A Randomized Controlled Trial Comparing Efficacy and Safety of Insulin Glargine 300 Units/mL Versus 100 Units/mL in Older People With Type 2 Diabetes: Results From the SENIOR Study

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OBJECTIVE

SENIOR compared the efficacy and safety of insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in older people (≥65 years old) with type 2 diabetes.

RESEARCH DESIGN AND METHODS

SENIOR was an open-label, two-arm, parallel-group, multicenter phase 3b trial designed to enroll ∼20% of participants aged ≥75 years. Participants were randomized 1:1 to Gla-300 or Gla-100, titrated to a fasting self-monitored plasma glucose of 5.0–7.2 mmol/L (90–130 mg/dL).

RESULTS

In total, 1,014 participants were randomized (mean age: 71 years). Comparable reductions in HbA_{1c} were observed from baseline to week 26 for Gla-300 (−0.89%) and Gla-100 (−0.91%) in the overall population (least squares mean difference: 0.02% [95% CI −0.092 to 0.129]) and for participants aged ≥75 years (−0.11% [−0.330 to 0.106]). Incidence and rates of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia events were low and similar between both treatment groups, with lower rates of documented symptomatic hypoglycemia with Gla-300. The lower risk of hypoglycemia with Gla-300 versus Gla-100 was more apparent in the subgroup aged ≥75 years versus the overall population. Significantly lower annualized rates of documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) hypoglycemia were observed (Gla-300: 1.12; Gla-100: 2.71; rate ratio: 0.45 [95% CI 0.25–0.83]).

CONCLUSIONS

Efficacy and safety of Gla-300 was demonstrated in older people (≥65 years of age) with type 2 diabetes, with comparable reductions in HbA_{1c} and similarly low or lower risk of documented symptomatic hypoglycemia versus Gla-100. A significant benefit in hypoglycemia reduction was seen in participants aged ≥75 years.

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Diabetes is common in older adults, affecting an estimated 20% of people 65–79 years of age (94 million people) worldwide in 2015 (1). Prevalence of type 2 diabetes increases with age owing to attenuated β-cell function and insulin resistance (2). Coupled with the growing proportion of older individuals in the global population (3) is an increasing requirement for effective diabetes management for older people.

Therapies for lowering blood glucose include several classes of oral antihyperglycemic drugs as well as injectables, such as rapid-acting and basal insulins and glucagon-like peptide receptor agonists. When insulin is used, a fine balance is required between achieving glycemic control and avoiding hypoglycemia. Compared with younger populations, older people with diabetes more often require insulin and are more prone to hypoglycemia for multiple reasons such as erratic food ingestion, insufficient adjustment of insulin dose, reduced responses to counterregulatory hormones, lower blood glucose threshold for autonomic symptoms, and higher blood glucose threshold for cognitive dysfunction. The latter leads to impaired awareness of hypoglycemia and an increased risk of severe hypoglycemia (4–7). Cognitive impairment in older adults may itself increase the risk of hypoglycemia owing to difficulties in diabetes management (8). Moreover, the frequent asymptomatic hypoglycemic episodes that may result from impaired awareness can further lower the threshold for autonomic symptoms and lead to further hypoglycemic episodes (9).

Hypoglycemic events in older people are associated with an increased incidence of acute cardiovascular events, impaired cognitive function, dementia, hospitalizations, and mortality (4,6,10–15). Hypoglycemia and its consequences are an even greater burden in people ≥75 years of age than in those 65–74 years of age, with hospitalization rates twofold higher (16). Furthermore, the care of older people is complicated by the diverse range of functional ability, cognitive function, comorbid conditions, and frailty present in this group (8). Despite these considerations, there are few long-term studies in this population demonstrating the possible benefits of better glycemic, blood pressure, and lipid control (17).

The basal insulin glargine is available as insulin glargine 100 units/mL (Gla-100; Sanofi, Paris, France) or insulin glargine 300 units/mL (Gla-300; Sanofi). Compared with Gla-100, Gla-300 provides more stable and prolonged steady-state pharmacokinetic and pharmacodynamic profiles, with blood insulin levels that more closely resemble normal physiological conditions (18,19). The EDITION 1, 2, and 3 trials compared the efficacy and safety of Gla-300 with Gla-100 in people with type 2 diabetes and demonstrated comparable glycemic control over 6 months, which was better sustained with Gla-300 throughout the 12-month study period, and a significantly lower risk of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia (definitions based on American Diabetes Association [ADA] criteria [20]) at night (0000–0559 h) and at any time of day (24 h) with Gla-300 compared with Gla-100. A recent post hoc analysis of participants ≥65 years of age with type 2 diabetes from EDITION 1–3 confirmed the comparable glycemic control and reduction in hypoglycemia risk for Gla-300 versus Gla-100 in this subgroup, with significantly lower rates of nocturnal (0000–0559 h) hypoglycemia (21).

The SENIOR study was the first prospectively designed clinical trial to address the efficacy and safety of basal insulin (insulin glargine) specifically in older people (≥65 years of age) with type 2 diabetes. The study was also designed such that ∼20% of the people enrolled would be ≥75 years of age to explore Gla-300 versus Gla-100 treatment in this population at elevated risk of hypoglycemia (6) and its consequences (4,6,10–15).

RESEARCH DESIGN AND METHODS

Study Design

SENIOR (NCT02320721) was a multinational, multicenter, phase 3b, active-controlled, randomized, open-label, two-arm parallel-group study in older people (≥65 years of age) with type 2 diabetes comprising a 4-week screening period, followed by a 26-week treatment period, conducted in 162 centers across 18 countries.

Key inclusion criteria were age ≥65 years, type 2 diabetes for ≥1 year treated with a pharmacologic antihyperglycemic regimen for ≥8 weeks before screening, and glycated hemoglobin (HbA_{1c}) at screening of 7.5–11% (58–97 mmol/mol) in insulin-naive participants or 7–10% (53–86 mmol/mol) in insulin-pretreated participants. Exclusion criteria included the chronic use of short-acting insulin, participants not on a stable basal insulin dose, and cognitive disorder and dementia (Mini-Mental State Examination score <24). A list of key exclusion criteria for the study is provided in Supplementary Table 1.

The study was approved by independent ethics review boards and conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

Randomization and Treatment

Participants were randomized 1:1 to receive Gla-300 or Gla-100. Randomization was stratified by HbA_{1c} at screening (<8.0/≥8.0% [<64/≥64 mmol/mol]), previous use of insulin (naive/pretreated), and use of sulfonylurea or meglitinide at screening (yes/no).

Basal insulins were self-administered once daily. Evening administration was recommended, although other times of day were permissible provided administration occurred at the same time each day ±3 h. Starting doses were determined by previous dose history: insulin-naive patients started on a dose of 0.2 units/kg, and participants pretreated with basal insulin received a starting dose equivalent to their median basal insulin dose of the 3 days before baseline, unless receiving NPH insulin more than once daily, in which case a dose 20% lower than the total daily dose was given. The insulin dose was adjusted every 3–4 days to achieve a target fasting self-monitored plasma glucose (SMPG) level of 5.0–7.2 mmol/L (90–130 mg/dL), the ADA-recommended target for healthy older individuals (8). Dose adjustments were as follows: an increase of 3 units if >7.2 mmol/L (>130 mg/dL) or a decrease of 3 units (or an adjustment at the investigators' discretion) if <5.0 mmol/L (<90 mg/dL) or in the event of two or more symptomatic or one severe hypoglycemic episode in the preceding week.

Participants continued their previous antihyperglycemic drugs, if approved for use with insulin, with the exception of thiazolidinediones, which were stopped at randomization.

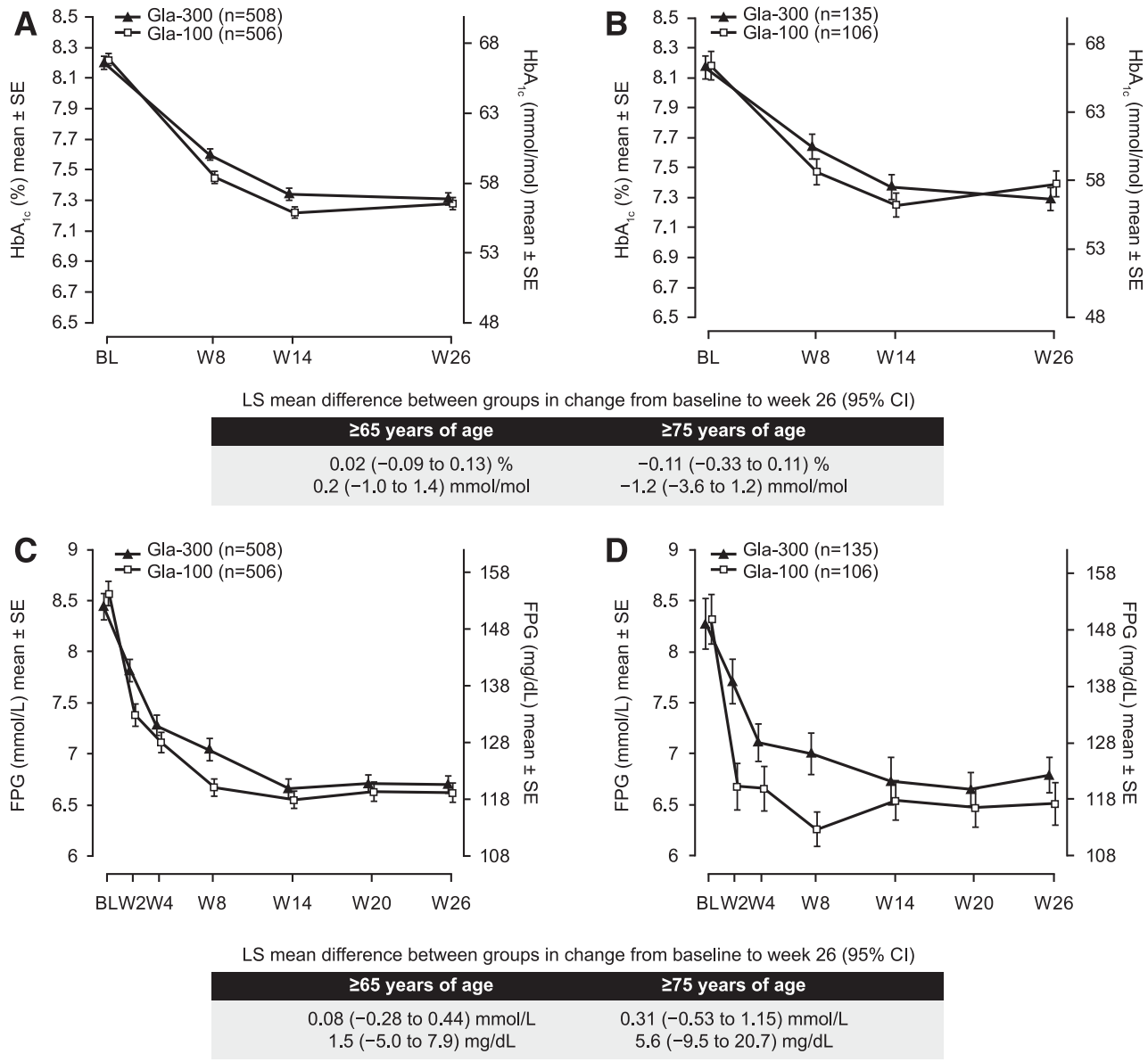


Figure 1—Mean (SE) HbA_{1c} in the overall population (*A*) and in participants ≥75 years of age (*B*) and mean (SE) FPG in the overall population (*C*) and in participants ≥75 years of age (*D*) by visit during the 26-week (W) treatment period (intent-to-treat population). BL, baseline; LS, least squares.

Outcomes

The primary efficacy end point was change in HbA_{1c} from baseline to week 26. The main secondary efficacy end points were the percentage of participants with one or more confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events occurring at any time of day (24 h) or at night (0000–0559 h or 2200–0859 h) over 26 weeks of treatment. Other secondary end points were assessed in the overall population and in a subgroup of participants ≥75 years of age. These included change in fasting plasma glucose (FPG) from baseline to week 26, the percentage of participants experiencing hypoglycemic events and annualized rates of hypoglycemia at either threshold (≤3.9 mmol/L [≤70 mg/dL] and <3.0 mmol/L [<54 mg/dL]) at any time of day [24 h] and at night [0000–0559 h] over 26 weeks of treatment), and the percentage of participants achieving HbA_{1c} <7.5 and <7.0% (58 and 53 mmol/mol) at the end of 26 weeks of treatment. A composite end point of HbA_{1c} target achievement (<7.5 or <7.0% [58 and 53 mmol/mol]) without confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia was also assessed. Hypoglycemia was defined based on the ADA workgroup definitions (20). Data are presented for documented symptomatic hypoglycemia, severe hypoglycemia, and as a combination of confirmed or severe hypoglycemic events.

Participant-reported outcomes (PROs) were assessed for mobility scores taken from the EQ-5D, the EuroQol Research Foundation's questionnaire that assesses five dimensions of health—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—as a single utility index and on a visual analog scale. Safety outcomes included treatment-emergent adverse events (TEAEs) and severe adverse events (SAEs).

Data Analysis and Statistics

A sample size of 460 randomized participants for each treatment group provided 98% power to show noninferiority of Gla-300 versus Gla-100 in HbA_{1c} change from baseline to week 26 on the basis of a true difference between the two groups of zero and a noninferiority margin of 0.3%. This calculation assumes a common SD of 1.1%, with a one-sided *t* test at the 2.5% significance level. Change in HbA_{1c} (primary end point) and FPG from baseline to week 26 were assessed using a multiple imputation approach for missing data and ANCOVA using fixed categorical effects of treatment group, randomization strata, and continuous fixed covariates of baseline value. Least squared mean and least squared mean differences were combined using the Rubin formula.

The main secondary end point and HbA_{1c} target achievement, with or without hypoglycemia, was analyzed using the Cochran–Mantel–Haenszel method with treatment group as a factor and stratified on randomization strata. Noninferiority and, subsequently, superiority of Gla-300 compared with Gla-100 was assessed for the primary and main secondary end points using a hierarchical step-down testing procedure (Supplementary Table 2), with two-sided tests for superiority performed at the level of $\alpha = 0.05$. Analyses of safety outcomes were descriptive. Analyses were performed for the overall population and for the subgroup of participants ≥75 years of age.

Exploratory analyses of the percentage of patients experiencing one or more confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events in the overall population were analyzed by prespecified baseline categories of age (65–70, 70–75, or ≥75 years), BMI (<30/≥30 kg/m^2), HbA_{1c} (<8.0/≥8.0% [<64/≥64 mmol/mol]), sulfonylurea or meglitinide use at screening (yes/no), diabetes duration (<10/≥10 years), history of diabetic neuropathy (yes/no), and estimated glomerular filtration rate categories (≥60, 30 to <60, or <30 mL/min/1.73 m^2). Mean HbA_{1c} and hypoglycemia (incidence and rates) by mobility PRO score subgroup ("no problems"/"slight to extreme problems") were also performed as exploratory analyses. HbA_{1c} by baseline mobility PRO score subgroup was assessed using a similar approach to the primary analysis. Analyses of hypoglycemia by baseline category subgroups were descriptive. Safety outcomes included TEAEs and SAEs.

RESULTS

Study Participants

A total of 1,014 participants were randomized to receive Gla-300 (*n* = 508) or Gla-100 (*n* = 506) (Supplementary Fig. 1); of these, 135 (26.6%) and 106 (20.9%) participants were ≥75 years of age for Gla-300 and Gla-100, respectively. Overall, baseline characteristics were similar for the Gla-300 and Gla-100 groups (Supplementary Table 3), although participants ≥75 years of age had a lower mean estimated glomerular filtration rate, longer duration of diabetes, a higher overall rate of diabetes-related complications, and a smaller proportion were previously treated with insulin compared with the overall population (Supplementary Table 3).

Glycemic Control

Change in HbA_{1c}

The primary objective of noninferiority of Gla-300 versus Gla-100 for change in HbA_{1c} from baseline to week 26 was met (Fig. 1*A*). Mean (SD) HbA_{1c} decreased similarly in both treatment groups, from 8.20% (0.91) for Gla-300 and 8.22% (0.92) for Gla-100 (66.1 [9.9] vs. 66.3 [10.1] mmol/mol) at baseline to 7.31% (0.91) and 7.28% (0.84) (56.4 [9.5] vs. 56.0 [9.2] mmol/mol), respectively.

Change in HbA_{1c} in Participants ≥75 Years of Age

Within the subpopulation of participants ≥75 years old, similar reductions in HbA_{1c} from baseline to week 26 were observed, from 8.17% (SD 0.89) to 7.29% (0.84) (65.9 [9.9] to 56.2 [9.2] mmol/mol) for Gla-300 and 8.18% (0.97) to 7.39% (0.87) (65.9 [10.64] to 57.3 [9.5] mmol/mol) for Gla-100 (Fig. 1*B*).

Plasma Glucose

Comparable reductions in mean FPG were observed for both treatment groups from baseline to week 26 in the overall population (Fig. 1*C*), with reductions of 1.68 (SD 0.12) mmol/L and 1.77 (0.14) mmol/L (30.4 [2.2] and 31.8 [2.4] mg/dL, respectively). Similar results were observed in participants ≥75 years of age (Fig. 1*D*).

Reduction in average 5-point SMPG and bedtime SMPG was comparable between treatment groups in the overall population and in participants ≥75 years of age (data not shown).

Hypoglycemia

Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or Severe Hypoglycemia

Superiority of Gla-300 versus Gla-100 for the main secondary efficacy end points, the proportion of participants in the intent-to-treat population experiencing one or more confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events occurring during either 2200–0859 h or 0000–0559 h, was not detected (Table 1).

For the safety population, the proportion of participants experiencing one or more confirmed or severe hypoglycemic events was similar for both treatment groups at both the ≤3.9 mmol/L (≤70 mg/dL) and <3.0 mmol/L (<54 mg/dL) thresholds at any time of day (24 h) (Fig. 2*A*). Similar results were observed at night (0000–0559 h) (Fig. 2*A*).

Table 1—Percentage of participants experiencing one or more confirmed or severe hypoglycemic events over 26 weeks of treatment (intent-to-treat population)

	% participants		RR Gla-300 vs. Gla-100[a]		
Confirmed or severe hypoglycemia	Gla-300 (*n* = 508)	Gla-100 (*n* = 506)	RR	95% CI	*P* value (CMH)
2200–0859 h	48.3	47.7	1.01	0.890–1.153	0.8415
0000–0559 h	20.2	22.5	0.90	0.706–1.140	—
Any time of the day (24 h)	59.4	62.7	0.95	0.859–1.046	—

Confirmed hypoglycemia defined as ≤3.9 mmol/L (≤70 mg/dL). [a]Relative risk (RR) stratified by randomization strata of screening HbA_{1c} (<8.0/≥8.0%), randomization strata of previous use of insulin (naive/pretreated), randomization strata of use of sulfonylurea or meglitinides at screening (yes/no), using a Cochran–Mantel–Haenszel (CMH) methodology.

Annualized event rates for confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia were similar between treatment groups, at night (0000–0559 h) or any time of day, but a trend toward lower rates with Gla-300 compared with Gla-100 was observed at the lower threshold of <3.0 mmol/L (<54 mg/dL) (Fig. 3*A*).

Documented Symptomatic Hypoglycemia

The results reported for documented symptomatic hypoglycemia were in keeping with those seen for confirmed or severe hypoglycemia. A comparable proportion of participants experienced one or more events in both treatment groups at any time of day (24 h) and at night (0000–0559 h); however, fewer participants experienced a hypoglycemic event at the lower glycemic threshold of <3.0 mmol/L (<54 mg/dL) with Gla-300 compared with Gla-100, although this was not significant (Fig. 2*A*).

A trend toward lower annualized event rates of hypoglycemia with Gla-300 versus Gla-100 was observed at both glycemic thresholds. These differences were statistically significant for anytime (24 h) for the ≤3.9 mmol/L (≤70 mg/dL) and for the <3.0 mmol/L (<54 mg/dL) threshold (Fig. 3*A*).

Severe Hypoglycemia

The incidence and annualized rate of severe hypoglycemia were low, with four participants (0.8%; 0.02 events per participant-year) in the Gla-300 group and three participants (0.6%; 0.01 events per participant-year) in the Gla-100 group reporting one event each.

Hypoglycemia in Participants ≥75 Years of Age

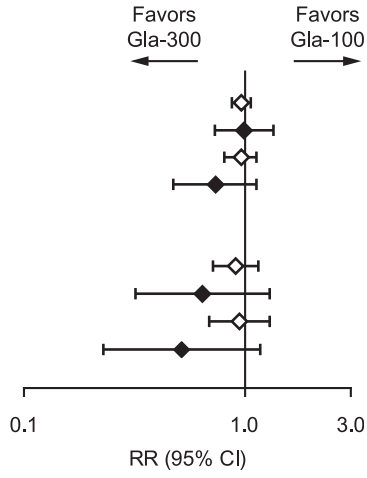
In general, the proportion of participants ≥75 years of age experiencing one or more hypoglycemic events was similar to the overall SENIOR population.

Within the subgroup of participants ≥75 years of age, the incidence of confirmed or severe hypoglycemic events for both glycemic thresholds and documented symptomatic hypoglycemia for the higher threshold were comparable between treatment groups at any time of day (24 h). The incidence of any time (24 h) documented symptomatic (<3.0 mmol/L [<54 mg/dL]) hypoglycemia was significantly lower with Gla-300 compared with Gla-100 (1.5% vs. 10.4%; relative risk 0.33; 95% CI 0.12–0.88) (Fig. 2*B*).

Statistically significant reductions in annualized rates of hypoglycemia at any time of day (24 h) were observed for Gla-300 compared with Gla-100 for confirmed (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycemia and documented symptomatic hypoglycemia at either glycemic threshold (Fig. 3*B*). Nocturnal

A

		Gla-300 (N=508)	Gla-100 (N=505)	RR (95% CI)
Hypoglycemia at any time of the day (24 h)		**n (%)**	**n (%)**	
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	295 (58.1)	306 (60.6)	**0.96 (0.87 to 1.06)**
	<3.0 mmol/L (<54 mg/dL)	72 (14.2)	73 (14.5)	**0.98 (0.73 to 1.33)**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	167 (32.9)	175 (34.7)	**0.95 (0.80 to 1.12)**
	<3.0 mmol/L (<54 mg/dL)	32 (6.3)	44 (8.7)	**0.73 (0.47 to 1.12)**
Nocturnal (00:00–05:59 h) hypoglycemia				
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	101 (19.9)	112 (22.2)	**0.90 (0.71 to 1.14)**
	<3.0 mmol/L (<54 mg/dL)	11 (2.2)	18 (3.6)	**0.63 (0.32 to 1.27)**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	61 (12.0)	65 (12.9)	**0.93 (0.68 to 1.29)**
	<3.0 mmol/L (<54 mg/dL)	6 (1.2)	14 (2.8)	**0.51 (0.23 to 1.15)**



B

		Gla-300 (N=135)	Gla-100 (N=106)	RR (95% CI)
Hypoglycemia at any time of the day (24 h)		**n (%)**	**n (%)**	
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	74 (54.8)	63 (59.4)	**0.91 (0.73 to 1.13)**
	<3.0 mmol/L (<54 mg/dL)	10 (7.4)	16 (15.1)	**0.52 (0.26 to 1.02)**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	33 (24.4)	36 (34.0)	**0.72 (0.48 to 1.08)**
	<3.0 mmol/L (<54 mg/dL)	2 (1.5)	11 (10.4)	**0.33 (0.12 to 0.88)**
Nocturnal (00:00–05:59 h) hypoglycemia				
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	25 (18.5)	22 (20.8)	**0.93 (0.55 to 1.59)**
	<3.0 mmol/L (<54 mg/dL)	0	4 (3.8)	**–**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	14 (10.4)	13 (12.3)	**0.87 (0.43 to 1.76)**
	<3.0 mmol/L (<54 mg/dL)	0	4 (3.8)	**–**

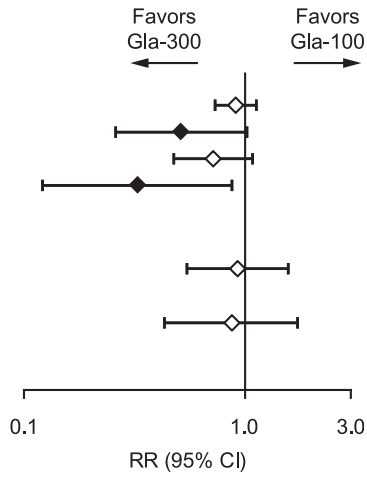
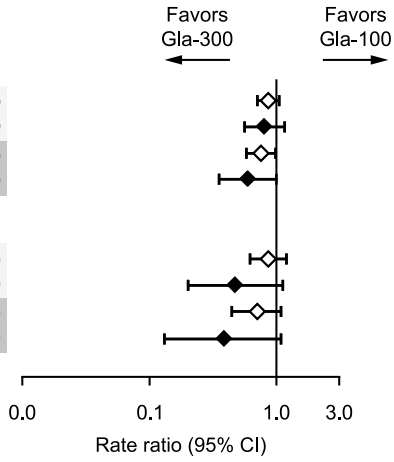


Figure 2—Incidence (number and percentage of participants experiencing one or more hypoglycemic events) for the overall population (≥65 years of age) (*A*) and for participants ≥75 years of age (safety population) (*B*). RR, relative risk.

A

		Gla-300 (N=508)	Gla-100 (N=505)	Rate ratio (95% CI)
Hypoglycemia at any time of the day (24 h)		**n (events per participant-year)**		
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	1291 (5.17)	1565 (6.36)	**0.83 (0.68 to 1.01)**
	<3.0 mmol/L (<54 mg/dL)	99 (0.40)	124 (0.50)	**0.78 (0.54 to 1.13)**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	461 (1.85)	630 (2.56)	**0.74 (0.56 to 0.96)**
	<3.0 mmol/L (<54 mg/dL)	43 (0.17)	71 (0.29)	**0.59 (0.35 to 1.00)**
Nocturnal (00:00–05:59 h) hypoglycemia				
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	213 (0.85)	267 (1.08)	**0.84 (0.60 to 1.17)**
	<3.0 mmol/L (<54 mg/dL)	13 (0.05)	26 (0.11)	**0.47 (0.20 to 1.08)**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	102 (0.41)	157 (0.64)	**0.68 (0.44 to 1.05)**
	<3.0 mmol/L (<54 mg/dL)	8 (0.03)	21 (0.09)	**0.38 (0.13 to 1.07)**



B

		Gla-300 (N=135)	Gla-100 (N=106)	Rate ratio (95% CI)
Hypoglycemia at any time of the day (24 h)		**n (events per participant-year)**		
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	295 (4.46)	320 (6.28)	**0.72 (0.48 to 1.07)**
	<3.0 mmol/L (<54 mg/dL)	12 (0.18)	26 (0.51)	**0.36 (0.15 to 0.89)**
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	74 (1.12)	138 (2.71)	**0.45 (0.25 to 0.83)**
	<3.0 mmol/L (<54 mg/dL)	2 (0.03)	18 (0.35)	**0.08 (0.02 to 0.42)**
Nocturnal (00:00–05:59 h) hypoglycemia				
Confirmed or severe	≤3.9 mmol/L (≤70 mg/dL)	45 (0.68)	58 (1.14)	**0.59 (0.29 to 1.23)**
	<3.0 mmol/L (<54 mg/dL)	0	8 (0.16)	–
Documented symptomatic	≤3.9 mmol/L (≤70 mg/dL)	18 (0.27)	36 (0.71)	**0.47 (0.19 to 1.19)**
	<3.0 mmol/L (<54 mg/dL)	0	8 (0.16)	–

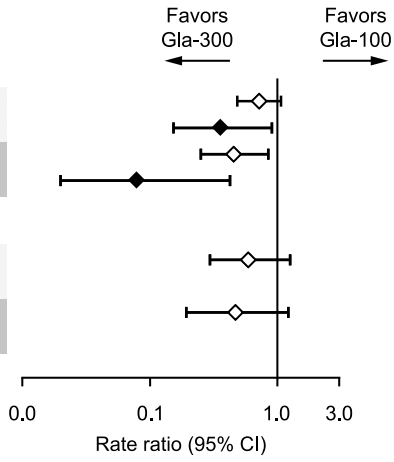


Figure 3—Annualized rates (events per participant-year) of hypoglycemia for the overall population (≥65 years of age) (*A*) and for participants ≥75 years of age (safety population) (*B*).

(0000–0559 h) incidence and rates were comparable between treatment groups for both confirmed and severe and for documented symptomatic hypoglycemia at the ≤3.9 mmol/L (≤70 mg/dL) threshold (Fig. 3*B*).

No severe hypoglycemic events were observed in participants ≥75 years of age.

Hypoglycemia Incidence by Baseline Characteristics

The results observed in the overall population were consistent across the baseline subgroups, with a similar percentage of participants experiencing confirmed or severe hypoglycemia and documented symptomatic hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) with Gla-300 compared with Gla-100 irrespective of age, BMI, HbA_{1c}, previous insulin use, sulfonylurea or meglitinide use, diabetes duration, nutritional status, diabetic neuropathy, or kidney function (Supplementary Fig. 2).

HbA_{1c} Target Achievement and Composite End Point

The proportion of participants achieving HbA_{1c} <7.5% (<58 mmol/mol) and <7.0% (<53 mmol/mol) was comparable between treatment groups for the overall population and for participants ≥75 years of age (Supplementary Table 4). Similar results were observed for the composite end points of HbA_{1c} target achievement without confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia, although significantly more participants in the ≥75 years age group achieved HbA_{1c} <7.5% (<58 mmol/mol) without confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia with Gla-300 versus Gla-100.

The incidence of confirmed or severe hypoglycemic events and documented symptomatic events (≤3.9 mmol/L [≤70 mg/dL]) was similar between treatment groups, irrespective of HbA_{1c} level achieved at week 26 (Supplementary Fig. 3).

Efficacy and Safety by Mobility PRO Score

The majority of participants (~60%) in both treatment groups reported no mobility problems, and few participants (<1.0%) reported extreme problems at baseline. No difference in mean HbA_{1c} change from baseline to week 26 was observed between participants who reported no mobility problems at baseline and those who reported slight to extreme problems (Supplementary Fig. 4). No differences were observed in the incidence or rates of hypoglycemia between treatment groups at any time of day or at night for participants who reported mobility problems at baseline and for those who did not (Supplementary Fig. 5).

Adverse Events

TEAEs were reported in 299 participants (58.9%) in the Gla-300 group and in 304 (60.2%) in the Gla-100 group

(Supplementary Table 5), with infections (25.8% and 29.7% for Gla-300 and Gla-100, respectively) the most commonly reported TEAEs. The incidence of TEAEs in participants ≥75 years of age was similar to the overall ≥65 years population (59.3% for Gla-300 and 54.7% for Gla-100) (Supplementary Table 5).

CONCLUSIONS

SENIOR was the first prospective study designed to evaluate the efficacy and safety of basal insulin in older people with type 2 diabetes, with ~20% of participants ≥75 years of age (4). Results of SENIOR demonstrate that the efficacy and safety profile of Gla-300 and Gla-100 observed in the EDITION studies (22–25) is also apparent in older adults (≥65 years of age) with type 2 diabetes. The incidence of TEAEs was similar between treatment groups for the overall population and for participants ≥75 years of age (54.7–60.2%) and was consistent with that observed for the older population of the EDITION studies (21).

Reductions in HbA_{1c} were comparable between treatment groups, with >50% of participants in either age group achieving HbA_{1c} of <7.5%. Reductions in FPG were also comparable between treatment groups and between age groups, indicating that insulin was adjusted similarly in the overall population and in participants ≥75 years of age.

A consistent trend for reduced hypoglycemia for Gla-300 versus Gla-100 was observed in the overall SENIOR population, with statistically significant reductions seen for rates of documented symptomatic hypoglycemia at any time of day (24 h). Interestingly, reductions in hypoglycemia for Gla-300 versus Gla-100 were more pronounced in individuals ≥75 years of age, who are known to be at a greater risk of hypoglycemia (4), with a significantly lower risk of documented symptomatic hypoglycemia at any time of day (24 h) observed with Gla-300 compared with Gla-100 in this subgroup. This is an important finding in an understudied and particularly vulnerable population and might be considered when deciding among basal insulin options in older adults, particularly in those older than 75 years. Although some differences were observed in baseline characteristics in the participants ≥75 years of age compared with the overall SENIOR population (predominantly age-related changes that may be expected), whether these differences contributed to the more pronounced hypoglycemia benefit with Gla-300 versus Gla-100 in the ≥75 years population is unknown because this is outside the remit of the present study.

When hypoglycemia incidence was assessed according to baseline characteristics (age, BMI, HbA_{1c}, previous insulin use, sulfonylurea or meglitinide use, diabetes duration, nutritional status, diabetic neuropathy, or kidney function), no differences were observed in hypoglycemia risk between treatment groups for any subgroup. In addition, hypoglycemia risk profiles did not differ between participants who reported mobility problems and those who did not. Hypoglycemia is associated with morbidities that may lead to physical dysfunction, and this can create a cyclical relationship between hypoglycemia and increased frailty (4). As such, it is reassuring to note that the hypoglycemia risk profiles for both insulins did not differ between participants who experienced mobility problems and those who did not. Furthermore, good glycemic control was demonstrated in both groups, suggesting that the observed comparable hypoglycemia profiles were not due to hypoglycemia avoidance through poor glycemic control.

The small differences in hypoglycemia risk reductions observed between Gla-300 and Gla-100 in the overall population in SENIOR may be due, in part, to the low number of hypoglycemic events observed. Participants in EDITION 2, for example, experienced a greater number of hypoglycemic events compared with SENIOR participants (Supplementary Table 6), and significant differences in hypoglycemia rates and incidence were observed between Gla-300 and Gla-100 (25). This hypothesis is supported by the comparable low incidence of hypoglycemia in SENIOR and EDITION 3 (Supplementary Table 6), with similarly few significant differences in hypoglycemia risk observed between treatment groups for both studies (22,23). Factors underpinning the low number of hypoglycemic events reported in SENIOR may include the higher glycemic treatment target set in SENIOR (5.0–7.2 mmol/L [90–130 mg/dL]) compared with that used in the EDITION trials (22–25) or the less frequent SMPG monitoring required for SENIOR, which, coupled with the lower perception of hypoglycemia symptoms in older individuals (4,5), may have allowed for undetected hypoglycemic events to have occurred. Impaired awareness of hypoglycemia in older people (≥65 years of age) may also explain the lack of nocturnal hypoglycemia risk reduction with Gla-300 versus Gla-100 in the present study, despite this being a consistent finding reported in all EDITION studies (22–25). For example, a study using continuous glucose monitoring to examine hypoglycemia in a population aged ≥69 years old reported that 93% of events were unrecognized (26). Given that the risk of hypoglycemia in older people is likely to be underestimated, the trend toward a greater reduction in hypoglycemic risk observed with Gla-300 versus Gla-100, which was consistent with those observed in the overall EDITION population (27,28) and in the older population of the EDITION studies (21), may be beneficial in older people and will be the focus of future real-world investigations.

In keeping with ADA recommendations for older people (8), the SENIOR study used a titration algorithm with a higher glycemic target of 5.0–7.2 mmol/L (90–130 mg/dL) compared with 4.4–7.2 mmol/L (80–130 mg/dL) recommended for the overall population, owing to the diversity of cognitive function, frailty, comorbidities, polypharmacy, and pathophysiology observed in older adults. Despite this, similar reductions in HbA_{1c} and FPG were observed in SENIOR compared with the overall EDITION population with type 2 diabetes (27,28) and the combined older (≥65 years) populations of EDITION 1–3 studies (21), where a lower glycemic target (4.4–7.2 mmol/L [80–130 mg/dL]) was used (22–25). Furthermore, >50% of participants in SENIOR achieved a target HbA_{1c} of <7.5% (<58 mmol/mol), similar to HbA_{1c} target achievement observed in participants ≥65 years of age from EDITION 1–3 (21). Hence, the results from SENIOR show that Gla-300 can be used in older people with type 2 diabetes, in accordance with the ADA safety recommendations to use higher glycemic targets, without compromising efficacy.

Limitations of SENIOR include the open-label design (owing to the different

pen injectors) and the lack of functional mobility assessments. Although mobility was assessed using PROs, the standardized EQ-5D questionnaire used may not have had sufficient sensitivity to detect any differences in mobility score during the course of the study. Owing to the relatively small number of hypoglycemic events reported, the power to detect significant differences in hypoglycemia risk was low. In addition, further analyses are required to explain the lower hypoglycemia risk with Gla-300 compared with Gla-100 observed in participants aged ≥75 years.

In summary, Gla-300 demonstrated good efficacy and safety in older people with type 2 diabetes, particularly in those of advanced age (≥75 years). In the overall population, comparable reductions in HbA_{1c} and lower rates of documented symptomatic hypoglycemia were observed with Gla-300 versus Gla-100. Although the risk of hypoglycemia was similar in all prespecified baseline characteristic subgroups, a greater reduction in the rate of documented symptomatic hypoglycemia with Gla-300 versus Gla-100 was observed in the subgroup of people ≥75 years of age. Results of SENIOR confirm those previously observed in both the overall and the older population of the EDITION 1–3 studies (21–23,25), with similar reductions in HbA_{1c} observed despite the less stringent glycemic target used in SENIOR, indicating that Gla-300 is suitable for use in this vulnerable population.

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