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Effectiveness and safety of insulin glargine 300 U/mL in insulin-naïve individuals according to diabetes duration: Results from the REALI European pooled data analysis

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Abstract

Aim: To evaluate the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) initiation according to diabetes duration (DD).

Materials and Methods: We analysed patient-level data from 2381 insulin-naïve individuals with type 2 diabetes (T2D), of whom 2349 (98.7%) were treated with Gla-300 for 24 weeks. Of the 2381 participants, 1048 (44.0%) had a DD of less than 8 years and 1333 (56.0%) had a DD of 8 years or longer. We further analysed the subgroups of participants having a DD of less than 4 years ($N = 450$), 4-8 years ($N = 598$), 8-12 years ($N = 627$) and 12 years or longer ($N = 706$).

Results: Mean ± standard deviation age was 60.2 ± 9.0 years in participants with a DD less than 8 years and 64.2 ± 8.8 years in those with a DD of 8 years or longer. At 24 weeks of Gla-300 therapy, HbA1c improved with a least-squares (LS) mean change from baseline of −1.88% (95% confidence interval [CI], −1.95 to −1.80) and −1.71% (95% CI, −1.77 to −1.65), respectively, resulting in a LS mean difference between groups of 0.17% (95% CI, 0.07 to 0.26; $P = .0005$). In the subgroup analysis, LS mean HbA1c reduction from baseline to week 24 was highest in participants with a DD of less than 4 years and lowest in participants with a DD of 12 years or longer. Overall, incidences of symptomatic and severe hypoglycaemia were low, irrespective of DD, without body weight changes.

Conclusions: Gla-300 was effective and safe in insulin-naïve individuals with T2D, regardless of DD. Improvement in HbA1c was greater when Gla-300 was initiated in participants with a DD of less than 4 years, although the difference between the groups was modest.

KEYWORDS
diabetes duration, Gla-300, insulin glargine 300 U/mL, insulin-naïve, type 2 diabetes

1 | INTRODUCTION

The management of type 2 diabetes (T2D) has substantially evolved over the last 2 decades, moving from a historical hierarchal approach by therapeutic class to a patient-centred approach. Indeed, because of the heterogeneity of the disease, medication choice is not only guided by glycaemic control, but also by weight-management goals, T2D duration, cardiovascular and renal risks, side effects, cost, access and individual preferences.[1]

The need for injectable medications with greater glucose-lowering action, such as insulin and glucagon-like peptide-1 receptor agonists, is particularly common in individuals with long diabetes duration.[1] Indeed, prolonged diabetes duration is independently associated with an increased risk of macrovascular and microvascular complications, stroke, dementia and death.[2–4] In particular, some individuals may benefit from early initiation of insulin, such as those with evidence of ongoing catabolism, symptoms of hyperglycaemia or very high HbA1c levels (> 10.0% [> 86 mmol/mol]) or blood glucose levels (≥ 300 mg/dL [≥ 16.7 mmol/L]).[1]

Initiating insulin therapy earlier in diabetes management offers unique advantages that surpass those of other glucose-lowering medications. It has been proposed that early insulin use could preserve beta-cell function by reducing the workload on these cells, thereby slowing the progression of beta-cell failure, a protective effect not typically provided by non-insulin therapies.[5] Moreover, compared with other glucose-lowering medications that primarily target insulin sensitivity or glucose production, early insulin therapy directly reduces glucotoxicity and addresses insulin deficiency, providing an immediate reduction in hyperglycaemia and decreasing the risk of diabetes-related complications.[1–5] Furthermore, because insulin is considered the most potent agent for lowering blood glucose levels, its early use may minimize the need for other glucose-lowering drugs, which can improve adherence and overall effectiveness.[1,6–10]

When initiating insulin in insulin-naïve individuals, longer-acting basal insulins, such as insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL, are the most convenient and preferred treatments that can be added to metformin and other non-insulin injectables because of a low hypoglycaemia risk and long duration of action.[1] Gla-300 is a second-generation, long-acting basal insulin analogue, given as a once-daily subcutaneous injection, and associated with a low risk of hypoglycaemia and weight gain.[11] In this respect, we performed a pooled data analysis based on the European REALI programme to assess the impact of diabetes duration on the effectiveness and safety of Gla-300 in insulin-naïve participants with T2D.

2 | METHODS

2.1 | Study design and patient population

The current analysis is based on pooled data from the European REALI programme including 14 multicentre, prospective, open-label studies conducted in 20 European countries, namely, Germany, Switzerland, Austria, Serbia, Hungary, Italy, Spain, the Netherlands, the Czech Republic, Bulgaria, Romania, France, Belgium, Greece, Poland, Denmark, Slovenia, Slovakia, Croatia and the UK.[12–25] Participants included within this analysis were insulin-naïve adults with inadequately controlled T2D, with or without non-insulin glucose-lowering agents, who were treated with Gla-300 for 24 weeks. Gla-300 was injected subcutaneously once daily, using a prefilled insulin pen at the same time of the day ±3 hours if needed, as specified in the summary of product characteristics.[26] There were no upper age limit restrictions in any study. Common exclusion criteria comprised previous insulin use, diagnosis of type 1 diabetes, pregnancy and/or breast-feeding, history of alcohol or drug abuse, the presence of any clinically relevant co-morbidity that could affect study results, known hypersensitivity or intolerance to Gla-300 or any of its excipients, and inability to self-measure blood glucose levels.[27]

For the purpose of this pooled analysis, as the median diabetes duration in this population was 8 years, participants were accordingly classified into two main groups: diabetes duration less than 8 years and diabetes duration of 8 years or longer. An additional subgroup analysis was performed dividing this population of participants into four subgroups: diabetes duration less than 4 years, diabetes duration of 4-8 years, diabetes duration of 8-12 years and diabetes duration of 12 years or longer.

2.2 | Ethics

All included studies were conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and were approved by the relevant institutional review boards/ethics committees. All participants provided written informed consent. Before data pooling, all patient information was de-identified and standardized for consistency. Consequently, no ethical approval was required for this pooled analysis.

2.3 | Endpoints

Efficacy outcomes were changes in HbA1c and fasting plasma glucose (FPG) from baseline to week 12 and week 24 of Gla-300 treatment, as well as the proportion of participants achieving HbA1c targets of less than 7.0% (< 53.0 mmol/mol), less than 7.5% (< 58.5 mmol/mol) and less than 8.0% (< 63.9 mmol/mol) at week 24. Safety endpoints included the percentages of participants having at least one hypoglycaemic event at any time-of-day or during the night, and hypoglycaemia event rates (events per patient-year). Changes in the daily dose of Gla-300 and body weight from baseline to week 12 and week 24 of Gla-300 treatment were also evaluated.

The definitions of hypoglycaemia[28] were predetermined in the current pooled analysis. Nocturnal hypoglycaemia was evaluated to exclude potential confounders relating to daytime activities and meal intake. Nocturnal hypoglycaemia was any event that occurred between 00:00 AM and 05:59 AM. Severe hypoglycaemia was defined as any event requiring assistance from another person to actively administer carbohydrates or glucagon, or to take other corrective actions. Symptomatic hypoglycaemia was defined as an

TABLE 1 Baseline characteristics according to diabetes duration per group.

Characteristic	Diabetes duration < 8 y (*N* = 1048)	Diabetes duration ≥ 8 y (*N* = 1333)	Overall population (*N* = 2381)
Age (y)	*n* = 973	*n* = 1290	*n* = 2263
Mean ± SD	60.2 ± 9.0	64.2 ± 8.8	62.5 ± 9.1
Median (Q1-Q3)	60.0 (54.0-66.0)	65.0 (58.0-70.0)	63.0 (56.0-69.0)
Female	*n* = 1048	*n* = 1332	*n* = 2380
n (%)	489 (46.7)	648 (48.6)	1137 (47.8)
Body weight	*n* = 917	*n* = 1213	*n* = 2130
Mean ± SD, kg	89.6 ± 15.6	86.7 ± 14.7	88.0 ± 15.2
Body mass index	*n* = 949	*n* = 1256	*n* = 2205
Mean ± SD, kg/m^2	31.6 ± 4.8	31.0 ± 4.8	31.3 ± 4.8
eGFR	*n* = 188	*n* = 386	*n* = 574
Mean ± SD, mL/min/1.73m^2	91.4 ± 20.5	85.7 ± 25.1	87.6 ± 23.8
Duration of diabetes	*n* = 1048	*n* = 1333	*n* = 2381
Median (Q1-Q3), y	4.0 (2.0-6.0)	12.0 (10.0-15.0)	8.0 (5.0-12.0)
Prior use of non-insulin glucose-lowering treatment, *n* (%)	537 (51.2)	768 (57.6)	1305 (54.8)
HbA1c	*n* = 1038	*n* = 1316	*n* = 2354
Mean ± SD, %	9.38 ± 1.53	9.16 ± 2.73	9.26 ± 2.28
Fasting plasma glucose	*n* = 528	*n* = 744	*n* = 1272
Mean ± SD, mg/dL	187.4 ± 52.9	186.9 ± 47.9	187.1 ± 50.0
Participants with ≥ 1 cardiovascular event or risk factor, *n* (%)	820 (78.2)	1185 (88.9)	2005 (84.2)
Participants with ≥ 1 diabetes complication, *n* (%)	241 (23.0)	417 (31.3)	658 (27.6)

Note: Means, medians and percentages are calculated based on data available for each variable.
Abbreviations: eGFR, estimated glomerular filtration rate; Q, quartile; SD, standard deviation.

event during which typical symptoms of hypoglycaemia occurred (e.g. sweating, hunger, shakiness, palpitations). Of note, symptoms of nocturnal hypoglycaemia may be subtle, and may include nightmares, waking up in the morning with damp clothes/sheets, morning headache and feeling unusually tired.[29] Other hypoglycaemic events (e.g. asymptomatic hypoglycaemia, symptomatic confirmed hypoglycaemia, daytime hypoglycaemia), as well as adverse reactions such as skin and subcutaneous tissue disorders, were not reported across all individual studies and hence were not included in the REALI analysis.[30]

2.4 | Statistical analysis

All outcome measures were analysed according to diabetes duration. The least-squares (LS) mean changes in HbA1c and FPG from baseline to weeks 12 and 24 of Gla-300 treatment were evaluated using a mixed model for repeated measures (MMRM), with fixed categorical effects of study, visit, diabetes duration and diabetes duration-by-visit interaction, as well as continuous fixed covariates of baseline HbA1c or FPG, age, baseline body mass index (BMI), baseline HbA1c or FPG value-by-visit interaction, age value-by-visit interaction and baseline BMI value-by-visit interaction. Individual participants (subjects) were included as the random effect. For these two efficacy endpoints, the LS mean differences between participants with a diabetes duration of less than 8 years and those with a diabetes duration of 8 years or longer and two-sided 95% confidence intervals (CIs) were estimated. All other efficacy and safety endpoints, as well as baseline demographic and disease characteristics, are described, with categorical variables presented as counts and percentages, and continuous variables as mean, standard deviation (SD), median, and first and third quartiles (Q1-Q3).

The comparison of demographics and baseline characteristics between individuals with diabetes durations of less than 8 and 8 years or longer was based on all included participants. Efficacy (i.e. HbA1c and FPG) and safety analyses were conducted on all participants who received at least one Gla-300 dose. There were missing participant baseline characteristics and missing outcome data in some studies; no imputation of missing data was performed. The MMRM was used specifically to account for missing data. All statistical tests were two-sided, with a *P* value of less than .05 considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Study population

The pooled analysis included a total of 2381 insulin-naïve participants, of whom 1048 (44.0%) had a diabetes duration of less than 8 years, while 1333 (56.0%) had a diabetes duration of 8 years or longer. Of the 2381 participants, 2349 (98.7%) received at least one dose of

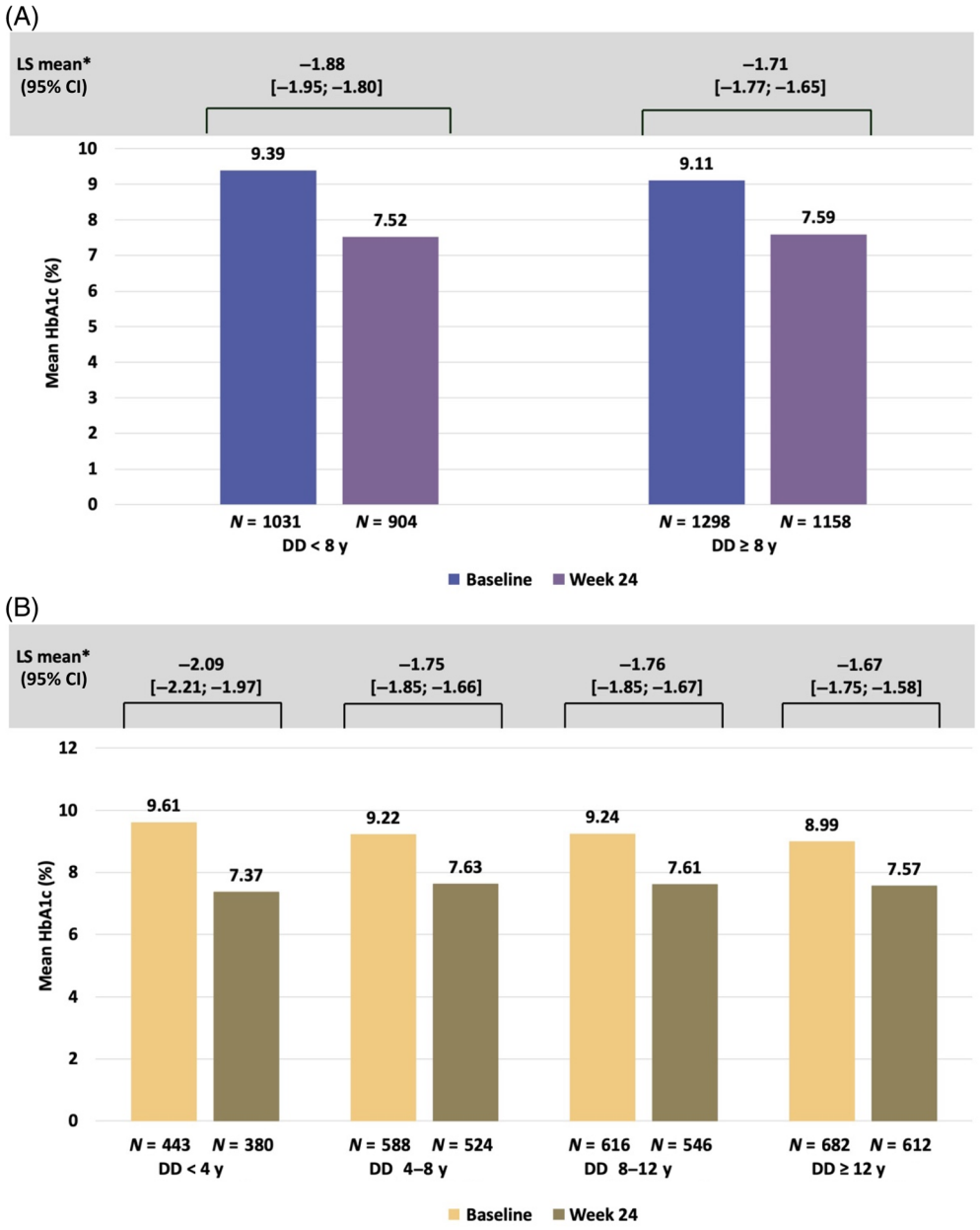

FIGURE 1 Mean HbA1c and LS mean change (95% CI) in HbA1c from baseline to week 24 of Gla-300 treatment according to diabetes duration, between A, The groups with diabetes durations of < 8 and ≥ 8 years, and B, The subgroups with diabetes durations of < 4, 4-8, 8-12 and ≥ 12 years. *The LS mean changes in HbA1c from baseline to weeks 12 and 24 were evaluated using a MMRM, with fixed categorical effects of visit, subgroup category and subgroup category-by-visit interaction, as well as continuous fixed covariates of baseline HbA1c, age, baseline BMI, baseline HbA1c value-by-visit interaction, age value-by-visit interaction and baseline BMI value-by-visit interaction. Study effect is considered as a fixed categorical effect in the analysis. A, The LS mean difference between participants with diabetes durations of < 8 and ≥ 8 years was 0.17% (95% CI, 0.07% to 0.26%; $P = .0005$). B, The LS mean difference between participants with diabetes durations of < 4 and ≥ 12 years was clinically significant, and the 95% CIs did not overlap between the two subgroups, suggesting a statistically significant difference. BMI, body mass index; CI, confidence interval; DD, diabetes duration; Gla-300, insulin glargine 300 U/mL; LS, least-squares; MMRM, mixed model for repeated measures.

Gla-300 and were consequently included in the efficacy and safety analyses.

Table 1 summarizes the demographics and baseline characteristics of the overall study population ($N = 2381$). The mean ± SD age was 60.2 ± 9.0 years in participants with a diabetes duration of less than 8 years, and 64.2 ± 8.8 years in participants with a diabetes duration of 8 years or longer. Overall, BMI and gender were balanced between the two groups, and more than one-half of participants (1310/2333; 56.2%) had a BMI of 30 kg/m^2 or higher.

Out of the 2381 study participants, 1305 (54.8%) previously used at least one non-insulin glucose-lowering treatment (Table S1). Mean ± SD baseline HbA1c and baseline FPG were 9.38% ± 1.53% and

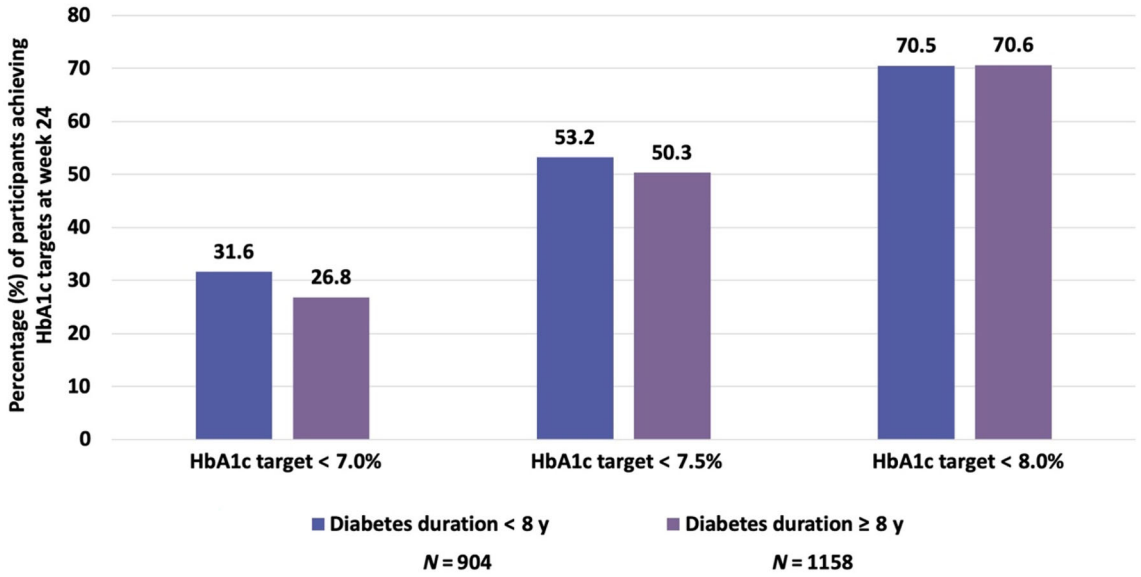

FIGURE 2 Percentage of participants achieving HbA1c targets of < 7.0%, < 7.5% and < 8.0% at week 24 of the study. A Chi-square test performed for each of the three targets showed a statistically significant difference between groups with diabetes durations of less than 8 years and of 8 years or longer at week 24 for the target HbA1c < 7.0% ($P = .015$), whereas there was no statistically significant difference for the targets of HbA1c < 7.5% and < 8.0% ($P = .183$ and $P = .965$, respectively)

187.4 ± 52.9 mg/dL in participants with a diabetes duration of less than 8 years, and 9.16% ± 2.73% and 186.9 ± 47.9 mg/dL in participants with a diabetes duration of 8 years or longer, respectively. A total of 2005 participants (84.2%) had at least one cardiovascular risk factor or event (Table S2), and 658 participants (27.6%) reported diabetes complications (Table S3).

In the additional subgroup analysis, mean ± SD age was 58.9 ± 8.8 years in participants with a diabetes duration of less than 4 years, 61.1 ± 9.0 years in participants with a diabetes duration of 4-8 years, 62.6 ± 8.8 years in participants with a diabetes duration of 8-12 years, and 65.6 ± 8.6 years in participants with a diabetes duration of 12 years or longer. At baseline, mean BMI was similar between the subgroups, although it was slightly lower in participants with a diabetes duration of 12 years or longer (Table S4).

3.2 | Change in HbA1c

Among the 2349 treated study participants, overall mean ± SD HbA1c decreased by 1.71% ± 1.57% from 9.23% ± 1.42% at baseline to 7.56% ± 1.07% at week 24. The MMRM evaluated the LS mean change in HbA1c in patients having an HbA1c value available at baseline and at one postbaseline timepoint. The LS mean change in HbA1c from baseline to week 24 was −1.88% (95% CI, -1.95% to -1.80%) in participants with a diabetes duration of less than 8 years and −1.71% (95% CI, -1.77% to -1.65%) in participants with a diabetes duration of 8 years or longer (Figure 1A). The LS mean difference between the two groups was 0.17% (95% CI, 0.07% to 0.26%; $P < .001$). In both groups, mean HbA1c decreased mainly during the first 12 weeks of Gla-300 treatment and continued to decrease up to week 24.

In the additional subgroup analysis, mean ± SD HbA1c decreased from baseline to week 24 in all subgroups, with the greatest reduction observed in patients with a diabetes duration of less than 4 years, and the lowest in participants with a diabetes duration of 12 years or longer. The LS mean change was −2.09% (95% CI, -2.21% to -1.97%) among participants with a diabetes duration of less than 4 years and −1.67% (95% CI, -1.75% to -1.58%) among participants with a diabetes duration of 12 years or longer (Figure 1B).

Overall, 28.9% of all study participants reached the HbA1c target of less than 7.0% at week 24, 51.6% reached the target of less than 7.5% and 70.5% reached the target of less than 8.0%. At week 24, an HbA1c target of less than 7.0% was achieved by 31.6% and 26.8% of participants with a diabetes duration of less than 8 years and 8 years or longer, respectively (Figure 2). More participants with a diabetes duration of less than 4 years achieved HbA1c targets of less than 7.0% and less than 7.5% at week 24 of Gla-300 therapy than participants with a diabetes duration of 4-8, 8-12 or 12 years or longer (Table S5).

3.3 | Change in FPG

Overall, mean ± SD FPG decreased by 56.3 ± 53.3 mg/dL from 187.2 ± 50.3 mg/dL at baseline to 131.6 ± 37.9 mg/dL at week 24. The LS mean change in FPG from baseline to week 24 was −55.8 (95% CI, −59.5 to −52.2) mg/dL in participants with a diabetes duration of less than 8 years and was −57.2 (95% CI, −60.0 to −54.4) mg/dL in participants with a diabetes duration of 8 years or longer. The LS mean difference between the two groups was −1.3 (95% CI, −5.8 to 3.2) mg/dL ($P = .56$). In line with changes in HbA1c, the reduction in FPG

TABLE 2 Incidence and event rate of any time-of-day and nocturnal hypoglycaemic events according to diabetes duration.

	Diabetes duration < 8 y (*N* = 1040)	Diabetes duration ≥ 8 y (*N* = 1309)	Overall population (*N* = 2349)
Severe hypoglycaemia			
Participants with ≥ 1 event, *n* (%)	2 (0.2)	8 (0.6)	10 (0.4)
Total number of events (event rate)	2 (0.004)	9 (0.015)	11 (0.011)
Symptomatic hypoglycaemia			
Participants with ≥ 1 event, *n* (%)	55 (5.3)	103 (7.9)	158 (6.7)
Total number of events (event rate)	160 (0.35)	257 (0.44)	417 (0.40)
Severe nocturnal hypoglycaemia			
Participants with ≥ 1 event, *n* (%)	0	2 (0.2)	2 (0.1)
Total number of events (event rate)	0	3 (0.005)	3 (0.003)
Symptomatic nocturnal hypoglycaemia			
Participants with ≥ 1 event, *n* (%)	5 (0.5)	31 (2.4)	36 (1.5)
Total number of events (event rate)	15 (0.032)	64 (0.110)	79 (0.076)

Note: Percentages are based on *N*. Event rates are based on total patient-year exposure.

mainly occurred during the first 12 weeks and continued during the following weeks.

3.4 | Hypoglycaemic events

During the 24-week Gla-300 treatment period, incidences and event rates for symptomatic and severe hypoglycaemia occurring at any time-of-day and during the night were overall low among the 2349 treated study participants, with no major differences between participants with a diabetes duration of less than 8 years and 8 years or longer (Table 2). Overall, any time-of-day symptomatic hypoglycaemia was reported in 6.7% of participants, and nocturnal symptomatic hypoglycaemia was reported in 1.5% of participants. Severe hypoglycaemia at any time-of-day and during the night occurred in less than 1% of the study population (Table 2). Patients with a diabetes duration of 8 years or longer had a numerically higher incidence of symptomatic hypoglycaemia compared with those with a diabetes duration of less than 8 years: 7.9% versus 5.3% reported experiencing at least one event at any time of day, with an event rate of 0.44 versus 0.35, respectively. For nocturnal hypoglycaemia, 2.4% versus 0.5% reported at least one symptomatic event, with an event rate of 0.110 versus 0.032, respectively.

3.5 | Insulin dose and body weight

Figure 3 summarizes the change in Gla-300 doses throughout the study. The mean ± SD Gla-300 dose increased similarly by 0.13 ± 0.14 U/kg/day in participants with a diabetes duration of less than 8 years and by 0.14 ± 0.15 U/kg/day in participants with a diabetes duration of 8 years or longer from baseline to week 24. The most important increases in Gla-300 daily dose occurred within the first 12 weeks. Likewise, in the four subgroups, mean ± SD change in Gla-300 daily dose from baseline to week 24 ranged from 0.11 ± 0.14 to 0.14 ± 0.14 U/kg/day.

There were no major changes in body weight from baseline to week 24. The mean ± SD change in body weight from baseline to week 24 was 0.07 ± 3.65 kg in participants with a diabetes duration of less than 8 years and 0.38 ± 3.24 kg in participants with a diabetes duration of 8 years or longer. Participants with a diabetes duration of less than 4 years had a mean reduction of 0.19 ± 4.1 kg in body weight, while participants in the other subgroups had a slight increase of 0.24 ± 3.3 to 0.4 ± 3.5 kg in body weight from baseline to week 24.

4 | DISCUSSION

Our analysis evaluated the effectiveness and safety of Gla-300 in insulin-naïve participants with diabetes durations of less than 8 years or 8 years or longer, based on the median diabetes duration of 8 years. Although our study population may include individuals who had a comparatively short duration of diabetes at the time of insulin initiation, this median duration is in line with several cross-sectional studies performed in patients with T2D.[31–33] For instance, in a study from the UK of 224 000 people with T2D, the median diabetes duration was estimated at 7.9 years in 2019.[31] However, it is worth noting that a delayed T2D diagnosis in some patients could contribute to underestimating the actual diabetes duration.

Compared with participants with a shorter diabetes duration, those with a longer diabetes duration in our analysis were, on average, older, with a lower estimated glomerular filtration rate, and increased cardiovascular co-morbidities and diabetes complications. These differences could be related to age and progression of the disease over time.[3,6,33,34] Irrespective of diabetes duration, Gla-300 showed overall clinically important improvements in HbA1c, with a slightly greater HbA1c decrease in participants with a shorter diabetes duration

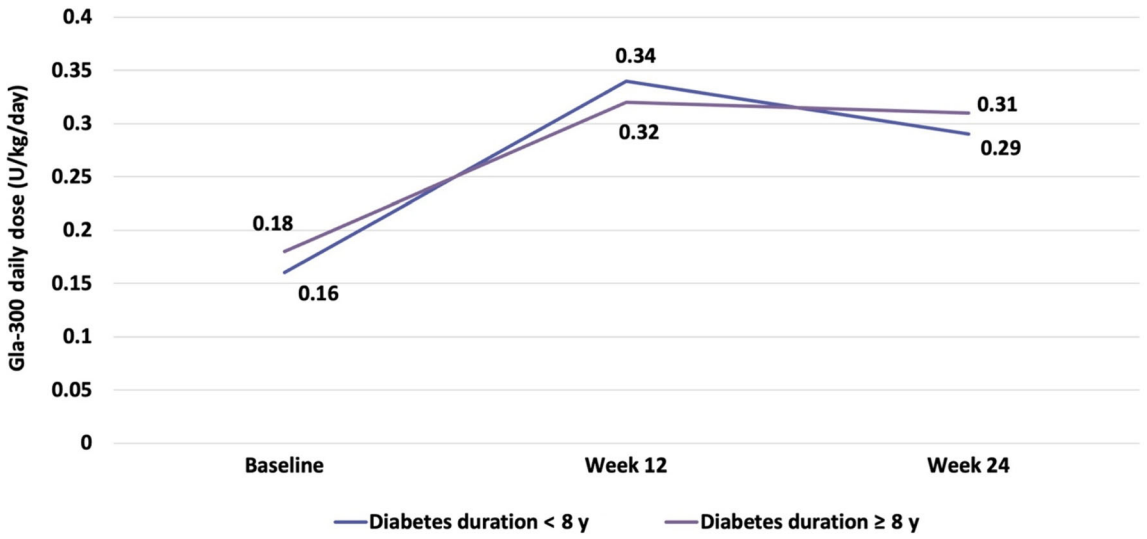

FIGURE 3 Mean Gla-300 daily dose (in U/kg/day) at baseline and at weeks 12 and 24. Gla-300, insulin glargine 300 U/mL.

(< 8 years) compared with those with a longer duration. The magnitude of the difference between the two diabetes duration strata is modestly low to have a clinically important effect. The HbA1c improvement in participants with a shorter diabetes duration (< 8 years) was mainly driven by an HbA1c reduction in the subgroup of participants with a diabetes duration of less than 4 years, who had the highest baseline mean HbA1c (9.61%) and had experienced the greatest HbA1c improvement from baseline to week 24 (LS mean change of −2.09%). Furthermore, in this subgroup, the difference in the mean HbA1c change, when compared with the group with a diabetes duration of 8 years or longer, was approximately −0.38%, hence of potentially clinically relevant magnitude. By contrast, participants with a diabetes duration of 12 years or longer had the lowest baseline HbA1c with the least improvement in HbA1c. In addition to HbA1c benefits, reported hypoglycaemia rates were low, with no major differences between the two groups, and the effect of Gla-300 on body weight was neutral across the different groups.

To date, studies evaluating the effect of diabetes duration on glycaemic control remain limited. ITAS, which included insulin-naïve participants with T2D uncontrolled on non-insulin glucose-lowering therapies, showed that Gla-300 led to a reduction in HbA1c from baseline to week 24 with a low risk of hypoglycaemia.[35,36] In a post hoc subgroup analysis of ITAS based on a 10-year cut-off for diabetes duration, improvements in glycaemic control were similar in either patient or physician-managed subgroups.[37] Another retrospective cohort study from Japan examined the effect of the timing of insulin therapy initiation on glycaemic control in participants with T2D and a high baseline HbA1c (mean ± SD: 10.35% ± 2.01%).[38] Those who started insulin injections within 3 years after T2D diagnosis had significantly greater reductions in mean HbA1c at 1, 3 and 5 years after insulin initiation than participants with a longer diabetes duration (i.e. 4-6, 7-9 or ≥ 10 years): −4.52% ± 2.61% at 1 year ($P < .01$); −4.34% ± 2.24% at 3 years ($P < .01$); and −4.88% ± 2.87% at 5 years ($P < .01$).[38] Although T2D in Japanese people may have some particularities, findings from the REALI analysis concur with the results of the Japanese retrospective study,[38] indicating that earlier insulin use in the treatment of individuals with T2D may result in greater glycaemic control improvement.

HbA1c targets should be individualized, based on age, cognitive function and functional status, co-morbidities and other patient-specific factors.[34] Although the proportions of participants achieving HbA1c targets of less than 7.0%, less than 7.5% and less than 8.0% were similar between the two groups in the current analysis, participants with a diabetes duration of less than 8 years had a higher baseline mean HbA1c (9.38% vs. 9.16%), which suggests that, at a comparable mean baseline HbA1c, these participants may be more probable to reach HbA1c targets than participants with a longer diabetes duration. The unexpected lower baseline HbA1c in individuals with a diabetes duration of 8 years or longer may, in part, be attributed to a higher proportion of patients taking two or more non-insulin glucose-lowering agents (67.4% vs. 51.0%), according to available data on previous non-insulin glucose-lowering treatment.

The Canadian INSIGHT trial[6] randomly assigned insulin-naïve participants with T2D to receive insulin glargine 100 U/mL (Gla-100) in addition to their current therapy or conventional glycaemic management with the intensification of oral glucose-lowering therapy and insulin avoidance.[6] At 24 weeks, participants in the Gla-100 group reached the primary endpoint of two consecutive HbA1c levels of 6.5% or less before participants on intensified oral glucose-lowering therapy ($P = .041$), and had lower HbA1c and FPG levels. Importantly, these benefits were more probable to be achieved in participants who were not yet receiving glucose-lowering therapies at baseline and with a diabetes duration of less than 5 years.[6] Hence, even without prior insulin use, participants with a shorter diabetes duration are more probable to reach HbA1c targets on basal insulin therapy.[6] In fact, insulin therapy, especially in the early stages of T2D, up to 5 years after manifestation, was shown to be linked to improvements in β-cell function and hepatic insulin resistance as a result of the rapid

improvement of glucotoxicity and lipotoxicity.[39] Thus, insulin, in particular second-generation basal insulins, may represent one of the most convenient ways to protect pancreatic B-cell function early on, thereby preserving endogenous insulin biosynthesis, providing an insulin-sparing strategy in the long run, and reducing the risk of hypoglycaemia and weight gain. Consequently, timely insulinization may be an additional aid to prevent hyperglycaemia-driven diabetes complications.[39]

In terms of safety, Gla-300 has been consistently associated with a reduced risk of weight gain and hypoglycaemia, which may be related to its smooth and even pharmacokinetic and pharmacodynamic profiles.[40–42] In the EDITION 3 study enrolling insulin-naïve people with T2D, Gla-300 was associated with a significantly lower risk of hypoglycaemia over the 6-month treatment period and less body weight gain than Gla-100 (LS mean increase of 0.49 kg for Gla-300 vs. 0.71 kg for Gla-100).[40] The BRIGHT study also showed comparable hypoglycaemia incidence and rates, which were generally low, between Gla-300 and insulin degludec 100 U/mL over the 24-week treatment period.[41] Overall, the reported low incidence of hypoglycaemia associated with Gla-300 may reassure individuals with T2D to initiate and optimize their insulin therapy and to better control their disease in the long term, regardless of the duration of their diabetes.[42]

In our analysis, Gla-300 dose increased by a mean ± SD of 0.13 ± 0.15 U/kg/day from baseline to week 24, and almost doubled in both groups. In the randomized ITAS, EDITION 3, and BRIGHT trials, the average Gla-300 dose increased by 0.30-0.40 U/kg/day at week 24.[36,40,41] The increase in Gla-300 daily dose observed in our analysis was lower compared with the changes in Gla-300 dose observed in the ITAS, EDITION 3, and BRIGHT randomized clinical trials. This could be attributed to several factors, such as different protocols for titrating insulin doses or different criteria for dose adjustment, and underestimation of insulin dose changes in observational studies.

The limitations of the current pooled analysis include the comparatively short Gla-300 treatment duration, a heterogeneous reporting of previous non-insulin glucose-lowering treatment, and the lack of evaluation of adherence to Gla-300 therapy. Another limitation may be the presence of a potential reporting bias, which is inherent to observational studies, that could result in under- or over-reporting of hypoglycaemia. The current analysis also has several strengths, including the large sample size, the prospective nature of the evaluated studies, the balanced number of participants between groups allowing a robust evaluation, and the application of standardized endpoint definitions to reduce study-specific differences. To the best of our knowledge, this is the first pooled analysis examining the impact of diabetes duration on the glycaemic efficiency and safety of Gla-300 in insulin-naïve participants with T2D. The current REALI analysis contributes to the available evidence regarding the impact of diabetes duration on T2D treatment outcomes and may support the recommendations in the guidelines to individualize diabetes therapy taking into account diabetes duration.[1]

In conclusion, the REALI pooled database analysis confirmed the effectiveness and safety of Gla-300 in insulin-naïve people with T2D, regardless of diabetes duration. Gla-300 therapy was associated with improved glycaemic control without weight gain and with a low incidence of reported symptomatic and severe hypoglycaemia. A greater, and potentially clinically relevant, HbA1c improvement was observed when Gla-300 was started early in participants with a diabetes duration of less than 4 years.

AUTHOR CONTRIBUTIONS

All the authors contributed to the project design and the analysis plan. CM performed the statistical analysis of the data. All the authors were involved in the interpretation of the data, writing and reviewing drafts of the manuscript, and approved the final version for submission.

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CONFLICT OF INTEREST

DM-W has acted as a consultant and has served on the speaker bureau for Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi. NF has received research support and has acted as a consultant for Gedeon Richter, Abbott Singapore, Galderma, ALK, AstraZeneca, Ipsen, Vertex, Sanofi, Thea, Aimmune, Novartis, Novo Nordisk, Allergan, Alliance and Merck Sharp & Dohme. RCB has served on the speaker bureau for Sanofi, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca and Janssen, and has served on the advisory panel for Merck Sharp & Dohme, Eli Lilly, Sanofi and Johnson & Johnson. CM is an IDDI employee and has acted as a biostatistics contractor for Sanofi. CV is an IVIDATA employee. MB is an employee and stakeholder of Sanofi. PG has received advisory board and speaker honoraria from Abbott, AbbVie, Amgen, AstraZeneca, Bayer, Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Organon, Sanofi and Servier. DM has acted as a consultant and/or has served on the speaker bureau for Almirall, Eli Lilly, Esteve, Ferrer, Janssen, Menarini, Merck Sharp & Dohme, Novo Nordisk and Sanofi.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16008.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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