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Efficacy and Safety of Insulin Glargine 300 U/mL in North Americans and Non-North Americans with Type 2 Diabetes: A Patient-Level Meta-Analysis of the EDITION 1, 2 and 3 Studies

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Abstract

Objective: To assess efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus (vs) insulin glargine 100 U/mL (Gla-100) in North American and non-North American people with type 2 diabetes mellitus on different background therapies.

Methods: A patient-level meta-analysis of three international studies (EDITION 1, 2 and 3) was performed to examine glycemic control and hypoglycemia over 6 months in 2496 participants including 1420 participants in a North American sub-population (Gla-300, N=700; Gla-100, N=720). Endpoints included change in glycated hemoglobin (HbA1c), percentage of patients at target HbA1c at Month 6, incidence and rate of hypoglycemic events, change in body weight and insulin dose, as well as incidence of adverse events.

Results: Mean change in HbA1c was comparable for Gla-300 and Gla-100 in both regions (P=0.8347 for treatment-by-subgroup interaction). There were no regional differences in the percentage of participants achieving target HbA1c <7% (53.0 mmol/mol) or <7.5% (58.5 mmol/mol). The cumulative number, the incidence rates, as well as the annualized rates of confirmed (≤3.9 mmol/L and the lower threshold of <3.0 mmol/L) or severe hypoglycemia at any time of the day or during the night were lower with Gla-300 vs Gla-100; this was not affected by the region (all P>0.1). North American participants treated with Gla-300 gained less weight than North American participants treated with Gla-100 (least squares mean change 0.64 kg vs 1.15 kg), whereas in non-North American participants the change in weight tended to be similar in both treatment groups (0.36 kg vs 0.32 kg). Treatment with Gla-300 and Gla-100 was well tolerated in both regions.

Conclusion: Gla-300 provided comparable glycemic control to Gla-100 with consistently less hypoglycemia at any time of day and during the night, regardless of the region (North America/outside North America).

Keywords: Type 2 diabetes mellitus; Insulin glargine; EDITION studies; Meta-analysis; Glycemic control; Hypoglycemia; Safety

Introduction

Diabetes mellitus is currently affecting 415 million people worldwide. In North America and the Caribbean the number is estimated to be 44 million [1]. In the face of this global epidemic, the development of reliable, convenient, and safe treatment options for type 2 diabetes mellitus (T2DM) is becoming increasingly important. T2DM is characterized by an ongoing need to introduce additional treatment in order to maintain adequate glycemic targets. While many agents for treating T2DM exist, with longer durations most patients with T2DM will require insulin treatment. Insulin therapy is often initiated with basal insulin added to a number of oral anti-diabetic agents in patients requiring additional treatment for hyperglycemia.

Despite the proven efficacy and safety of insulin [2,3] barriers against its use exist such as concerns about hypoglycemia and weight gain. Harris et al. found that family physicians waited an average of 9.2 years before initiating insulin in patients with T2DM, at which point glycated hemoglobin (HbA1c) levels were well above target and diabetes-related complications had begun to develop [4]. Once insulin was initiated or intensified, 68% of patients were still above the HbA1c target of 7% and 20% of patients still had poor glycemic control (HbA1c>9.0%).

Insulin glargine 300 U/mL (Gla-300) is a once-daily long-acting basal insulin developed to improve glycemic control in type 1 and type 2 diabetes. Pharmacokinetic (PK) and pharmacodynamic (PD) action profiles of Gla-300 are more constant and prolonged compared with insulin glargine 100 U/mL (Gla-100), due to a more gradual and extended release of glargine from the subcutaneous depot. This translates into continued blood glucose control beyond 24 hours [5]. The clinical development program for Gla-300 included six Phase III studies, known as the EDITION program [6]. EDITION 1, 2 and 3 were studies comparing the efficacy and safety of Gla-300 with Gla-100 in people with T2DM using basal and mealtime insulin with metformin, basal insulin with oral antidiabetic drugs (OADs), and only OADs (insulin-naive), respectively [7-9]. A patient-level meta-

analysis of the three studies enabled glycemic control and hypoglycemia to be examined over 6 months in 2496 patients on a variety of background therapies [10]. The meta-analysis confirmed the results of the individual studies and showed that Gla-300 was as effective as Gla-100 in improving glycemic control with a lower risk of hypoglycemia at any time of day and during the night. The large dataset included in the meta-analysis provided increased validity to generalize the results across different populations with T2DM. However, a variety of factors that could influence treatment outcomes still need to be considered. The present analysis assessed geographic aspects by evaluating the consistency of effects seen with Gla-300 and Gla-100 in the North American and non-North American population. The analysis of these two populations was prompted by previous reports on regional differences in subjects' baseline characteristics and treatment outcomes [11-14]. For example, a meta-analysis of 17 randomized controlled trials associated intensive glycemic control in T2DM patients with increases in all-cause mortality, cardiovascular mortality, and severe hypoglycemia in North America but not in the rest of the world [15]. On the other hand, no significant difference in the effects of intensive glycemic control between regions was found in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial for any outcome, including mortality, vascular endpoints, and severe hypoglycemic episodes [16]. Furthermore, since practice guidelines and practice patterns for diabetes management vary by region [17,18], it is important to know if initiation of different types of basal insulin at various stages in diabetes management may lead to different effects on glycemic control in different regions. The present patient-level meta-analysis examined potential regional variations in efficacy and safety of Gla-300 and Gla-100 in North American and non-North American subjects with T2DM.

Subjects and Methods

Study design and participants

Full details of the methodology, participant selection, and endpoints of the EDITION 1, 2, and 3 studies have been published previously [7-9]. In brief, each of the three studies followed a multi-center, randomized, open-label, two-arm, parallel-group design. The studies were conducted in Europe (Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Latvia, Lithuania, Netherlands, Portugal, Romania, Russia, Slovakia, Spain, Sweden), Japan, North-America (Canada, Mexico, United States of America), South Africa, and South America (Chile). Participants with T2DM meeting the WHO diagnostic criteria [19] ≥18 years of age were included. Other inclusion criteria were current therapy with basal and mealtime insulin with or without metformin for at least 1 year in EDITION 1, treatment with basal insulin combined with OADs for at least 6 months in EDITION 2, or use of OADs (insulin-naïve) for at least 6 months in EDITION 3.

Each of the studies began with a 2-week screening period followed by a 6-month initial treatment period and a 6-month extension period. Only data from the 6-month initial treatment period are reported here. Protocols for all three studies were approved by the appropriate ethics committees. The studies were conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent. The studies were registered with ClinicalTrials.gov under the registration numbers NCT01499082 (EDITION 1), NCT01499095 (EDITION 2), and NCT01676220 (EDITION 3).

Randomization and masking

Patients were randomized (1:1 ratio) to receive either Gla-300 (Sanofi, Paris, France) or Gla-100 (Lantus [Sanofi]) administered subcutaneously once daily for 6 months. Randomization was performed using a centralized interactive voice or internet response system and was stratified by HbA1c at screening (<8.0 or ≥8.0% [<64 or ≥64 mmol/mol]) and, in EDITION 3, geographical region (non-Japan/Japan). Due to differences in injection devices, these were open-label studies.

Interventions

Study interventions were previously described in detail [7-9]. Briefly, Gla-300 or Gla-100 injections were to be given in the evening from before dinner to bedtime but at the same time for each participant throughout the study. The dosage was generally adjusted weekly to a target of fasting self-measured plasma glucose (SMPG) of 4.4 to 5.6 mmol/L (80 to 100 mg/dL).

Outcomes

Endpoints of the patient-level meta-analysis included change in HbA1c from baseline to Month 6 and percentage of patients at target HbA1c (<7% [53 mmol/mol] and <7.5% [58.5 mmol/mol]) at Month 6. Hypoglycemic events were categorized according to the American Diabetes Association definitions [20] and recorded as previously described [7-10]. In addition to the threshold of ≤3.9 mmol/L (70 mg/dL), hypoglycemic events with a plasma glucose concentration of <3.0 mmol/L (54 mg/dL) were analyzed separately. For the analysis of hypoglycemic events, confirmed events (with or without symptoms) and severe events were combined. The following hypoglycemia parameters were analyzed: number and percentages of participants with at least one hypoglycemic event occurring at any time of the day (24 hours) or during the night (nocturnal, 00:00 to 05:59 hours), cumulative number of hypoglycemic events per participant, as well as the number of events per participant-year (annualized rate). Further efficacy endpoints of the meta-analysis included change in body weight and insulin dose from baseline to Month 6. Adverse events were evaluated for an overview of safety.

Data analysis and statistics

The statistical analysis was performed as described previously [7-10] with some modifications. The change in HbA1c was analyzed using a mixed model for repeated measurements adjusted for region, region-by-treatment, region-by-visit and region-by-treatment-by-visit interactions as fixed effects. Insulin dose and body weight were analyzed descriptively. Body weight was further analyzed using an analysis of covariance (ANCOVA) model based on a meta-analysis with region and region-by-treatment interaction as fixed effects. For hypoglycemic events, analyses of rate ratio were based on an overdispersed Poisson regression model adjusted for randomization strata of screening HbA1c and region-by-treatment interaction as fixed effects and logarithm of the treatment-emergent period as offset. Analyses of relative risk were based on the Cochran-Mantel-Haenszel method stratified by randomization strata of screening HbA1c. Cumulative mean number of hypoglycemic events by participant was analyzed using Nelson-Aalen estimates. Descriptive statistics were

used for adverse events. Analyses were performed using the randomized, the safety, and the modified intention-to-treat (mITT) populations. The randomized population was defined as all screened patients who originally met inclusion criteria and signed the informed consent allocated to a treatment arm and recorded in the database. The safety population was defined as all patients randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered. The mITT population included all randomized patients who received at least one dose of study drug and had both a baseline and at least one post-baseline assessment of any efficacy variables available.

It should be noted that a pooled analysis of only the EDITION 2 and EDITION 3 studies was pre-specified in the statistical analysis plans. However, the consistent design and results allowed a pooled analysis of all three studies [10]. The present analysis of the regional sub-populations of EDITION 1, 2 and 3 was not pre-specified and should be considered exploratory. Therefore, adjustments were not made for multiple testing.

Results

Study population

Out of the global population included in the pooled analysis of the three EDITION studies (N=2496), 1247 participants were randomized to Gla-300 and 1249 were randomized to Gla-100. A total of 1420 participants were from North America (Gla-300, N=700; Gla-100, N=720), 1076 were from other countries (Gla-300, N=547; Gla-100, N=529). The safety population included 1414 participants in the North American sub-population (Gla-300, N=695; Gla-100, N=719) and 1074 in the non-North American subpopulation (Gla-300, N=547; Gla-100, N=527). A total of 1402 North Americans (Gla-300, N=692; Gla-100, N=710) and 1072 non-North Americans (Gla-300, N=547; Gla-100, N=525) were included in the mITT population. Demographics and baseline characteristics of the North American and non-North American participants in the pooled analysis population (all three studies) are shown in Table 1.

	North-American		Non-North-American	
	Gla-300 N=700	**Gla-100 N=720**	**Gla-300 N=547**	**Gla-100 N=529**
Age (years)	58.5 (9.7)	58.0 (10.2)	58.9 (8.6)	59.2 (8.4)
Age: ≥65 years, n (%)	197 (28.1)	196 (27.2)	132 (24.1)	137 (25.9)
Gender: male, n (%)	395 (56.4)	416 (57.8)	262 (47.9)	233 (44.0)
Race, n (%)				
Caucasian/White	584 (83.4)	603 (83.8)	512 (93.6)	492 (93.0)
Black	88 (12.6)	92 (12.8)	2 (0.4)	2 (0.4)
Asian/Oriental	20 (2.9)	17 (2.4)	28 (5.1)	32 (6.0)
Other	8 (1.1)	8 (1.1)	5 (0.9)	3 (0.6)
Ethnicity, n (%)				
Hispanic	128 (18.3)	132 (18.4)	88 (16.1)	89 (16.8)
Not Hispanic	572 (81.7)	587 (81.6)	459 (83.9)	440 (83.2)
Weight, kg	102.8 (23.8)	103.7 (22.2)	96.1 (20.9)	94.7 (19.9)
BMI, kg/m^2	35.4 (7.2)	35.5 (6.8)	33.8 (6.4)	33.9 (5.8)
Duration of diabetes, years	13.0 (7.6)	12.7 (7.8)	12.4 (6.8)	12.6 (7.0)
Duration of basal insulin, years[a]	5.4 (4.7)	5.2 (4.7)	5.1 (4.3)	5.1 (3.9)
Prior use of insulin glargine, n (%)[a]	345 (90.8)	375 (94.9)	328 (77.4)	322 (79.5)
Previous basal insulin dose, U/kg[a]	0.7 (0.3)	0.7 (0.3)	0.6 (0.2)	0.6 (0.2)

Values are mean (SD) unless otherwise stated. Abbreviations: BMI, Body Mass Index; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL. [a]In patients previously using insulin.

Table 1: Baseline characteristics of all randomized participants.

Glycemic control

HbA1c decreased from baseline to Month 6 to a similar extend in all groups: In North American participants, the least squares (LS) mean change from baseline was -0.99% (SE 0.036) with Gla-300 and -1.00% (SE 0.036) with Gla-100. In non-North Americans, mean HbA1c decreased by -1.05% (SE 0.039) in the Gla-300 group and by -1.04% (SE 0.040) in the Gla-100 group (Table 2). Mean decline in HbA1c from baseline to Month 6 was comparable for Gla-300 and Gla-100 in both regions (no evidence of heterogeneity of treatment effect across subgroups, P=0.8347). At Month 6, the LS mean difference between

Gla-300 and Gla-100 in the change of HbA1c was 0.00 (95% confidence interval [CI] -0.094 to 0.104)% in the North American population and -0.01 (95% CI -0.120 to 0.099)% in non-North American participants (Table 2). HbA1c <7% (53.0 mmol/mol) was achieved by 36.4 and 34.2% of North-American participants receiving Gla-300 and Gla-100, respectively (Table 2). In the non-North American population the percentages were 36.0% with Gla-300 and 37.1% with Gla-100 (P for subgroup-by-treatment interaction=0.350). Over 50% of participants reached HbA1c <7.5% (58.5 mmol/mol) in both treatment groups with no noted regional differences (P for subgroup-by-treatment interaction=0.719).

	North American		Non-North American		P-value[a]
	Gla-300 N=692	Gla-100 N=710	Gla-300 N=547	Gla-100 N=525	
HbA1c, %					
Baseline mean	8.33	8.34	8.26	8.28	
Month 6 mean	7.24	7.25	7.27	7.29	
LS mean change (SE)	-0.99 (0.036)	-1.00 (0.036)	-1.05 (0.039)	-1.04 (0.040)	
LS mean difference (95% CI)	0.00 (-0.094 to 0.104)		-0.01 (-0.120 to 0.099)		0.8347
Participants at target HbA1c at Month 6, n (%)					
HbA1c <7% (53.0 mmol/mol)	252 (36.4)	243 (34.2)	197 (36.0)	195 (37.1)	0.35
HbA1c <7.5% (58.5 mmol/mol)	362 (52.3)	368 (51.8)	309 (56.5)	285 (54.3)	0.719

Abbreviations: Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; LS, least squares; mITT, modified intention-to-treat. [a]P-value for subgroup by treatment interaction.

Table 2: HbA1c outcomes (mITT population).

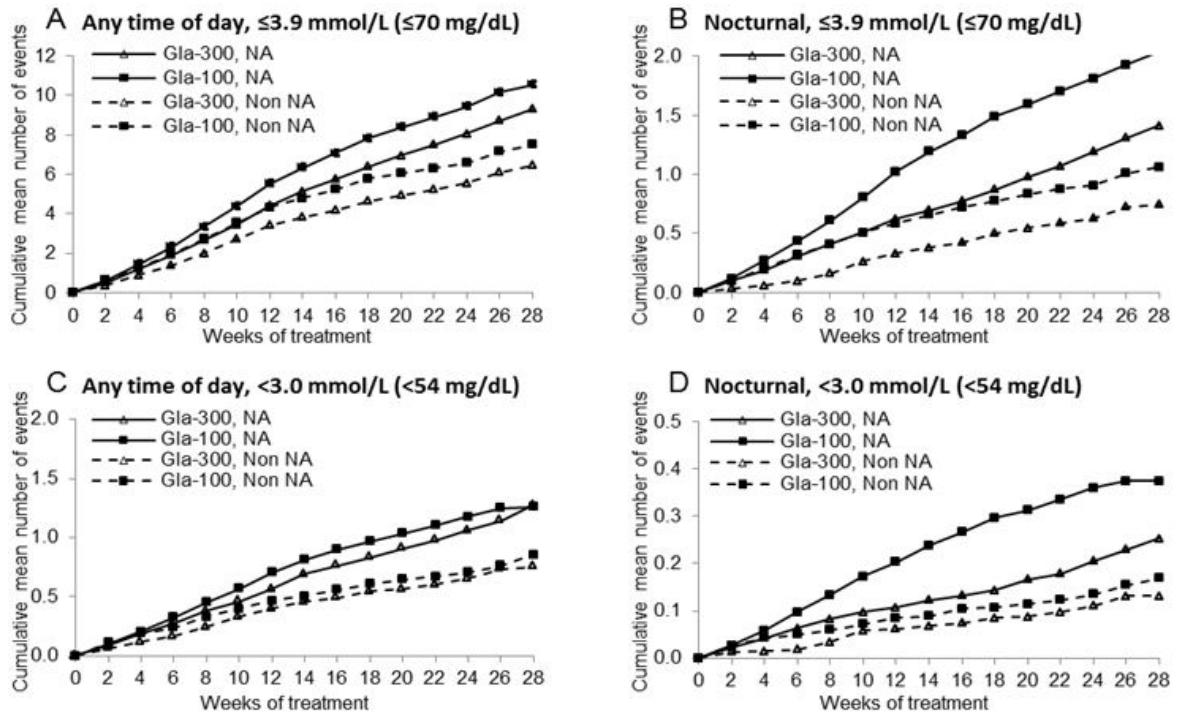

Figure 1: Cumulative mean number of confirmed or severe hypoglycemic events (A, C) at any time of day (24 hours) and (B, D) during the night (00:00-05:59 hours) for pooled analysis of all three studies (safety population). Hypoglycemia was confirmed by a plasma glucose concentration of (A, B) ≤3.9 mmol/L (≤70 mg/dL) and (C, D) <3.0 mmol/L (<54 mgl/dL). Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; NA, North American; Non NA, Non-North American.

Hypoglycemia

The cumulative number of confirmed (≤3.9 mmol/L and <3.0 mmol/L) or severe hypoglycemia occurring at any time (24 hours) or at night (nocturnal, 00:00 to 05:59 hours) was lower with Gla-300 compared with Gla-100 (Figure 1). This was consistent for North American and non-North American participants. At month 6, the incidence of confirmed or severe hypoglycemia at any time (24 hours) and during the night (00:00-05:59 hours) was lower with Gla-300 versus (vs) Gla-100 at the ≤3.9 and <3.0 mmol/L threshold and was not affected by the region (North America vs non-North America, no evidence of heterogeneity effect across subgroups, P>0.05).

The annualized rates (events per participant-year) of confirmed or severe hypoglycemia at any time of the day (24 hours) and during the night (00:00 - 05:59 hours) were lower with Gla-300 compared with Gla-100 at the ≤3.9 and <3.0 mmol/L threshold regardless of the region (no evidence of heterogeneity effect across subgroups, P>0.05; Figure 2).

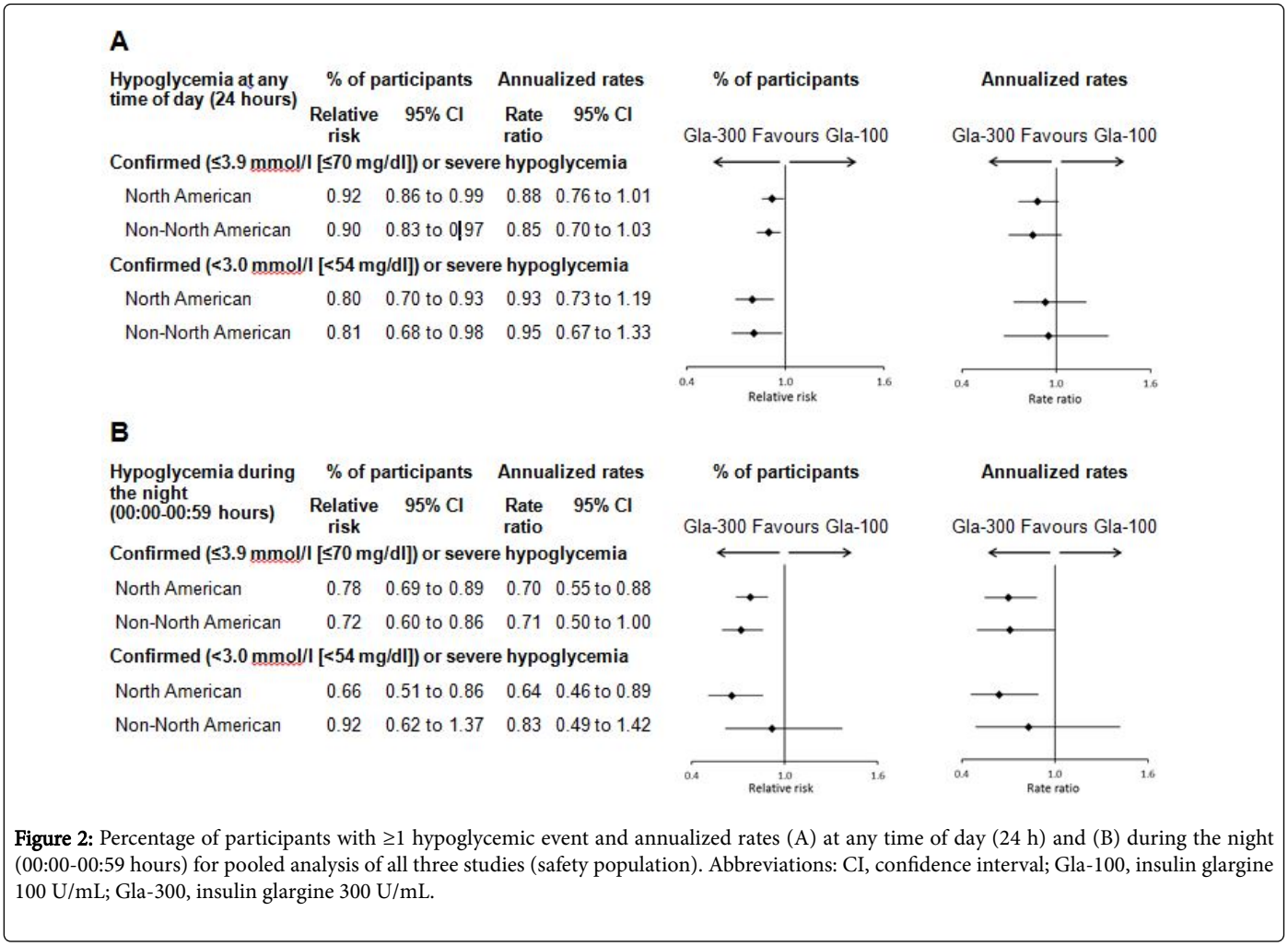

Figure 2: Percentage of participants with ≥1 hypoglycemic event and annualized rates (A) at any time of day (24 h) and (B) during the night (00:00-00:59 hours) for pooled analysis of all three studies (safety population). Abbreviations: CI, confidence interval; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL.

Body weight

The change in weight over the course of the study is shown in Figure 3A. The treatment effect on weight was significantly different between North American and non-North American participants (P for treatment-by-subgroup interaction=0.0496). North American participants entered the EDITION 1, 2, and 3 studies with a higher weight and BMI than their non-North American counterparts (Table 1).

At Month 6, North American participants receiving Gla-300 had gained less weight than those receiving Gla-100 (LS mean change 0.64 [SE 0.13] vs 1.15 [SE 0.13] kg). The LS mean difference between the two treatment groups was 0.51 (95% CI 0.86 to 0.15) kg.

In non-North American participants the increase in body weight was comparable between the Gla-300 and Gla-100 groups (LS mean change 0.36 [SE 0.15] vs 0.32 [SE 0.15] kg), with a LS mean difference between the two treatment groups of 0.03 (95% CI -0.37 to 0.43) kg. The weight gain in Gla-300 treated participants was comparable between North Americans and non-North Americans (LS mean change 0.64 and 0.36 kg, respectively).

Insulin dose

Absolute basal insulin doses increased from 48.84 and 50.87 U/day to 87.63 and 80.96 U/day in North-American participants treated with Gla-300 and Gla-100, respectively. In non-North American participants, basal insulin doses increased from 50.45 U/day to 83.00 U/day with Gla-300 and 49.88 U/day to 71.36 U/day with Gla-100.

Daily basal insulin doses per kg body weight with Gla-300 vs Gla-100 after 6 months were 0.85 vs 0.77 U/kg/day in North American participants and 0.84 vs 0.75 U/kg/day in non-North American participants, representing a 10.4% and 12.0% higher dose with GLA-300 in North American and non-North American participants, respectively (Figure 3B).

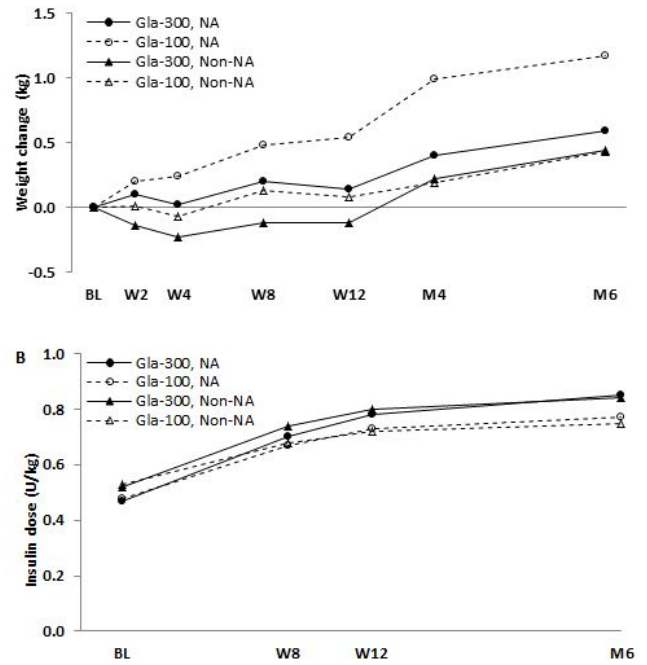

Figure 3: (A) Body weight change by visit during the 6-month treatment period for pooled analysis of all three studies (descriptive statistics, safety population). (B) Insulin dose by visit during the 6-month treatment period for pooled analysis of all three studies (descriptive statistics, modified intention-to-treat population). Abbreviations: BL, baseline; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; M, month; W, week.

Adverse events

Both Gla-300 and Gla-100 were well tolerated with a numerically higher rate of adverse events in the North American population (Table 3).

The higher incidences of adverse events in North Americans vs non-North Americans were seen across the different system organ classes (SOCs), but were especially obvious in the SOC infections and infestations (36.1 vs 23.3%), mainly driven by a higher incidence of upper respiratory tract infections (8.5% vs 1.7%).

The number of treatment-emergent serious adverse events was low and comparable between both treatment arms regardless of the region. Likewise, the percentage of participants discontinuing due to adverse events was low and similar between treatment groups, irrespective of the region.

	North-American		Non-North American	
	Gla-300 (N=695)	**Gla-100 (N=719)**	**Gla-300 (N=547)**	**Gla-100 (N=527)**
Patients with, n (%)				
Any TEAE	466 (67.1%)	449 (62.4%)	246 (45.0%)	220 (41.7%)
Any treatment-emergent SAE	38 (5.5%)	36 (5.0%)	27 (4.9%)	26 (4.9%)
Any TEAE leading to death	1 (0.1%)	0	3 (0.5%)	3 (0.6%)
Any TEAE leading to permanent treatment discontinuation	11 (1.6%)	10 (1.4%)	6 (1.1%)	6 (1.1%)
Abbreviations: Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; TEAE, treatment-emergent adverse event; SAE, serious adverse event				

Table 3: Overview of treatment-emergent adverse events (safety population).

Discussion

The use of basal insulin is considered an essential component for management of T2DM when HbA1c targets cannot be achieved [21]. However, variations in diabetes management strategies, degrees of achieved glycemic control, and utilization rates of insulin exist among regions of the world [17,18]. Gla-300 is an attractive option for diabetes treatment as it has been shown to provide a more even steady-state activity profile and longer glycemic control than Gla-100 [22]. The current patient-level meta-analysis demonstrated that Gla-300 is as effective as Gla-100 in improving glycemic control and reducing hypoglycemia in a large population of patients with T2DM on different background therapies, both within and outside of North America.

EDITION 1, 2, and 3 were large-scale clinical studies to evaluate the efficacy and safety of Gla-300 in a broad and diverse population of people with T2DM over a period of 6 months. Combining the datasets of the three studies provided a population size large enough to thoroughly investigate the effects of Gla-300 across all background therapies as well as in special sub-populations. The present post-hoc analysis assessed the consistency of glycemic control and hypoglycemia in the North American sub-population compared to the non-North American population.

The effectiveness of Gla-300 with regard to glycemic control has been shown in the individual EDITION studies as well as in the meta-analysis of the three studies combined [7-10]. The present post-hoc analysis confirms the improvement in glycemic control with a reduction in HbA1c of approximately -1% which was consistent and comparable in North American and non-North American participants. However, this required an increase of about 10% in the dose of Gla-300. The units per kg of insulin required were comparable in North American and non-North American participants. The mean HbA1c at Month 6 was between 7.2 and 7.3% in all groups, suggesting appropriate titration of basal insulin across the different geographical regions.

In the overall pooled analysis of EDITION 1, 2 and 3 the relative reduction in rate of confirmed (≤3.9 mmol/L [70 mg/dL]) or severe hypoglycemia during the night (00:00 to 05:59 hours) was 31% with Gla-300 compared to Gla-100 [10]. The present analysis confirmed these findings with relative differences in rates of 30% in North American and 29% in non-North American participants. Thus, the

lower risk of confirmed (≤3.9 mmol/L [70 mg/dL]) or severe hypoglycemia during the night with Gla-300 vs Gla-100 was consistent regardless of the region. Similarly, the rate of confirmed (≤3.9 mmol/L [70 mg/dL]) or severe hypoglycemia at any time of the day (24 hours) was reduced with Gla-300 vs Gla-100 with a relative difference of 12% in North American and 15% in non-North American participants. The corresponding relative difference in rate was 14% in the overall pooled analysis [10]. The lower percentage of participants experiencing hypoglycemia and the reduction in annualized rate of hypoglycemia with Gla-300 vs Gla-100 provide a clinically relevant benefit. Episodes of hypoglycemia are associated with various complications, reduced quality of life, and are a significant part of the health care costs associated with the disease [23,24]. Furthermore, the fear of hypoglycemia has been shown to be a major barrier to starting insulin therapy in patients with diabetes mellitus [25-27]. Thus, the effects seen with Gla-300 across different geographical regions are encouraging and suggest that Gla-300 may have an important value as part of the treatment regimen for T2DM.

Participants who received Gla-300 in the three EDITION studies gained less weight compared with those who received Gla-100 (LS mean difference -0.28 kg, 95% CI -0.55 to -0.01, P=0.039) [10]. The present subgroup analysis revealed that this difference seems to be mainly driven by a significantly higher weight gain in North American participants on Gla-100. The reason for this increased weight gain is unclear, but might be related to different dietary patterns among the two regions. Nevertheless, regional differences did not have an influence on weight when Gla-300 was used, since weight increased by less than 1 kg in both North American and non-North American participants on Gla-300. The risk of weight gain is one of the major concerns that delay timely introduction or intensification of insulin therapy [28-30]. Consequently, the observed neutral effect of Gla-300 on weight is promising and warrants further investigation. One of the possible causes may be the more even PK and PD profile and longer duration of action of Gla-300, extending glucose control well beyond 24 hours [22]. It has been suggested that the PK profiles of traditional intermediate-acting human insulin which show a pronounced peak effect [31] may potentiate nocturnal hypoglycemia, compensatory eating behavior, and glucose variability that lead to weight gain [29]. Gla-300 provides predictable and stable 24-hour glycemic control as a result of low fluctuation (low within-day variability) and high reproducibility (low between-day variability) in insulin exposure [32] which may preclude adverse effects like hypoglycemia and associated weight gain.

A basal insulin dose increase in both treatment groups over the study period was observed [10]. The increase in dose was higher in the Gla-300 arm and was comparable in both the North American and non-North American population. The reason for the higher daily dose required with Gla-300 remains unclear. One hypothesis is that it might be due to the slightly lower bioavailability of Gla-300 related to a longer subcutaneous deposition time and degradation by tissue peptidases [7]. The additional insulin did not result in increased hypoglycemia or weight gain which would be in keeping with that hypothesis.

As with the pooled analysis [10], the strengths of the present analysis include the large number of enrolled participants and the similarities between the individual studies in terms of design. Limitations include the open-label nature of the protocols and the short duration. In addition, dividing the overall participant pool into a North American and non-North American population is rather broad and does not account for differences such as race and ethnicity within those two populations. Limited power due to small numbers precluded assessment of differences between smaller sub-divisions of the North American and non-North American populations. Furthermore, the present analysis was post-hoc and the results should therefore be interpreted with caution.

In summary, the present patient-level meta-analysis of the EDITION 1, 2, and 3 studies showed that Gla-300 provides comparable glycemic control to Gla-100 in North American and non-North American people with T2DM, with consistently less hypoglycemia at any time of the day and during the night. The utility of Gla-300 was not different in diverse populations or affected by different regional aspects of treating diabetes.

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Author Contributions

I Hramiak, Z Punthakee, M Groleau, P Javadi, and V Woo participated in the development of the analysis plan, interpretation of the results, and article writing. G. Bigot performed the statistical analysis and reviewed the article. All authors had full access to the meta-analysis data and had final responsibility to submit the article for publication.

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