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ORIGINAL RESEARCH

Association of Patient Profile with Glycemic Control and Hypoglycemia with Insulin Glargine 300 U/mL in Type 2 Diabetes: A Post Hoc Patient-Level Meta-Analysis

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ABSTRACT

Aims: To examine the association of baseline patient characteristics with study outcomes in people with type 2 diabetes receiving insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100), over a 6-month period.

Methods: A post hoc patient-level meta-analysis using data from three multicenter, randomized, open-label, parallel-group, phase 3a studies of similar design, in people previously receiving either basal and prandial insulin, basal insulin + oral antihyperglycemic drugs, or no prior insulin (EDITION 1, 2 and 3, respectively). The endpoints, glycated hemoglobin (HbA_{1c}), hypoglycemia, body weight change, and insulin dose were investigated by subgroups: age (< 65 and ≥ 65 years), body mass index (BMI; < 30 and ≥ 30 kg/m^2), age at onset (< 40, 40–50, and > 50 years), and diabetes duration (< 10 and ≥ 10 years).

Results: Reduction in HbA_{1c} was comparable between insulins, regardless of subgroup. The lower risk of ≥ 1 nocturnal (00:00–05:59 h) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemic event with Gla-300 versus Gla-100 was also unaffected by participant characteristics. While heterogeneity of treatment effect between diabetes duration subgroups was seen for the risk of ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemic event at any time (24 h), treatment

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effect consistently favored Gla-300; no evidence of heterogeneity was observed for the other subgroups. Annualized rates of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemia and body weight change were not influenced by participant characteristics; a similar pattern was observed with insulin dose.
Conclusions: Comparable glycemic control was observed with Gla-300 versus Gla-100, with less hypoglycemia, regardless of age, BMI, age at onset or diabetes duration.
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PLAIN LANGUAGE SUMMARY

Treatments for patients with type 2 diabetes aim to reduce the levels of blood glucose and can include injections with insulin. However, care must be taken to prevent blood glucose levels falling too low (a state called hypoglycemia). Previous studies have shown that insulin glargine 300 units/mL (Gla-300) provides similar reductions in blood glucose levels as insulin glargine 100 units/mL (Gla-100) but is less likely to cause hypoglycemia. However, different patients may respond differently to treatments depending on their individual clinical and biological characteristics. The aim of this study was to evaluate how different profiles of patients with type 2 diabetes responded to Gla-300 and Gla-100 injections. Patients were grouped by different ages, weights, age at diabetes diagnosis, and number of years since diagnosis of diabetes. We found that Gla-300 and Gla-100 reduced glycated hemoglobin (HbA_{1c}; a marker of blood glucose control over the previous 2–3 months) similarly, regardless of how patients were grouped. However, patients treated with Gla-300 were less likely to experience hypoglycemia than those treated with Gla-100, and this association was also true regardless of different patient characteristics. We therefore concluded that Gla-300 is an effective and safe treatment in patients with type 2 diabetes, regardless of their age, weight, age at diabetes diagnosis, and years since diagnosis.

INTRODUCTION

Type 2 diabetes (Type 2 DM) is a heterogeneous disease, with a population that exhibits diverse clinical and biological characteristics [1, 2]. Current recommendations for the management of Type 2 DM encourage a patient-centered approach [3], such that less stringent glycemic targets (e.g. glycated hemoglobin [HbA_{1c}] < 64 mmol/mol [8.0%]) may be considered on an individual basis [4], to take into account, for example, factors such as polypharmacy, comorbidities, frailty, renal disease, and reduced life expectancy found to be associated with increased risk of hypoglycemia. To most appropriately individualize treatments and glycemic targets, it is important to understand how the characteristics of each individual might affect the outcomes of treatment. Studies investigating potential predictors of response have highlighted several demographic and clinical factors that may influence the effectiveness of particular diabetes therapies, as well as the attainment of glycemic targets [5–8].

Insulin glargine 300 U/mL (Gla-300; Toujeo®; Sanofi S.A., Paris, France) is a long-acting basal insulin analog with prolonged and more stable pharmacokinetic and pharmacodynamic profiles than insulin glargine 100 U/mL (Gla-100; Lantus®; Sanofi S.A.) [9]. The EDITION program included three multinational clinical studies that compared the efficacy and safety of Gla-300 to those of Gla-100 in different populations of people with Type 2 DM [10–12]. In the individual EDITION studies and a post hoc, patient-level meta-analysis, Gla-300 provided comparable glycemic control to Gla-100 with fewer hypoglycemia events over 6 months of treatment [10–13]. Change in body weight was low in both treatment groups, with slightly less weight gain in patients receiving Gla-300 [10–13].

The objective of the current post hoc analysis was to investigate the potential association of participant characteristics with key outcomes reported from the EDITION 1–3 trials, in Type 2

DM participants randomized to Gla-300 or Gla-100. The characteristics chosen for this post hoc analysis were those previously reported to influence glycemic control in participants with Type 2 DM [5–8]. For example, age, body weight, and duration of diabetes have been shown to be associated with change in HbA_{1c} [5]. Similarly, multivariate analyses in individuals with Type 2 DM showed a higher success rate of achieving glycemic control targets in older participants, those with higher body mass index (BMI), and those with a shorter duration of diabetes [7]. In addition, older people with Type 2 DM are at a greater risk of hypoglycemia than are younger individuals [14]. In the current analysis, glycemic control, hypoglycemia, and body weight were assessed in subgroups of participants defined by age, BMI, age at onset of diabetes, and duration of diabetes, in a patient-level meta-analysis of data from the three trials over a 6-month period.

METHODS

Study Design

This post hoc analysis was performed on patient-level data from the EDITION 1, EDITION 2, and EDITION 3 studies. EDITION 1, 2, and 3 were multicenter, randomized, open-label, two-arm, parallel-group, phase 3a studies with 6-month treatment periods (NCT01499082, NCT01499095, and NCT01676220, respectively), the study designs of which have been described previously [10–12]. All participants were ≥ 18 years of age with a diagnosis of Type 2 DM (according to World Health Organization criteria) [15], and prior to study enrolment they were receiving either basal (≥ 42 units/day) and prandial insulin therapy with or without metformin for at least 1 year (EDITION 1) [10], at least 6 months of basal insulin treatment (≥ 42 units/day) in combination with oral anti-hyperglycemic drugs (OADs) (EDITION 2) [11], or at least 6 months of OADs and were insulin naïve (EDITION 3) [12]. In the EDITION 2 and 3 studies, participants discontinued the use of sulphonylurea 2 months prior to screening and at baseline, respectively. In all three studies, participants were randomized (1:1) to receive once-daily evening injections of either Gla-300 or Gla-100, and they were titrated to a fasting self-monitored plasma glucose target of 4.4–5.6 mmol/L (80–100 mg/dL).

For the current analysis, the patient-level dataset from EDITION 1, 2, and 3 was grouped according to baseline: age (< 65 and ≥ 65 years), BMI (< 30 and ≥ 30 kg/m^2), age at onset of diabetes (< 40, 40–50, and > 50 years), and diabetes duration (< 10 and ≥ 10 years). The cut-offs in the age at onset analysis, which were not predefined, were chosen to be clinically meaningful, while limiting the difference in sample size between subgroups.

Outcomes

The analysis was carried out for the following endpoints, from baseline to treatment month 6: change in HbA_{1c} (%); number and percentage of participants with at least one hypoglycemic event, and annualized rates of hypoglycemia (events per participant-year), both nocturnal (00:00–05:59 h) and at any time of day (24 h), and change in body weight. Daily basal insulin dose and change in dose from baseline to treatment month 6 was also reported by subgroup.

Hypoglycemia was defined as confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe, or as documented symptomatic (≤ 3.9 mmol/L [≤ 70 mg/dL]), based on American Diabetes Association (ADA) categories described at the time when the EDITION studies were undertaken [16]. The confirmed or severe definition of hypoglycemia combined three ADA categories: documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and severe hypoglycemia.

Data Analysis and Statistics

For each endpoint considered, differences of treatment effect across subgroups were assessed with a heterogeneity test. Differences of treatment effect across subgroups were only considered to be relevant if evidence of heterogeneity was observed ($p < 0.05$). The p values of

the heterogeneity test were generated using a subgroup-by-treatment interaction.

Change in HbA_{1c} was analyzed using a mixed model for repeated measurements. The percentage of participants with at least one hypoglycemic event was analyzed using the Cochran–Mantel–Haenszel method, and annualized rates of hypoglycemia (events per participant-year) were analyzed using an overdispersed Poisson regression model. Change in body weight was assessed using an analysis of covariance model (ANCOVA), from baseline to last on-treatment value. Daily basal insulin dose was assessed using descriptive statistics.

Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the appropriate local or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

Baseline Characteristics

In total, 2496 participants were included in this patient-level meta-analysis of the three EDITION Type 2 DM studies, of whom 1247 were randomized to Gla-300 and 1249 were randomized to Gla-100. Baseline characteristics of this study population have been reported previously [13] and are summarized together with the age at onset of diabetes in Table 1. Mean age, BMI, age at onset of diabetes, and diabetes duration were similar in both treatment arms.

Table 1 Baseline characteristics of the population with type 2 diabetes included in this patient-level meta-analysis of the EDITION 1, 2, and 3 studies (randomized population)

Baseline characteristics	Gla-300 (n = 1247)	Gla-100 (n = 1249)
Age, years	58.7 ± 9.3	58.5 ± 9.5
Gender (male), n (%)	657 (52.7)	649 (52.0)
Ethnic group, n (%)		
Caucasian	1096 (87.9)	1095 (87.7)
Black	90 (7.2)	94 (7.5)
Asian	48 (3.8)	49 (3.9)
Other	13 (1.0)	11 (0.9)
BMI, kg/m^2	34.7 ± 6.9	34.8 ± 6.4
Age at onset of diabetes, years	46.5 ± 9.6	46.4 ± 9.9
Duration of diabetes, years	12.7 ± 7.2	12.6 ± 7.5
HbA_{1c}, mmol/mol (%)	67 (8.31 ± 0.92)	67 (8.32 ± 0.91)

BMI Body mass index, *HbA_{1c}* glycated hemoglobin
Values are presented as the mean ± standard deviation unless otherwise stated. Age, BMI, duration of diabetes, gender, and HbA_{1c} have been published previously [13]

Glycemic Control

Reduction in HbA_{1c} over the 6-month study period was comparable between the Gla-300 and Gla-100 treatment arms, regardless of age, BMI, age at onset of diabetes, or diabetes duration (Fig. 1). These findings were consistent with the overall pooled study population. No evidence of heterogeneity of treatment effect across subgroups was observed over the 6-month treatment period ($p > 0.05$).

Hypoglycemia

The lower risk of nocturnal (00:00–05:59 h) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemia with Gla-300 versus Gla-100 seen in the overall pooled study population was not affected by age, BMI, age at onset of diabetes, or diabetes duration, as no evidence of heterogeneity of treatment effect across subgroups was seen over the 6-month treatment period ($p > 0.05$; Fig. 2a). Similarly, the lower risk of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemia at any time of day

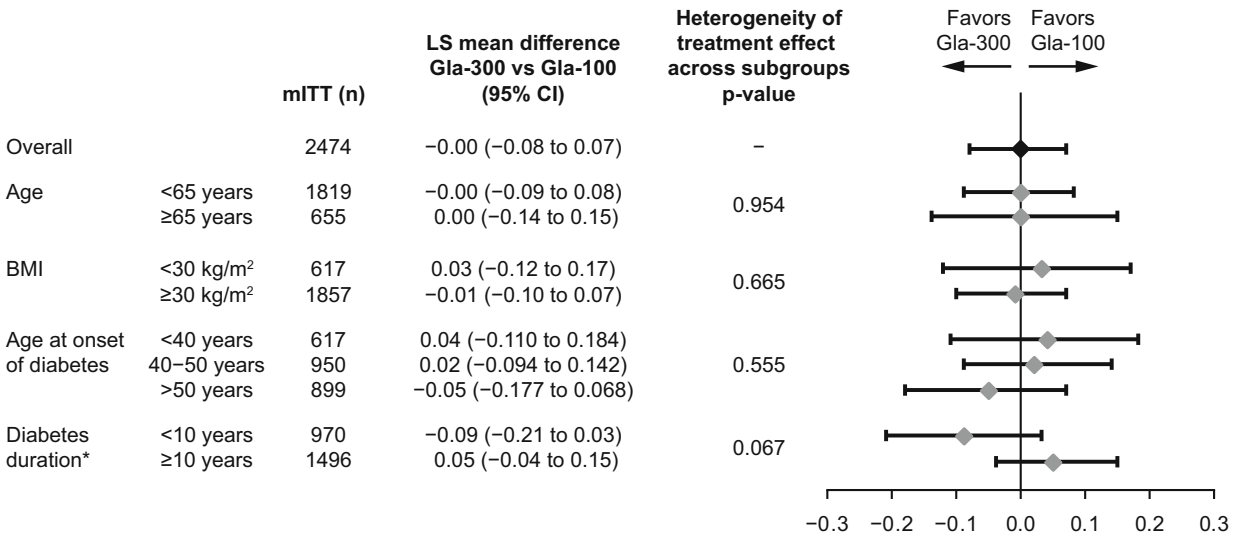


Fig. 1 Reduction in glycated hemoglobin (HbA_{1c} [%]) in people with type 2 diabetes (Type 2 DM) over 6 months of treatment by subgroup (mITT population; pooled data from EDITION 1, 2 and 3). *Diabetes duration not available for 8 participants. *BMI* Body mass index, *CI* confidence interval, *Gla-300/Gla-100* insulin glargine 300 units/mL/insulin glargine 100 units/mL, *LS* least squares, *mITT* modified intent-to-treat

(24 h) with Gla-300 versus Gla-100 was not affected by age, BMI, or age at onset of diabetes (no evidence of heterogeneity of treatment effect across subgroups: $p > 0.05$; Fig. 2b). For the diabetes duration subgroup analysis, some degree of heterogeneity of treatment effect was observed between participants with a diabetes duration of < 10 years and those with a diabetes duration of ≥ 10 years ($p = 0.006$), although the treatment benefit was consistently in favor of Gla-300 regardless of diabetes duration (Fig. 2b).

When confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemic events were considered in terms of annualized rates (events per participant-year), no evidence of heterogeneity of treatment effect was observed across any subgroups, either at night (00:00–05:59 h) or at any time of day (24 h) ($p > 0.05$; Fig. 3a, b).

Similar findings were observed for documented symptomatic (≤ 3.9 mmol/L [≤ 70 mg/dL]) hypoglycemia, both in terms of relative risk and rate ratios; however, some degree of heterogeneity of treatment effect was observed for annualized rates at any time of day (24 h) between participants with a BMI of < 30 kg/m^2 and those with a BMI of ≥ 30 kg/m^2 ($p = 0.037$; Electronic Supplementary Material ([ESM] Figs. S1–2).

The risk of at least one severe hypoglycemic event at any time of day (24 h) was comparable between the Gla-300 and Gla-100 treatment arms, regardless of age, BMI, age at onset of diabetes, or diabetes duration (ESM Fig. S3). No evidence of heterogeneity of treatment effect across subgroups was observed for all subgroups (ESM Fig. S3).

Body Weight

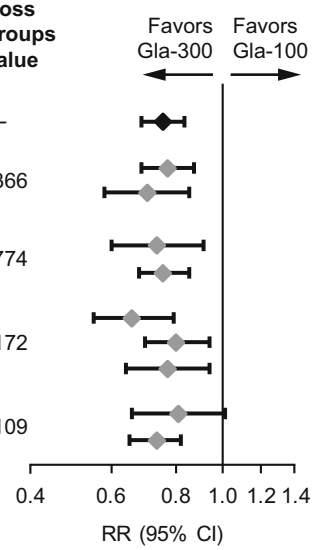
Over the 6-month treatment period, change in body weight was comparable between subgroups, with a trend for slightly less weight gain in those patients on Gla-300 compared with those on Gla-100 (Table 2). No evidence of heterogeneity of treatment effect was observed in the age, BMI, age at onset of diabetes, or diabetes duration subgroups ($p = 0.486$, 0.942, 0.566, 0.663, respectively).

Insulin Dose

Daily basal insulin dose increased over the 6-month treatment period in both treatment groups, with a slightly higher dose (10–16%) at

(a)

		Safety population (n)	Gla-300 (% participants)	Gla-100 (% participants)	RR Gla-300 vs Gla-100 (95% CI)	Heterogeneity of treatment effect across subgroups p-value
Overall		2488	30.0	39.8	0.75 (0.68 to 0.83)	–
Age	<65 years	1829	29.3	38.0	0.77 (0.68 to 0.87)	0.366
	≥65 years	659	31.8	44.9	0.70 (0.57 to 0.85)	
BMI	<30 kg/m²	619	29.7	40.4	0.73 (0.59 to 0.91)	0.774
	≥30 kg/m²	1869	30.1	39.6	0.75 (0.67 to 0.85)	
Age at onset of diabetes	<40 years	622	31.1	47.9	0.65 (0.54 to 0.79)	0.172
	40–50 years	954	33.8	40.6	0.80 (0.69 to 0.94)	
	>50 years	904	25.1	33.1	0.77 (0.63 to 0.94)	
Diabetes duration*	<10 years	980	21.8	26.3	0.81 (0.65 to 1.01)	0.109
	≥10 years	1500	34.9	48.9	0.73 (0.64 to 0.82)	



(b)

		Safety population (n)	Gla-300 (% participants)	Gla-100 (% participants)	RR Gla-300 vs Gla-100 (95% CI)	Heterogeneity of treatment effect across subgroups p-value
Overall		2488	65.5	72.0	0.91 (0.87 to 0.96)	–
Age	<65 years	1829	63.4	70.0	0.90 (0.85 to 0.96)	0.927
	≥65 years	659	71.6	77.4	0.93 (0.85 to 1.01)	
BMI	<30 kg/m²	619	66.7	74.7	0.89 (0.81 to 0.98)	0.654
	≥30 kg/m²	1869	65.1	71.2	0.91 (0.86 to 0.96)	
Age at onset of diabetes	<40 years	622	65.7	75.9	0.86 (0.79 to 0.95)	0.306
	40–50 years	954	67.1	72.9	0.91 (0.84 to 0.98)	
	>50 years	904	63.9	68.3	0.94 (0.86 to 1.03)	
Diabetes duration*	<10 years	980	55.0	56.6	0.96 (0.86 to 1.07)	0.006
	≥10 years	1500	72.2	82.5	0.88 (0.84 to 0.93)	

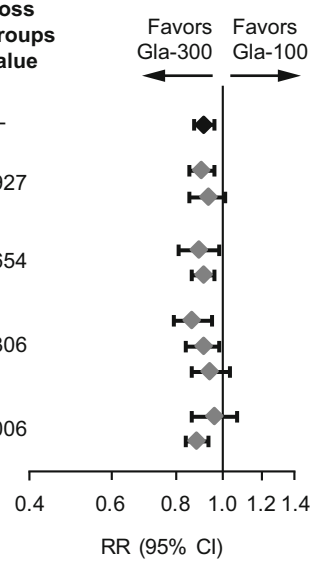
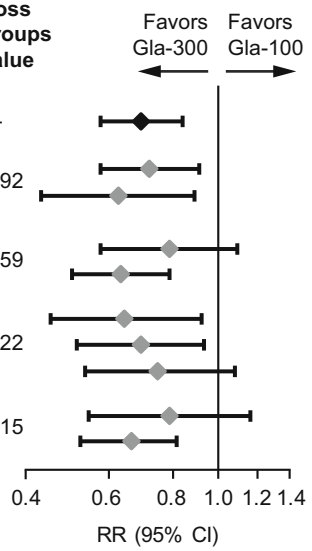


Fig. 2 Relative risk (*RR*) of experiencing confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemia during the night (00:00–05:59 h) (**a**) and at any time of day (24 h) (**b**), over 6 months of treatment by subgroup (% participants with ≥ 1 event; safety population; pooled data from EDITION 1, 2, and 3). *Diabetes duration not available for 8 participants

treatment month 6 for Gla-300 compared with Gla-100 in each of the subgroups (ESM Table S1). The treatment difference in change from baseline to month 6 was generally comparable across the subgroups (ESM Table S1).

(a)

		Safety population (n)	Gla-300 (Events per participant-year)	Gla-100 (Events per participant-year)	RR Gla-300 vs Gla-100 (95% CI)	Heterogeneity of treatment effect across subgroups p-value
Overall		2488	2.10	3.06	0.69 (0.57 to 0.84)	–
Age	<65 years	1829	2.06	2.86	0.72 (0.57 to 0.91)	0.492
	≥65 years	659	2.23	3.63	0.62 (0.43 to 0.89)	
BMI	<30 kg/m^2	619	2.93	3.64	0.79 (0.57 to 1.09)	0.259
	≥30 kg/m^2	1869	1.81	2.89	0.63 (0.50 to 0.79)	
Age at onset of diabetes	<40 years	622	2.34	3.64	0.64 (0.45 to 0.92)	0.822
	40–50 years	954	2.29	3.28	0.69 (0.51 to 0.93)	
	>50 years	904	1.76	2.41	0.75 (0.53 to 1.08)	
Diabetes duration*	<10 years	980	1.49	1.89	0.79 (0.54 to 1.16)	0.415
	≥10 years	1500	2.49	3.87	0.66 (0.52 to 0.82)	



(b)

		Safety population (n)	Gla-300 (Events per participant-year)	Gla-100 (Events per participant-year)	RR Gla-300 vs Gla-100 (95% CI)	Heterogeneity of treatment effect across subgroups p-value
Overall		2488	15.22	17.73	0.86 (0.77 to 0.97)	–
Age	<65 years	1829	14.24	16.47	0.87 (0.75 to 1.00)	0.877
	≥65 years	659	18.04	21.25	0.85 (0.69 to 1.05)	
BMI	<30 kg/m^2	619	15.24	19.76	0.75 (0.60 to 0.95)	0.218
	≥30 kg/m^2	1869	15.21	17.11	0.89 (0.78 to 1.02)	
Age at onset of diabetes	<40 years	622	16.18	22.87	0.71 (0.57 to 0.88)	0.107
	40–50 years	954	17.55	17.82	0.95 (0.80 to 1.14)	
	>50 years	904	12.36	14.04	0.91 (0.73 to 1.13)	
Diabetes duration*	<10 years	980	10.23	10.76	0.94 (0.75 to 1.19)	0.364
	≥10 years	1500	18.37	22.35	0.83 (0.73 to 0.95)	

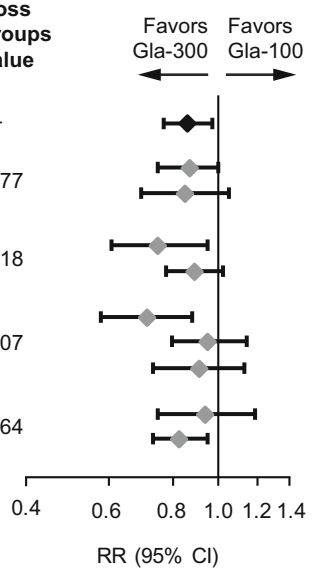


Fig. 3 Annualized rates of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycemia during the night (00:00–05:59 h) (**a**) and at any time of day (24 h) (**b**), over 6 months of treatment by subgroup (events per participant-year; safety population; pooled data from EDITION 1, 2, and 3). *Diabetes duration not available for 8 participants. *RR* rate ratio

DISCUSSION

Guidelines for the management of Type 2 DM recommend a patient-centered approach that considers the needs and preferences of each individual [3]. The outcomes of diabetes treatment can differ depending on an individual's characteristics [5–7, 17]. The objective of this

Table 2 Change in body weight (kg) over the 6-month treatment period in patient-level meta-analysis of the EDITION 1, 2 and 3 studies (safety population)

Patient parameters	Safety population (*n*)	LS mean difference in change from baseline to last on-treatment value: Gla-300 vs Gla-100 (95% CI)[a]	Heterogeneity of treatment effect across subgroups *p* value
Age, years			
< 65	1829	− 0.34 (− 0.65 to − 0.03)	0.486
≥ 65	659	− 0.12 (− 0.64 to 0.40)	
BMI, kg/m^2			
< 30	619	− 0.31 (− 0.84 to 0.23)	0.942
≥ 30	1869	− 0.28 (− 0.59 to 0.02)	
Age at onset of diabetes, years			
< 40	607	− 0.50 (− 1.04 to 0.03)	0.566
40–50	938	− 0.14 (− 0.57 and 0.29)	
> 50	879	− 0.24 (− 0.68 and 0.21)	
Diabetes duration, years			
< 10	980	− 0.19 (− 0.62 to 0.24)	0.663
≥ 10	1500	− 0.31 (− 0.66 to 0.03)	

CI confidence interval, *LS* least squares

[a] Last on-treatment value was defined as the value collected at or just prior to the last investigational product intake during the main treatment. Based on meta-analysis of the endpoint with subgroup and subgroup-by-treatment interactions as fixed effects

post hoc analysis of the EDITION studies was to examine the association between participant characteristics and study outcomes in people with Type 2 DM receiving Gla-300 versus Gla-100. Glycemic control was comparable between the treatment groups, as expected in a 'treat-to-target' study, but there was less nocturnal hypoglycemia in patients on Gla-300 than in those on Gla-100 regardless of participant age, BMI, age at onset of diabetes, or duration of diabetes. The benefits of Gla-300 observed across these subgroups were consistent with those observed in the overall pooled study population.

The heterogeneity of treatment effect observed across the diabetes duration subgroups (for risk of hypoglycemia at any time of day [24 h]) suggests that Gla-300 may be particularly beneficial in reducing hypoglycemia in people with a longer duration of diabetes (≥ 10 years) compared with Gla-100. However, these findings may have been driven by differences in the study populations reflecting the individual study inclusion criteria. Participants with a diabetes duration of < 10 years are most likely to have been from the EDITION 3 study, which enrolled insulin-naïve people with a mean diabetes duration of 10 years [12]. In contrast, the mean durations of diabetes in EDITION 1 and EDITION 2 were 16 years and 13 years, respectively [10, 11]. Other differences between the individual study populations could also have affected these findings; for example, the use of mealtime insulin in EDITION 1, which would have been overrepresented in the ≥ 10 years diabetes duration group, may have impacted hypoglycemia occurring during the day. However, it is interesting to note that there was a trend towards heterogeneity of treatment effect across the diabetes duration

subgroups for change in HbA_{1c}. It is therefore possible that the heterogeneity between the diabetes duration subgroups was due to a difference in treatment approaches in the two subgroups of participants—as those with a longer duration of diabetes are a more complex population and more likely to have a greater pharmacological treatment burden at baseline and an increased risk of hypoglycemia—rather than simply a difference between the treatments used.

Although a heterogeneity of treatment effect was observed between BMI subgroups for annualized rates of documented symptomatic ($\leq$ 3.9 mmol/L [$\leq$ 70 mg/dL]) hypoglycemia at any time of day (24 h), the benefit of Gla-300 versus Gla-100 (in terms of direction of effect) was apparent in both BMI subgroups.

An earlier age at onset of diabetes has also been associated with higher HbA_{1c} [8], as well as being linked to a greater risk of diabetes complications, such as diabetic retinopathy and more severe albuminuria, in people with Type 2 DM [18, 19]. In the current analysis, those with an earlier age at onset showed a trend towards having higher baseline BMI and body weight (ESM Table S2), which may suggest a specific phenotype for this subgroup; however, this may be expected based on the pathophysiology of diabetes, and further analysis is required to confirm this.

There was a trend for lower weight gain in patients on Gla-300 compared with those on Gla-100, as observed in the EDITION studies [10, 12, 13, 20], and no evidence of heterogeneity of treatment effect across the subgroups of participant characteristics was observed. As also previously observed in the EDITION studies [10, 12, 13, 20], a slightly higher mean basal insulin dose was seen at month 6 with Gla-300 compared with Gla-100. In the current analysis, insulin dose profiles appeared to be unaffected by participant characteristics, although this parameter was not assessed statistically.

The limitations of this study include the post hoc exploratory nature of the analysis. An imbalance in the number of participants across the subgroups may have introduced some bias within the analysis. Nevertheless, the cut-offs chosen are meant to demonstrate the lack of association between these participant characteristics and treatment outcomes with Gla-300 versus Gla-100. Furthermore, the age cut-off ($\geq$ 65 years) is aligned with that used throughout the ADA guidelines for the treatment of older people with diabetes [21]. In addition, other imbalances between subgroups may have affected the results. For example, the age at onset of diabetes subgroup of participants < 40 years had a higher proportion of individuals from the EDITION 1 study than did the other studies. However, it should be noted that the cut-offs for the age at onset of diabetes subgroup were chosen to ensure a comparable number of participants in each subgroup. Finally, EDITION 3 contributed a greater proportion of participants to the subgroup BMI < 30 kg/m^2 than did EDITION 1 and 2. These imbalances could have potentially impacted the results of risk/rates of hypoglycemia at any time of day, due to the use of prandial insulin therapy.

An individual's characteristics may also influence the effectiveness of specific therapies; for example, metformin has been shown to be less effective than intensive lifestyle changes in people with low BMI and in older people [22, 23]. Given the potential impact on response to therapy, the profile of an individual can influence clinical decisions relating to disease management and treatment at the individual level. When considering initiating or switching to basal insulin therapy with Gla-300, it is reassuring that in this analysis the benefits of Gla-300 were consistent regardless of subgroup, suggesting that age, BMI, age at onset of diabetes, and diabetes duration are not important influencing factors for such treatment decisions.

CONCLUSION

The comparable glycemic control of Gla-300 versus Gla-100 with less hypoglycemia seen in the EDITION studies of people with Type 2 DM was observed irrespective of participant age, BMI, age at onset of diabetes, or duration of diabetes in this analysis.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the appropriate local or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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

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