol/mol) at week 24. However, after controlling for baseline HbA1c levels, the mean change in HbA1c from baseline to week 24 was comparable in the Deg-100 and Gla-300 groups, as were the mean HbA1c level and percentage of patients with HbA1c levels ≤7% (53 mmol/mol) at week 24. These results are in line with the efficacy of Deg-100 and Gla-300 reported by their pivotal clinical trials in achieving and maintaining glycemic control in people with type 1 diabetes[4–8] and agree with comparable glycemic control reported by the BRIGHT and CONCLUDE trials in type 2 diabetes.[17,36]

These glycemic effects were achieved with nearly 20% lower doses of basal insulin in the Deg-100 versus Gla-300 group and with no differences in the coefficient of glucose variation, body mass index, or hypoglycemia occurrence. With regard to the latter, it is noteworthy that hypoglycemic episodes remained comparable between treatment groups when considering <3.9 mmol/L, <3.0 mmol/L, symptomatic nocturnal hypoglycemia, and severe hypoglycemia. The smaller diurnal fluctuations in glucose levels derived from the lower plasma excursions of these second-generation basal insulin analogs better reproduce physiologic basal insulin secretion with a reduced risk of hypoglycemia.[20,21]

The results of a recent systematic review[23] showed lower total and basal insulin doses and fewer episodes of severe hypoglycemia with insulin Deg-100 compared with Gla-300. Specifically, there was a 57% lower rate of severe hypoglycemia in the insulin Deg-100 group, especially in the nocturnal period. However, the authors acknowledge a low certainty of evidence regarding this finding and recommend direct comparison trials. They observed no significant differences in HbA1c or other hypoglycemia outcomes between these insulins.

In the OneCARE study [24], 199 participants with type 1 diabetes and inadequate metabolic control (HbA1c >7.5%) were included. A flash glucose monitoring device was used at least one month before the study visits. Authors described similar time in range (TIR) 3.88-10.0 mmol/L (70–180 mg/dl) throughout whole day in both groups. However, at night, TIR 3.88-10.0 mmol/L (70–180 mg/dl) and TIR 3.88-7.77 mmol/L (70–140 mg/dl) were significantly higher in the Gla-300 group compared to the Deg-100, and time above range (10.0 mmol/L [180 mg/dl]) was significantly lower in the Gla-300 group. They did not find any significant difference in time

below range 3.0-3.88 mmol/L (70-54 mg/dl) or 3.0 mmol/L (<54 mg/dl). However, the lack of randomization, that authors acknowledge as a limitation of the study, might have been associated to a selection bias, as insulin Deg-100 participants had a longer diabetes duration and more diabetes related complications (retinopathy) than participants from Gla-300 group. The study design of randomized clinical trial, the In Range Study, aimed to compare the efficacy of Gla-300 versus Deg-100 in adult subjects with type 1 diabetes using continuous glucose monitoring was published, [37] however, the results have not been published yet.

Pragmatic study designs, as in this INEOX study, may be required to help elucidate any differences between these insulins in day-to-day clinical practice.

Although our subjects in the Deg-100 group perceived a higher frequency of hypoglycemia according to the DTSQ at baseline, there were no significant differences between the Deg-100 and Gla-300 groups in either perceived frequency of hypoglycemia/hyperglycemia or overall treatment satisfaction at week 24. Similarly, patient quality of life according to the DQOL questionnaire did not differ significantly between treatment groups at week 24. Nonetheless, the overall DQOL and treatment satisfaction scores improved during the treatment with Deg-100 and Gla-300, respectively, in line with previous trials reporting improvements in quality of life domains when receiving second-generation basal insulin analog treatment.[7,9,12]

Given the lack of differences found between Deg-100 and Gla-300 in treatment satisfaction and quality of life, along with their comparable metabolic control efficacy, the choice of second-generation basal insulin analogs in clinical practice may be determined by more pragmatic factors such as access or costs.[17]

Some data appear to indicate that Gla-300 is associated with lower costs due to its lower unit price, but other healthcare-related costs such as those derived from daily dose requirements, hospital-related costs, or those resulting from emergency department visits should also be considered to determine whether any cost differences can be offset.[38] Martin et al.,[23] in their systematic review, found that in adults with type 1 diabetes, Deg-100 appeared to be more cost-effective than Gla-300 due to lower insulin requirements and fewer episodes of severe hypoglycemia associated with Deg-100 use. More cost-effectiveness comparisons are needed to provide clinicians and national healthcare systems with valuable information to consider when prescribing second-generation basal insulin analogs for type 1 diabetes in routine clinical practice.

To our knowledge, this is the first non-laboratory-sponsored randomized clinical trial comparing the effects of Deg-100 and Gla-300 for type 1 diabetes under approved conditions of routine clinical practice for 24 weeks. Moreover, the assessment of quality of life and satisfaction with diabetes treatment provides information

concerning the impact of the use of Deg-100 and Gla-300 on patients' lives that may complement and support other objective findings.

Nevertheless, we acknowledge that the study has certain limitations that should be considered when interpreting its results, including its single-center and open-label nature. The absence of continuous glucose data may be the main limitation of this study. The participants were not using these devices during the study because the Spanish Healthcare System only began funding the continuous glucose monitoring systems for adult subjects with type 1 diabetes in January 2020. Even though continuous glucose monitoring could not be performed, the identification of mild symptomatic hypoglycemic episodes might be accurate as it resulted from the analysis of all glucometer data from self-monitoring blood glucose levels performed during the 24-week study follow-up by the Emminens eConecta® platform. However, the possibility that hypoglycemia may have occurred and was not confirmed by capillary blood glucose can not be ruled out, although participants were instructed to check blood glucose whenever they had symptoms of hypoglycemia. On the other hand, asymptomatic hypoglycemia could not be correctly assessed due to the lack of continuous glucose monitoring in the study. Results of the Clarke test analysis showed no differences in the perception of hypoglycemia between study groups neither at the beginning nor at the end of the study, so we could infer that asymptomatic hypoglycemia might have a similar impact on the assessment of hypoglycemia in both groups. Despite the limitations in the hypoglycemic events evaluation, we found an incidence of mild hypoglycemia and nocturnal hypoglycemia similar to those published by Lamounier RN et al. in a paper reviewing the incidence rate of hypoglycemia in people with type 1 diabetes mellitus using self-monitoring blood glucose.[39] In any case, our results concerning hypoglycemia need to be confirmed in further studies using continuous glucose monitoring systems. The reduced number of visits for follow-up and adjustment of the insulin dose could be considered a limitation, but as our trial resembles routine clinical practice, it may allow our results to be accurately extrapolated to the daily clinical setting. The data on daily bolus doses could not be rigorously retrieved due to the absence of 6 months of manual or electronic patient diaries.

4.1. Conclusion

The second-generation basal insulin analogs Deg-100 and Gla-300 show similar metabolic efficacy for type 1 diabetes, with nearly 20% lower doses of basal insulin in patients receiving Deg-100. With regard to safety outcomes, we found differences in the incidence rate of hypoglycemia < 3.9 mmol/L and < 3.0 mmol/L between Deg-100 and Gla-300, but no differences in nocturnal hypoglycemia and severe hypoglycemia. Switching to either Deg-100 or Gla-300 seems to improve patient quality of life, regardless of which is used. These findings warrant further longer-term confirmation, including assessments of hypoglycemia and glucose fluctuations with

continuous glucose monitoring, real-world evidence data, and cost-effectiveness analyses that may be of value to optimize national healthcare resources.

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CONTRIBUTION STATEMENT

María S. Ruiz de Adana contributed to the study design, conducting the study/data collection, analysis and interpretation of data, and writing the manuscript. Marta E. Domínguez, Virginia Morillas, Natalia Colomo, Rosario Vallejo-Mora, Mercedes Guerrero, Eva García-Escobar, Mónica Carreira, Yanina Romero-Zerbo, Francisca Linares, Isabel González-Mariscal, Francisco J. Bermúdez-Silva, Gabriel Olveira, and Gemma Rojo-Martínez contributed to conducting the study/data collection, analysis and interpretation of data, and writing the manuscript. All authors gave final approval of the version to be published.

AUTHOR DISCLOSURE STATEMENT

Declaration of interest: none.

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TABLES

Table 1 – Baseline participant characteristics

Participant characteristics	Deg-100 (*N*=129)	Gla-300 (*N*=131)	*P*
Age, years, mean±SD	38.2±10.8	39.4±12.2	0.428
Male, *n* (%)	74 (57.8)	72 (55.0)	0.644
Body mass index, kg/m^2, mean±SD	25.1±4.1	25.2±4.0	0.762
Smoking, *n* (%)	37 (30.3)	44 (35.8)	0.540
Hypertension, *n* (%)	18 (14.4)	27 (21.1)	0.164
Chronic diabetes complications, *n* (%)			
Nephropathy	11 (8.7)	9 (7.0)	0.603
Retinopathy	30 (23.8)	32 (24.8)	0.853
Polyneuropathy	8 (6.3)	3 (2.3)	0.114
Diabetes duration, years, mean±SD	18.9±10.7	19.5±12.1	0.683
Basal insulin analogs, *n* (%)			
Gla-100	79 (61.6)	89 (67.9)	0.294
Detemir	49 (38.3)	42 (32.1)	0.294
Rapid-acting insulin analogs, *n* (%)			
Aspart	51 (39.8)	63 (48.1)	
Lispro	45 (35.2)	39 (29.8)	0.406
Glulisine	32 (25.0)	29 (22.1)	
Non-insulin antidiabetic drugs, *n* (%)			
Metformin	18 (14.3)	16 (12.6)	0.694
GLP-1 receptor analog monotherapy	0 (0.0)	2 (1.6)	0.157
HbA1c, % (mmol/mol)	7.7±1.1 (61±12)	7.9±1.0 (63±11)	0.044

Deg-100, insulin degludec 100 IU/mL; Gla-100: insulin glargine 100 IU/mL; Gla-300, insulin glargine 300 IU/mL; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; SD, standard deviation.

Table 2 – Efficacy outcome measures throughout the study

Efficacy outcome measure		Deg-100		Gla-300		*P*
		Mean±SD	*N*	*Mean±SD*	*N*	
HbA1c, % (mmol/mol)	Baseline	7.7±1.1 (61±12)	128	7.9±1.0 (63±10)	131	0.044
	Week 24	7.6±1.1 (60±12)	125	7.8±1.1 (62±12)	130	0.315
	Change [a]	0.07±0.76 (0.72±8.33)	124	0.16±0.77 (1.77±8.54)	125	0.320
HbA1c ≤7% (53 mmol/mol), *n* (%)	Baseline	41 (32.0)	128	25 (19.1)	131	0.018
	Week 24	45 (36.3)	125	37 (29.4)	130	0.244
Capillary blood glucose level, mmol/L [b]	Baseline	9.1±2.2	118	9.2±2.0	126	0.730
	Week 24	8.7±2.1	124	9.0±2.2	120	0.382
Glucose measurements/day [b]	Baseline	3.7±1.7	107	3.2±1.4	117	0.017
	Week 24	3.3 ±1.4	124	3.4±1.2	117	0.652
CV, % [b]	Baseline	45.4±9.6	115	44.6±9.2	124	0.502
	Week 24	46.3±10.6	124	44.4±9.7	119	0.136
Body mass index, kg/m^2	Baseline	25.1±4.1	128	25.2±4.0	129	0.762
	Week 24	25.5±4.1	124	25.3±4.1	125	0.825

CV, coefficient of glucose variation; Deg-100, insulin degludec 100 IU/mL; HbA1c, glycosylated hemoglobin; Gla-300, insulin glargine 300 IU/mL; SD, standard deviation.

[a] Change in HbA1c levels from baseline to week 24 controlled for baseline HbA1c levels. [b] Within the previous 2 weeks.

Table 3 – Safety outcome measures throughout the study

Safety outcome		Deg-100			Gla-300			p
		Events/person-year (95% CI)	*N*		*Events/person-year (95% CI)*	*N*		
Incidence rate of hypoglycemia with blood glucose < 3.9 mmol/L	Week 24 [b]	115.24 (112.57-117.98)	121		99.01 (96.51-101.57)	119		<0.001
Incidence rate of hypoglycemia with blood glucose < 3.0 mmol/L	Week 24 [b]	41.17 (39.59-42.82)	121		34.29 (32.83-35.81)	119		<0.001
Incidence rate of nocturnal hypoglycemia	Week 24 [b]	15.34 (14.38-16.36)	121		15.07 (14.10-16.10)	116		0.707
Incidence rate of severe hypoglycemia	Week 24 [b]	0.28 (0.18-0.45)	128		0.21 (0.13-0.36)	131		0.441
		Mean±SD	*N*	*p[1]*	*Mean±SD*	*N*	*p[1]*	
Number of hypoglycemic episodes with blood glucose < 3.9 mmol/L								
	Baseline [a]	5.85±5.45	123		5.05±5.13	127		0.230
	Week 24 [a]	5.90±5.11	124	0.795	5.17±4.08	119	0.764	0.218
	Week 24 [b]	57.62 ±41.70	121		49.50±43.76	119		0.143
Ratio number of hypoglycemic episodes <3.9 mmol/L per SMBG measurements	Week 24 [b]	0.11±0.09	121		0.09±0.07	115		0.060
Number of hypoglycemic episodes with blood glucose < 3.0 mmol/L								
	Baseline [a]	2.17±2.77	123		1.74±2.42	126		0.190
	Week 24 [a]	2.06±2.70	123	0.634	1.58±2.13	117	0.224	0.132
	Week 24 [b]	20.59±21.19	121		17.14±22.36	119		0.222
Ratio number of hypoglycemic episodes <3.0 mmol/L per SMBG measurements	Week 24 [b]	0.04±0.05	121		0.03±0.03	116		0.067
Number of nocturnal hypoglycemic episodes								
	Baseline [a]	1.06±1.65	118		2.12±12.05	118		0.345
	Week 24 [a]	0.95±1.28	123	0.581	1.08±1.49	118	0.317	0.458
	Week 24 [b]	7.97 ±10.0	118		7.53±8.87	118		0.728
Ratio number of nocturnal hypoglycemic episodes per SMBG measurements	Week 24 [b]	0.02±0.02	119		0.01±0.01	114		0.615
Number of severe hypoglycemic episodes								
	Baseline [c]	0.19±0.71	128		0.15±0.58	131		0.634
	Week 24 [b]	0.14±0.69	128	0.525	0.12±0.46	131	0.319	0.635

Deg-100, insulin degludec 100 IU/mL; Gla-300, insulin glargine 300 IU/mL; SD, standard deviation; SMBG: self-monitoring blood glucose.

[a] Within the previous 2 weeks; [b] Within the 24-week study follow-up; [c] Within the previous 6 months.

[1] Comparison between baseline and week 24.

Table 4 – Patient-reported outcomes throughout the study

Patient-reported outcome measure		Deg-100		Gla-300		*P*
		Mean±SD	*N*	*Mean±SD*	*N*	
DTSQ scores [a]						
Hyperglycemia	Baseline	3.4±1.6	114	3.4±1.5	120	0.685
perception	Week 24	0.5±2.7	115	0.7±1.7	104	0.535
Hypoglycemia	Baseline	3.0±1.7	113	2.2±1.6	120	<0.001
perception	Week 24	-0.03±1.72	117	0.07±1.58	104	0.650
Total score	Baseline	24.3±6.	108	24.5±6.3	119	0.886
	Week 24	11.0±5.3	113	9.5±6.7	104	0.075
DQOL scores						
Treatment satisfaction	Baseline	34.3±9.0	109	35.4±10.3	111	0.390
	Week 24	33.4±9.5	107	33.4±9.4	97	0.976
Treatment impact	Baseline	33.1±10.1	101	31.3±9.1	109	0.166
	Week 24	33.4±10.5	108	32.1±10.8	95	0.367
Diabetes worry	Baseline	9.8±3.3	115	9.4±3.4	122	0.311
	Week 24	9.8±3.7	118	9.1±3.3	103	0.144
Social/vocational worry	Baseline	13.3±5.7	109	12.7±4.8	117	0.351
	Week 24	13.0±5.2	108	12.5±4.9	97	0.494
Total score	Baseline	88.8±24.0	94	87.2±22.5	100	0.637
	Week 24	87.7±22.7	93	87.8±24.1	83	0.971

Deg-100, insulin degludec 100 IU/mL; DQOL, Diabetes Quality of Life; DTSQ, Diabetes Treatment Satisfaction Questionnaire; Gla-300, insulin glargine 300 IU/mL; SD, standard deviation. [a] The DTSQ status version (DTSQs) was used at baseline, and the DTSQ change version (DTSQc) was used at week 24.

FIGURE LEGENDS

Figure 1 – HbA1c at baseline and week 24 in the Deg-100 and Glar-300 groups.

Data are mean and 95% confidence intervals. Deg-100, insulin degludec 100 IU/mL; Gla-300, insulin glargine 300 IU/mL.

- Deg-100 and Gla-300 had similar effect on HbA1c in adults with type 1 diabetes.
- Basal insulin requirements were lower for Deg-100 than for Glar-300.
- Higher incidence rate of hypoglycemia < 3.9 mmol/L and < 3.0 mmol/L in Deg-100 group.
- Differences in the incidence rate of hypoglycemia should be confirmed.