Efficacy and Safety of Insulin Glargine 300 Units/mL (Gla-300) Versus Insulin Glargine 100 Units/mL (Gla-100) in Children and Adolescents (6–17 years) With Type 1 Diabetes: Results of the EDITION JUNIOR Randomized Controlled Trial

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Diabetes Care 2020;43:1512–1519 | https://doi.org/10.2337/dc19-1926

OBJECTIVE

To compare efficacy and safety of insulin glargine 300 units/mL (Gla-300) and 100 units/mL (Gla-100) in children and adolescents (6–17 years old) with type 1 diabetes.

RESEARCH DESIGN AND METHODS

EDITION JUNIOR was a noninferiority, international, open-label, two-arm, parallel-group, phase 3b trial. Participants were randomized 1:1 to Gla-300 or Gla-100, titrated to achieve fasting self-monitored plasma glucose levels of 90–130 mg/dL (5.0–7.2 mmol/L), with continuation of prior prandial insulin. The primary end point was change in HbA_{1c} from baseline to week 26. Other assessments included change in fasting plasma glucose (FPG), hypoglycemia, hyperglycemia with ketosis, and adverse events.

RESULTS

In 463 randomized participants (Gla-300, $n = 233$; Gla-100, $n = 230$), comparable least squares (LS) mean (SE) reductions in HbA_{1c} were observed from baseline to week 26 (−0.40% [0.06%] for both groups), with LS mean between-group difference of 0.004% (95% CI −0.17 to 0.18), confirming noninferiority at the prespecified 0.3% (3.3 mmol/mol) margin. Mean FPG change from baseline to week 26 was also similar between groups. During the 6-month treatment period, incidence and event rates of severe or documented (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia were similar between groups. Incidence of severe hypoglycemia was 6.0% with Gla-300 and 8.8% with Gla-100 (relative risk 0.68 [95% CI 0.35–1.30]). Incidence of any hyperglycemia with ketosis was 6.4% with Gla-300 and 11.8% with Gla-100.

CONCLUSIONS

Gla-300 provided similar glycemic control and safety profiles to Gla-100 in children and adolescents with type 1 diabetes, indicating that Gla-300 is a suitable therapeutic option in this population.

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Received 27 September 2019 and accepted 20 April 2020

Clinical trial reg. no. NCT02735044, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.12174711.

Tight glycemic control in individuals with type 1 diabetes can delay the onset or slow the progression of microvascular and macrovascular complications (1,2). In children and adolescents with type 1 diabetes, hyperglycemia may also be associated with changes in brain gray matter and white matter (3,4). Minimizing the risk of hypoglycemia is also important, as it is associated with a number of complications, including altered autonomic responses, loss of consciousness, coma, or convulsions (5,6) and, in children and adolescents with type 1 diabetes, alterations in spacial memory and acute complications, including dead-in-bed syndrome (7,8). Moreover, fear of hypoglycemia can cause anxiety and changes in self-management behaviors, potential barriers to euglycemia, and affects many aspects of patients' and family members' lives (9). Consequently, optimal insulin therapy options for children and adolescents with diabetes should provide effective glycemic control while minimizing the risk of hypoglycemia and hyperglycemia.

Insulin glargine 100 units/mL (Gla-100) is a long-acting human insulin analog approved for use in children in the U.S. and Europe (10,11). While the prolonged duration of action of Gla-100 provided effective once-daily dosing in most people with diabetes, there was evidence of waning around 24 h in some patients with type 1 diabetes (12).

Insulin glargine 300 units/mL (Gla-300) is a second-generation basal insulin analog with improved pharmacokinetic and pharmacodynamic properties compared with Gla-100 (13,14). In the pivotal EDITION series of randomized controlled trials, Gla-300 provided glycemic control comparable with that of Gla-100 in adults with type 1 or type 2 diabetes, in addition to a lower risk of hypoglycemia in adults with type 2 diabetes and similar hypoglycemia risk in adults with type 1 diabetes (15–20). Gla-300 also provides a prolonged duration of activity (beyond 24 h) compared with Gla-100, which may facilitate flexibility in dosing without the need for two daily injections (13,21).

Consequently, the EDITION JUNIOR study was undertaken to compare the efficacy and safety of Gla-300 with those of Gla-100 in children and adolescents aged 6–17 years with type 1 diabetes. Studies in these age-groups are important to evaluate safety, and to account for the unique clinical characteristics of children and adolescents with type 1 diabetes, such as insulin sensitivity and the ability to provide self-care (3,22).

RESEARCH DESIGN AND METHODS

Study Design

EDITION JUNIOR (NCT02735044) was an open-label, randomized, two-arm, parallel-group, phase 3b international study comparing Gla-300 with Gla-100 in children and adolescents with type 1 diabetes. Participants were screened at 105 clinical centers across 24 countries (Argentina, Brazil, Bulgaria, Canada, Chile, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Latvia, Macedonia, Mexico, Poland, Romania, Russian Federation, Serbia, Spain, Sweden, U.K., and U.S.). The study consisted of a 2-week screening period, followed by a 26-week efficacy and safety treatment period, a further 26-week safety extension period, and ending with a 4-week follow-up period. The study protocol was approved by the respective independent ethics committees or institutional review boards of all participating clinical centers and was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice.

Inclusion and Exclusion Criteria

Inclusion criteria were children and adolescents aged between 6 and 17 years, with type 1 diabetes for ≥1 year with previous receipt of basal insulin plus fast-acting insulin therapy, with an HbA_{1c} between ≥7.5% and ≤11.0% (amended from the initial HbA_{1c} inclusion criteria of ≥7.5% and ≤10.0%, to facilitate recruitment). Written or oral informed assent was obtained from each participant, and written informed consent was obtained from the parent(s) or legal guardian according to the regulatory and legal requirements of the participating country.

Key exclusion criteria included the use of premix insulins or human insulin with meals in the 3 months prior to screening, use of an insulin pump 6 months before the screening visit or plans to switch to pump treatment within the 6 months after screening, use of any other glucose-lowering agent in the 3 months prior to screening, use of systemic glucocorticoids for ≥1 week in the 3 months prior to screening, hospitalization for diabetic ketoacidosis or a history of severe hypoglycemia accompanied by seizure or unconsciousness in the 3 months prior to screening, and presence of a severe or unstable, clinically relevant nondiabetes disorder or mental condition that would impede the implementation of the study protocol or interfere with the evaluation of study medication.

Randomization

Participants were randomized 1:1 to Gla-300 (Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) or Gla-100 (Sanofi-Aventis) treatment. Randomization was stratified at screening by HbA_{1c} (<8.5% and ≥8.5%) and by age (<12 years and ≥12 years), configured to ensure that ≥30% of participants would be <12 years of age.

Treatment

Gla-300 and Gla-100 were self-administered or administered by the parent or guardian as a once-daily subcutaneous injection either in the morning or evening. Once the time of day was determined for dosing, each dose was to be administered at the same time each day to maintain an interval at or close to 24 h between doses. The starting dose of Gla-300 or Gla-100 was the same as the median of the total daily basal insulin doses in the 3 days before the baseline visit, or, if basal insulin (such as NPH insulin or insulin detemir) was used more than once daily, the starting dose was ~20% less than the previous median total daily dose. As summarized in Supplementary Table 1, dose of either insulin was titrated to a fasting self-monitored plasma glucose (SMPG) target of 90–130 mg/dL (5.0–7.2 mmol/L), with avoidance of hypoglycemia. Doses were adjusted weekly, but no more than every 3–4 days, with best efforts made to complete uptitration by 6–12 weeks. Fast-acting mealtime insulin analogs were continued during the study. The starting dose of prandial insulin was the same as at baseline, and doses were titrated at the discretion of the physician to a 2-h postprandial SMPG target of <180 mg/dL (<10.0 mmol/L), with avoidance of hypoglycemia.

Outcome Measures

The primary efficacy end point was change in HbA_{1c} from baseline to week 26. Secondary efficacy end points included change from baseline to week

26 in fasting plasma glucose (FPG), the percentage of participants reaching target HbA_{1c} of <7.5% (58 mmol/mol) at week 26 or target FPG of ≤130 mg/dL (≤7.2 mmol/L) at week 26. These were accompanied by composite end points of glycemic target achievement without documented (<54 mg/dL [<3.0 mmol/L]) or severe hypoglycemia during the last 3 months of the 6-month randomized period. Change from baseline to week 26 in prebreakfast SMPG was included as an exploratory efficacy end point.

Safety end points included hypoglycemic events at the ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L) blood glucose thresholds, defined in line with American Diabetes Association, European Association for the Study of Diabetes, and International Society of Pediatric and Adolescent Diabetes recommendations (5,22–25). Other safety end points included events of hyperglycemia with ketosis. Biochemical analyses were self-measured by ketone meter and glucose meter; meters and relevant equipment (e.g., lancets and test strips) were provided for each participant and were the same across all sites. Ketones were measured when: SMPG was ≥252 mg/dL (≥14 mmol/L) in an unwell child; or when SMPG remained ≥252 mg/dL (≥14 mmol/L) without substantial decline ~60–120 min after an additional dose of rapid-acting insulin; or during illness with fever or vomiting, irrespective of the SMPG value. Incidence of treatment-emergent adverse events (TEAE) was also analyzed.

Data Analyses

Efficacy analyses were performed in the intent-to-treat (ITT) population, defined as all randomized participants regardless of treatment adherence and analyzed according to the treatment allocated by randomization. The safety population was defined as the randomized population who received one or more doses of Gla-300 or Gla-100, analyzed according to treatment received. The sample size of 225 randomized participants for each treatment was selected to ensure that the upper bound of the two-sided 95% CI for the adjusted mean HbA_{1c} difference between Gla-300 and Gla-100 would not exceed a noninferiority margin of 0.3% (3.3 mmol/mol as per regulatory guidance (26,27)) with at least 92% power. The calculation assumed a common SD of 0.95% with a one-sided test at the 2.5 significance level and a true difference of 0% in HbA_{1c} between treatment groups.

All efficacy end points were analyzed during the main 6-month randomized period, i.e., regardless of treatment discontinuation. The primary efficacy end point of change from baseline to week 26 in HbA_{1c} was assessed with ANCOVA using fixed categorical effects of treatment group, randomization stratum of age-group at screening visit (<12 years and ≥12 years), and continuous fixed covariates of baseline HbA_{1c} value. Prior to ANCOVA, a multiple imputation approach was used to handle missing data, where missing values were modeled on data from patients in the same treatment groups for whom change in HbA_{1c} data were available, according to whether the patient permanently discontinued therapy during the main 6-month randomized period or not. Least squares (LS) mean and LS mean differences between groups were combined using the Rubin formula. The primary end point analyses used a stepwise testing approach: firstly, noninferiority of Gla-300 versus Gla-100 in HbA_{1c} reduction from baseline to week 26 was assessed using a noninferiority margin of 0.3% (3.3 mmol/mol); secondly, a test for superiority was performed if noninferiority was demonstrated. Tests for the primary end point were performed one-sided at the level $\alpha = 0.025$. HbA_{1c} change from baseline to week 26 was also analyzed according to the following baseline subgroups: age-group (<12 and ≥12 years), screening HbA_{1c} (<8.5% and ≥8.5%), sex, race, ethnicity (Hispanic and not Hispanic), geographic region (North America, South/Latin America, Western Europe, Eastern Europe, and rest of the world), baseline BMI percentile, baseline standard Tanner puberty stage (prepubertal, adolescent, and adult) (Supplementary Table 2), baseline estimated glomerular filtration rate categories (mL/min/1.73 m^2; 60 to <90, ≥90), and duration of diabetes (<2, 2 to <5, and ≥5 years).

Change in FPG was assessed using a similar approach to that of the primary HbA_{1c} analysis, with the addition of randomization stratum of screening HbA_{1c} (<8.5% and ≥8.5%) in the model. The lower limit of quantification for the FPG measurements was 5.05 mg/dL (0.28 mmol/L); values less than this limit were imputed per convention, as the limit of quantification divided by 2. Other continuous secondary end points were analyzed with an ANCOVA model including treatment group, randomization stratum of screening HbA_{1c} (<8.5 and ≥8.5%), and randomization stratum of age-group at screening visit (<12 and ≥12 years) and the baseline end point value as a covariate. Categorical end point analyses, including the proportion of participants achieving glycemic targets and the proportion of participants experiencing hypoglycemia, were analyzed using the Cochran-Mantel-Haenszel method with treatment group as factor, stratified on randomization strata. Event rates of hypoglycemia were analyzed using a negative binomial regression model. Safety end points were analyzed descriptively during the main 6-month on-treatment period, defined as the period from first basal insulin treatment up to the month 6 visit or up to 2 days after the last treatment dose—whichever came first.

RESULTS

Study Participants

As shown in Supplementary Fig. 1, 616 participants were screened for eligibility in the study, of whom 463 were randomized 1:1 to receive Gla-300 (n = 233) or Gla-100 (n = 230) (ITT population). In the main 6-month treatment period, 233 participants were exposed to Gla-300 and 228 participants were exposed to Gla-100 (safety population) (Supplementary Fig. 1). Across both groups, a high and comparable percentage of participants completed the main 6-month treatment period (Gla-300, 96.6%; Gla-100, 93.9%), and 6-month safety extension period (Gla-300, 93.1%; Gla-100, 90.0%). Baseline characteristics and demographics were generally well balanced (Table 1).

Glycemic Control and Insulin Dose

Baseline HbA_{1c} and FPG levels were similar in the two treatment groups (Table 1). Mean HbA_{1c} decreased similarly in both treatment groups from baseline to week 26 (Fig. 1*A*); LS mean (SE) decreases in HbA_{1c} from baseline to week 26 for Gla-300 and Gla-100 were virtually identical: −0.40% (0.06%) and −0.40% (0.06%), respectively (Fig. 1*B*). Specifically, the LS mean difference between Gla-300 and Gla-100 in change in HbA_{1c} from baseline to week 26 was 0.004% (95% CI −0.17 to 0.18), with the upper bound of the 95% CI (0.18) lower than the predefined noninferiority

Table 1—Baseline characteristics (randomized population)

	Gla-300	Gla-100	All
N	233	230	463
Age, years	12.9 (2.9)	12.9 (2.9)	12.9 (2.9)
Race, *n* (%)			
Number	232	226	458
White	211 (90.9)	211 (93.4)	422 (92.1)
Black or African American	8 (3.4)	6 (2.7)	14 (3.1)
Asian	11 (4.7)	6 (2.7)	17 (3.7)
Japanese	9 (3.9)	6 (2.7)	15 (3.3)
Multiple, *n* (%)	2 (0.9)	2 (0.9)	4 (0.9)
American Indian or Alaska Native/ black or African American, *n* (%)	1 (0.4)	0	1 (0.2)
Black or African American/white, *n* (%)	1 (0.4)	2 (0.9)	3 (0.7)
Unknown, *n* (%)	0	1 (0.4)	1 (0.2)
Ethnicity, *n* (%)			
Number	233	230	463
Hispanic or Latino	63 (27.0)	77 (33.5)	140 (30.2)
Not Hispanic or Latino	168 (72.1)	150 (65.2)	318 (68.7)
Not reported	2 (0.9)	3 (1.3)	5 (1.1)
Baseline BMI percentile	67.52 (26.62)	69.13 (26.64)	68.32 (26.61)
Baseline Tanner puberty stage evaluation, *n* (%)			
Number	232	229	461
Prepubertal	56 (24.1)	66 (28.8)	122 (26.5)
Adolescent	121 (52.2)	103 (45.0)	224 (48.6)
Adult	55 (23.7)	60 (26.2)	115 (24.9)
Duration of type 1 diabetes (years)	5.7 (3.4)	5.6 (3.2)	5.7 (3.3)
Median	5.2	4.9	5.1
Q1, Q3	2.9, 7.7	3.2, 7.5	3.1, 7.6
Minimum, maximum	1.0, 17.1	1.0, 15.8	1.0, 17.1
Age at onset of type 1 diabetes (years)	7.71 (3.47)	7.76 (3.43)	7.74 (3.45)
Median	7.81	7.94	7.82
Q1, Q3	5.1, 10.3	5.2, 10.2	5.2, 10.3
Minimum, maximum	0.4, 15.0	0.6, 15.5	0.4, 15.5
Previous BI daily dose (units/kg)	0.48 (0.19)	0.50 (0.22)	0.49 (0.21)
Median	0.44	0.45	0.45
Q1, Q3	0.34, 0.58	0.35, 0.59	0.35, 0.58
Minimum, maximum	0.05, 1.15	0.13, 1.75	0.05, 1.75
Previous mealtime insulin daily dose (units/kg)	0.49 (0.23)	0.48 (0.24)	0.48 (0.23)
Median	0.48	0.48	0.48
Q1, Q3	0.32, 0.61	0.32, 0.61	0.32, 0.61
Minimum, maximum	0.00, 1.35	0.00, 1.44	0.00, 1.44
HbA_{1c} (%)	8.65 (0.88)	8.61 (0.87)	8.63 (0.88)
Median	8.55	8.50	8.50
Q1, Q3	8.0, 9.2	7.9, 9.2	7.9, 9.2
Minimum, maximum	7.0, 13.1	6.9, 11.3	6.9, 13.1
HbA_{1c} (mmol/mol)	71.09 (9.65)	70.60 (9.50)	70.85 (9.57)
Median	69.95	69.41	69.41
Q1, Q3	63.94, 77.06	62.85, 77.06	62.85, 77.06
Minimum, maximum	53.0, 119.7	51.9, 100.0	51.9, 119.7
FPG (mmol/L)*	11.25 (5.01)	11.35 (5.07)	11.30 (5.03)
Median	11.13	11.17	11.17
Q1, Q3	7.23, 14.79	7.55, 14.56	7.47, 14.65
Minimum, maximum	0.1, 23.6	1.5, 25.3	0.1, 25.3
FPG (mg/dL)*	202.70 (90.31)	204.51 (91.28)	203.60 (90.70)
Median	200.41	201.23	201.23
Q1, Q3	130.25, 266.40	136.00, 262.30	134.57, 264.00
Minimum, maximum	2.5, 425.0	27.0, 455.0	2.5, 455.0

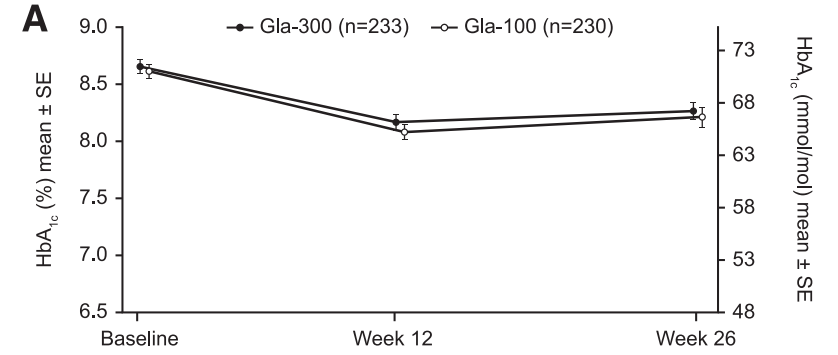
Data are mean (SD) unless otherwise stated. BI, basal insulin. *FPG values below the lower limit of quantification (<0.28 mmol/L [<5.05 mg/dL]) were imputed as 0.14 mmol/L (2.52 mg/dL).

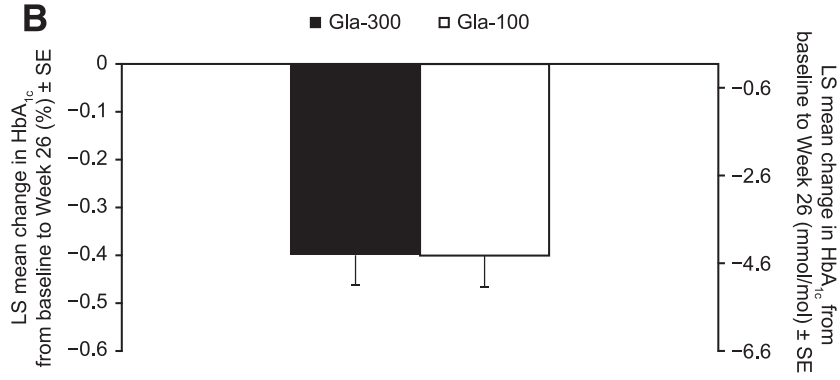
margin of 0.3% (3.3 mmol/mol), thereby demonstrating noninferiority of Gla-300 versus Gla-100 in HbA_{1c} reduction. Superiority of Gla-300 relative to Gla-100 was not demonstrated ($P = 0.965$). HbA_{1c} reductions from baseline to week 26 were generally consistent across different clinical subgroups (data not shown). The greatest reductions in HbA_{1c} across both treatment groups were seen over the initial 12 weeks, in line with the main titration period (Fig. 1*A*). Change in HbA_{1c} at week 52 is shown in Supplementary Table 3.

The percentage of participants reaching target HbA_{1c} (<7.5% [58 mmol/mol]) at week 26 was also comparable for the Gla-300 (26.2%) and Gla-100 (23.5%) groups, as was the proportion of participants reaching target HbA_{1c} at week 26 without an event of severe or documented (<54 mg/dL [<3.0 mmol/L]) hypoglycemia during the last 3 months of the 6-month randomized period (Gla-300, 4.3% and Gla-100, 4.8%).

A similar decrease in FPG was observed in both groups from baseline to week 26; namely, a LS mean (SE) reduction of −10.1 (6.7) mg/dL (−0.56 [0.37] mmol/L) for Gla-300 and −9.9 (6.7) mg/dL (−0.55 [0.37] mmol/L) for Gla-100 (Fig. 1*C*). The percentage of participants reaching target FPG ≤130 mg/dL (≤7.2 mmol/L) at week 26 was 27.5% for the Gla-300 group and 26.5% for the Gla-100 group. Similarly, the proportion of participants with FPG ≤130 mg/dL (≤7.2 mmol/L) at week 26 without an event of severe or documented (<54 mg/dL [<3.0 mmol/L]) hypoglycemia during the last 3 months of the 6-month randomized period was 9.4% and 7.4% of participants in the Gla-300 and Gla-100 groups, respectively.

Prebreakfast SMPG mean (SD) change from baseline to week 26 decreased in both treatment groups: by −23.9 (61.7) mg/dL (−1.33 [3.43] mmol/L) for Gla-300 and −14.3 (62.9) mg/dL (−0.79 [3.49] mmol/L) for Gla-100. Daily mealtime insulin doses remained stable over the study (Supplementary Fig. 2). Mean (SD) daily mealtime insulin dose was 0.46 (0.24) units/kg and 0.43 (0.20) units/kg for Gla-300 and Gla-100, respectively, representing a mean (SD) change in mealtime insulin from baseline to week 26 of −0.03 (0.24) units/kg for Gla-300





	Gla-300	Gla-100
LS mean (SE) change, %	−0.40 (0.06)	−0.40 (0.06)
LS mean (SE) change, mmol/mol	−4.36 (0.69)	−4.40 (0.69)
LS mean difference between groups, % (95% CI)	0.004 (−0.17 to 0.18)	
LS mean difference between groups, mmol/mol (95% CI)	0.043 (−1.88 to 1.96)	

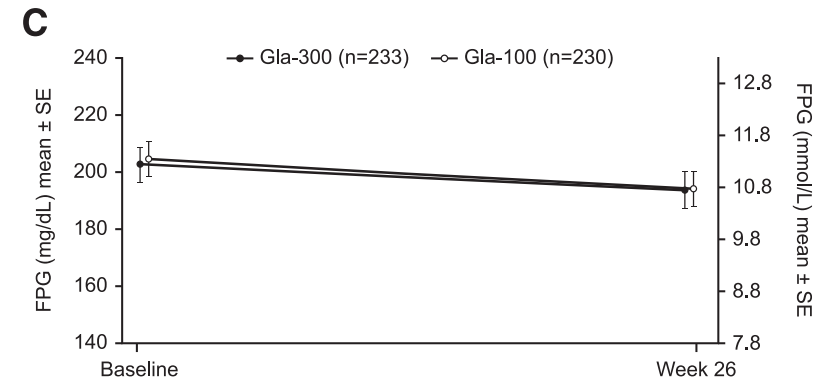


Figure 1—Glycemic control. Mean (SE) HbA_{1c} by visit (*A*) and LS mean change (*B*) during the 26-week randomized period. *C*: FPG by visit during the 26-week randomized period (ITT population).

and −0.02 (0.17) units/kg for Gla-100. At week 26, the mean (SD) daily basal insulin dose for Gla-300 was 0.62 (0.23) units/kg compared with 0.57 (0.24) units/kg for Gla-100, representing a mean (SD) increase in daily long-acting insulin from baseline to week 26 of 0.15 (0.15) units/kg for Gla-300 vs. 0.08 (0.14) units/kg for Gla-100. Mean (SD) daily basal insulin doses remained consistent to week 52 in the Gla-300 group (0.61 [0.22] units/kg) and the Gla-100 group (0.57 [0.25] units/kg). The greatest mean change (SD) in basal insulin dose from baseline occurred within the first 12 weeks for both treatment groups, with a greater increase in dose with Gla-300 versus Gla-100 (Supplementary Fig. 2) (Gla-300, 0.13 [0.13]; Gla-100, 0.06 [0.11]).

Safety Assessments

Hypoglycemia

The majority of participants experienced ≥1 severe or documented (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemic events at any time of day during the main 6-month treatment period, with similar incidence between treatment groups (97.0% and 97.8% for Gla-300 and Gla-100, respectively) (Supplementary Fig. 3*A*). Incidence of hypoglycemia during the main 6-month treatment period was similar between treatment groups for all hypoglycemia definitions at both the ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L) blood glucose thresholds, both at any time of day (24 h) and at night (0000–0559 h) (Supplementary Fig. 3*A*). No differences in hypoglycemic incidence were observed between Gla-300 and Gla-100 when comparing the younger (<12 years) and older (≥12 years) subgroups (data not shown). Incidence of severe hypoglycemia was 6.0% in the Gla-300 group and 8.8% in the Gla-100 group (relative risk 0.68 [95% CI 0.35–1.30]) (Supplementary Fig. 3*A*). The number of participants reporting ≥1 serious adverse events (SAE) of hypoglycemia was 6 (2.6%) in the Gla-300 group and 10 (4.4%) in the Gla-100 group.

During the main 6-month treatment period, annualized event rates for severe or documented (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia at any time of day were similar for Gla-300 and Gla-100 (90.3 and 90.0 events per participant-year, respectively) (Supplementary Fig. 3*B*). Similar event rates were also seen between treatment groups for all hypoglycemia definitions at both the ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L) blood glucose thresholds, both at any time of day (24 h) and at night (0000–0559 h) (Supplementary Fig. 3*B*). Event rates for severe hypoglycemia at any time of day were 0.2 vs. 0.3 events per participant-year, for Gla-300 versus Gla-100 groups, respectively (rate ratio 0.69 [95% CI 0.32–1.50]) (Supplementary Fig. 3*B*).

The results observed for the main 6-month treatment period were generally consistent with those observed during the initial 8 weeks of treatment (data not shown) and for the entire 12-month study period (6-month treatment period and 6-month safety extension period) (Supplementary Table 4); the occurrence of hypoglycemia events was evenly distributed month-to-month throughout the entire 12-month treatment period and

was similar in both treatment groups (Supplementary Fig. 4).

Hyperglycemia With Ketosis

During the main 6-month treatment period, the number of biochemical hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L) events was 218 (1.90 events per participant-year) in the Gla-300 group and 146 (1.30 events per participant-year) in the Gla-100 group. More than 50% of all documented ketone values ≥1.5 mmol/L with SMPG ≥252 mg/dL (≥14 mmol/L) were reported by two participants (one in each treatment group) (Table 2). These participants had a medical history of diabetic ketoacidosis or frequent hyperglycemia, with high ketone values measured during the screening period and throughout the study (6-month treatment period and 6-month extension period). A subsequent ad hoc sensitivity analysis of this end point was conducted, which excluded the two participants with >30 events of hyperglycemia with ketosis. The number of events of hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L) was 57 (0.50 events per participant year) in the Gla-300 group and 77 (0.69 events per participant year) in the Gla-100 group (Table 2).

During the main 6-month treatment period, the number of participants (%) with ≥1 TEAE of hyperglycemia with ketosis by Preferred Term was 15 (6.4%) in the Gla-300 group vs. 27 (11.8%) in the Gla-100 group. Diabetic ketoacidosis was reported as an SAE in one participant (0.4%) in the Gla-300 group and four participants (1.8%) in the Gla-100 group (Supplementary Table 5). The number of hyperglycemia with ketosis events was 34 (0.30 events per participant-year) for the Gla-300 group vs. 46 (0.41 events per participant-year) in the Gla-100 group.

When analyzed during the whole 12-month study period, which included the 6-month safety extension period, the number of participants and events of hyperglycemia with ketosis by biochemical analysis and Preferred Term were consistent with those observed during the main 6-month treatment period (Table 2 and Supplementary Tables 4 and 5).

Adverse Events

The incidence of all TEAE during the main 6-month treatment period was similar in the Gla-300 (n = 152 [65.2%]) and Gla-100 (n = 150 [65.8%]) groups (Table 3). Treatment-emergent SAE occurred in 7.3% (n = 17) and 9.2% (n = 21) of participants in the Gla-300 and Gla-100 groups, respectively. Of the TEAE reported, the most common for both Gla-300 and Gla-100 were nasopharyngitis (12.9% and 13.6%), headache (7.3% and 5.7%), upper–respiratory tract infection (6.9% and 5.7%), and ketosis (6.4% and 10.1%). One fatality occurred during the study in the Gla-300 group; the participant committed suicide, and the event was not considered related to the study treatment. No new or unexpected safety concerns were identified in the 6-month treatment period.

The incidence of all TEAE during the 12-month study period was similar between the Gla-300 (n = 167 [71.7%]) and Gla-100 groups (n = 168 [73.7%]) groups, with no new or unexpected safety concerns identified (Supplementary Table 4).

CONCLUSIONS

EDITION JUNIOR was the first study comparing the efficacy and safety of the second-generation basal insulin analog Gla-300 with the first-generation basal insulin analog Gla-100 in children and adolescents with type 1 diabetes. In this study, noninferiority of Gla-300 versus Gla-100 was established for change in HbA_{1c} from baseline to week 26. The secondary efficacy end points of HbA_{1c} and FPG target achievement were also similar between groups. Of note, HbA_{1c} and FPG levels remained similar between treatment groups during the 6-month safety extension period of the study. Consistent HbA_{1c} reductions were also observed across most clinically relevant subgroups.

In both the Gla-300 and Gla-100 groups, modest reductions in mean HbA_{1c} and FPG values were observed, which remained above current recommendations for children and adolescents throughout the study (28). These observations underscore the challenge of achieving and maintaining target HbA_{1c} levels in young people with type 1 diabetes, especially in adolescents who have insulin resistance due to puberty, a progressive reduction in residual endogenous insulin secretion, and who encounter the daily challenges of treating diabetes (22,29–31). Thus, it is not surprising that other studies with Gla-100, insulin detemir (IDet), or insulin degludec (IDeg) in children with type 1 diabetes also showed similar modest glycemia reductions and glucose control, when receiving multiple daily injections and monitoring SMPG (32,33).

As expected in a study of basal/bolus insulin regimens with intensive SMPG monitoring in individuals with type 1 diabetes, almost every patient (~98%) had at least one event of hypoglycemia of any type. Similar rates of hypoglycemia were observed in both treatment groups

Table 2—Number of biochemical events of hyperglycemia with ketosis (ketone ≥1.5 mmol/L) during the main 6-month treatment period (safety population)

	Gla-300 (N = 233)		Gla-100 (N = 228)	
Number of biochemical events	n participants (%)	n events (events per participant-year)	n participants (%)	n events (events per participant-year)
Any hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L)	18 (7.7)	218 (1.90)*	26 (11.4)	146 (1.30)†
Sensitivity analysis‡ Any hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L)		57 (0.50)		77 (0.69)

*One participant in the Gla-300 group presented with 161 events of hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L).
†One participant in the Gla-100 group presented with 69 events of hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L).
‡Ad hoc analysis for number of biochemical events (excluding two participants with >30 events of hyperglycemia with ketosis).

Table 3—TEAE during the main 6-month treatment period (safety population)

	n participants (%)	
	Gla-300 (*N* = 233)	Gla-100 (*N* = 228)
Participants with any TEAE	152 (65.2)	150 (65.8)
Participants with any treatment-emergent SAE	17 (7.3)	21 (9.2)
Participants with any TEAE leading to death	1 (0.4)	0
Participants with any TEAE leading to permanent treatment discontinuation	2 (0.9)	2 (0.9)
TEAE by primary system organ class		
Infections and infestations	97 (41.6)	105 (46.1)
Metabolism and nutrition disorders	26 (11.2)	38 (16.7)
Nervous system disorders	29 (12.4)	21 (9.2)
Respiratory, thoracic, and mediastinal disorders	28 (12.0)	12 (5.3)
Gastrointestinal disorders	34 (14.6)	22 (9.6)
Skin and subcutaneous tissue disorders	9 (3.9)	11 (4.8)
General disorders and administration site conditions	24 (10.3)	22 (9.6)
Injury, poisoning, and procedural complications	16 (6.9)	14 (6.1)

over the entire 12-month study period, at the ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L) blood glucose thresholds. While not significant, numerically lower incidence and rates of severe hypoglycemia were observed with Gla-300 during the first 6 months of treatment; this might suggest a slight benefit of Gla-300 versus Gla-100 in terms of hypoglycemia, although further evidence is required. Safety data over the 12-month study period showed that Gla-300 has a safety profile similar to that of Gla-100. Reassuringly, the incidence of hyperglycemia with ketosis and incidence and event rates of severe hypoglycemia tended to be lower with Gla-300 than Gla-100. Overall, the results of this study, in a large number of children and adolescents with type 1 diabetes, confirm the well-established safety profile of insulin glargine and show that there are no additional safety concerns for the use of Gla-300 compared with Gla-100 in children and adolescents with type 1 diabetes.

While Gla-100 provides once-daily dosing in most individuals with type 1 diabetes, there is evidence to suggest that a small population may benefit from twice-daily dosing to reduce the risk of hyperglycemia (particularly related to late-afternoon hyperglycemia, which may be pertinent to school lunchtime meals) or hypoglycemia, and improve glycemic control (12,34,35). In pharmacokinetic/pharmacodynamic studies in adults, exposure to Gla-300 was more stable and evenly distributed across the 24-h dosing interval with lower and delayed peak concentrations compared with Gla-100, thereby providing less glycemic variability over the dosing intervals (36), which could facilitate once-daily dosing. However, further studies in adults and pediatric populations are required to confirm this.

Daily basal insulin dose increased in both treatment arms, with a slightly greater increase observed with Gla-300 (0.15 units/kg) versus Gla-100 (0.08 units/kg). This dose difference is in line with previously reported results in adults with type 1 diabetes (18) and type 2 diabetes (15–17) and is consistent with the differences in bioavailability between Gla-300 and Gla-100 (37).

Of note, the EDITION JUNIOR data are consistent with findings of the BEGIN Young 1 study comparing IDeg with the first-generation long-acting insulin analog IDet in a population aged 1 to <18 years. As in the current study, results of BEGIN Young 1 showed similar glycemic efficacy in both treatment groups, with comparable rates of hypoglycemia (38).

The strengths of the EDITION JUNIOR study, the first comparing Gla-300 and Gla-100 in children and adolescents with type 1 diabetes, include the treat-to-target, randomized trial design; the large group of pediatric patients including 31% of participants aged <12 years; and the multinational nature of the study across global geographies. Limitations of the study include its open-label study design, that precluded blinding of trial participants to the identity of the two basal insulin analog pens. In addition, the study was not sufficiently powered to detect differences between treatment groups for hypoglycemia and hyperglycemia with ketosis. Given the tendency toward a lower incidence of hyperglycemia with ketosis observed with Gla-300 versus Gla-100 in this study, future studies sufficiently powered to detect potential differences between these basal insulin analogs would be of interest to explore whether Gla-300 may provide a suitable therapy option in individuals at high risk of hyperglycemia and ketosis.

In summary, the EDITION JUNIOR study showed that Gla-300 provides similar efficacy and safety to Gla-100 when used in combination with mealtime insulin in children and adolescents aged 6–17 years with type 1 diabetes. Therefore, Gla-300 may be a suitable therapeutic option in this age-group.

Acknowledgments. The authors thank the study participants, trial staff, and investigators for their participation.

Duality of Interest. Sanofi was the sponsor of the study and was responsible for the design and coordination of the trial, monitoring clinical sites, collecting and managing data, and performing all statistical analyses. The clinical trial considered in this analysis was sponsored by Sanofi, Paris, France. Editorial and writing assistance was provided by Jennina Taylor-Wells, of Fishawack Communications Ltd., Knutsford, U.K., and was funded by Sanofi. T.D. has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Medtronic, Novo Nordisk, Sanofi, and Roche; received research support from AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, and Roche; served on speakers bureaus for Abbott, Bayer, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, and Roche; and is a stock/shareholder in DreaMed Diabetes, Ltd. W.V.T. has served as a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Medtronic Diabetes, Novo Nordisk, and Takeda and served as a Data and Safety Monitoring Board member for Eisai Pharmaceuticals, MannKind, and Tolerion. D.R.F. has served on advisory panels for Medtronic, Novo Nordisk, Sanofi, and Abbott; received research support from AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, and Sanofi; and served on speakers bureaus for Abbott, AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, and Sanofi. T.K. has received an honorarium as a speaker for Sanofi. M.D. is an employee and shareholder of Sanofi. E.N. is an employee and shareholder of Sanofi. H.G. is an employee and shareholder of Sanofi. M.W. is an employee and shareholder of Sanofi. T.B. has received honoraria for participation on advisory boards for Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, Medtronic, and Bayer HealthCare and as a speaker for AstraZeneca, Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi, and Roche and owns stocks of DreaMed Diabetes, Ltd. T.B.'s institution has received research grant support and travel expenses from Abbott Diabetes Care, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz, and Diamyd Medical. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors were involved in developing the initial concept for

analysis and data acquisition. All authors contributed to interpreting the findings and writing, reviewing, and editing the manuscript. T.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the ISPAD (International Society for Pediatric and Adolescent Diabetes) 45th Annual Conference, Boston, MA, 30 October–2 November 2019.

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