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Insulin glargine 300 U/mL vs 100 U/mL in people ≥75 years old with T2DM: secondary analysis of the SENIOR study

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INTRODUCTION

- The prevalence of type 2 diabetes (T2DM) increases with age owing to attenuated β-cell function.[1]
- The IDF estimated that in 2015, 94 million people 65–79 years of age worldwide were affected by diabetes.[2]
- Older people with T2DM have an increased risk of hypoglycemia for reasons including renal failure, cognitive dysfunction and impaired awareness of hypoglycemia.[3–5]
- Hypoglycemia in older persons may have adverse impacts including acute cardiovascular events, impaired cognitive function, dementia, hospitalization, disability and mortality.[3–5]
- Reducing the risk of hypoglycemia is particularly important in individuals ≥75 years of age as:
  - Up to 93% of hypoglycemic events are unrecognized by people aged ≥69 years.[6]
  - The impact of hypoglycemia is particularly severe, with hospitalization rates two-fold higher in individuals ≥75 years of age versus those 65–74 years of age.[7]
- SENIOR investigated the efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus 100 U/mL (Gla-100) in elderly participants (≥65 years of age) with T2DM.
- Results of pre-planned subgroup analyses in participants <75 years and ≥75 years are presented.

OBJECTIVE

As people ≥75 years of age with T2DM are at high risk of hypoglycemia and associated complications, this secondary analysis of data from the SENIOR study compared the efficacy and safety of Gla-300 and Gla-100 in this population versus participants ≥65 to <75 years of age.

METHODS

- **Design:** SENIOR (NCT02320721) was a phase 3b international, multicenter, active-controlled, randomized, open-label, 2-arm, parallel-group study. The study comprised a 4-week screening period followed by a 26-week treatment period.
- **Randomization and treatment:** Randomization was stratified by screening HbA_{1c} (<8.0 vs ≥8.0 %), previous insulin use (Yes/No), and sulfonylurea or meglitinide use at screening (Yes/No). Insulin was titrated to a fasting self-monitored plasma glycose (SMPG) of 90–130 mg/dL (5.0–7.2 mmol/L; ADA-recommended target for healthy older individuals)[3]; this was a higher target than used in the EDITION studies.[8–11] Insulins were self-administered once daily at the same time (preferably evening) ± 3 hours.
- Key inclusion criteria: Participants ≥65 years of age who were either insulin naïve or receiving basal insulin were included. Baseline HbA_{1c} was 7.5–11.0 % for insulin-naïve participants or 7.0–10.0 % for basal-only participants.
  - Enrollment was designed to recruit ≥20% of participants ≥75 years of age.
- **Primary endpoint:** Change in HbA_{1c} from baseline to week 26.
- **Secondary endpoints:**
  - Percentage of participants experiencing ≥1 hypoglycemic event and annualized rates of hypoglycemia at ≤70 mg/dL (≤3.9 mmol/L) or <54 mg/dL (<3.0 mmol/L) thresholds occurring at any time of day (24 h) or at night (00:00–05:59 h) over 26 weeks of treatment.
  - Adverse events (AEs).
- **Data analysis and statistics:**
  - Change in HbA_{1c} from baseline to week 26 was assessed using an analysis of covariance model with missing values imputed by multiple imputation approach.
  - Subgroup analyses according to randomization strata were performed on the primary endpoint following similar methodology as the primary analysis.
  - A stepwise closed testing approach was used to assess non-inferiority and then superiority for the primary endpoint. Tests were performed one-sided at level α=0.025.
  - Hypoglycemia was assessed using a Cochran–Mantel–Haenszel (CMH) method with treatment group as a factor and stratified by randomization strata.
  - Analyses of safety endpoints were descriptive.

RESULTS

- **Study participants:**
  - Of 1014 participants, 241 were ≥75 years of age (**Table 1**).

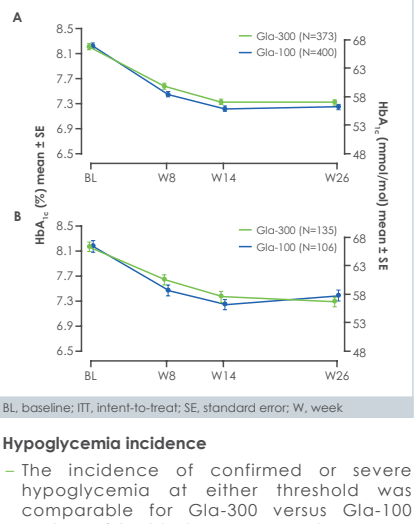
Table 1: Demographic and baseline characteristics (randomized population)

	Participants <75 years of age		Participants ≥75 years of age	
	Gla-300 (N=373)	Gla-100 (N=400)	Gla-300 (N=135)	Gla-100 (N=106)
Age, years	68.7 (2.7)	68.9 (2.8)	78.0 (2.7)	78.1 (3.5)
Gender, male, n (%)	174 (46.6)	216 (54.0)	76 (56.3)	61 (57.5)
Race, n (%)				
Caucasian/white	306 (82.0)	337 (84.3)	111 (82.2)	85 (80.2)
Black	12 (3.2)	10 (2.5)	5 (3.7)	2 (1.9)
Asian/oriental	32 (8.6)	26 (6.5)	8 (5.9)	6 (5.7)
Other	23 (6.2)	27 (6.8)	11 (8.1)	13 (12.3)
BMI, kg/m²	31.4 (5.6)	31.7 (5.8)	29.7 (5.0)	29.5 (5.1)
eGFR, mL/min/1.73 m²	78.6 (23.5)	77.6 (21.9)	66.9 (19.9)	67.0 (23.1)
HbA_{1c}, (%)	8.21 (0.92)	8.23 (0.91)	8.17 (0.89)	8.18 (0.97)
Duration of diabetes, years	14.7 (7.8)	14.7 (7.4)	16.9 (9.1)	18.0 (8.4)
Previous insulin daily dose, U/kg	0.43 (0.26)	0.42 (0.24)	0.40 (0.26)	0.36 (0.22)
Prior use of SU or meglitinides, n (%)	188 (50.4)	199 (49.8)	61 (45.2)	50 (47.2)

Data are mean (SD) unless otherwise stated. BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; SU, sulfonylureas

- **Glycemic control:**
  - Non-inferiority in mean change in HbA_{1c} between treatment groups was achieved for the <75 years (least squares mean difference [standard error; SE]: 0.06 [−0.067, 0.179] %) and ≥75 years (−0.11 [SE: −0.330, 0.106] %) subgroups (**Figure 1**).
  - Pre-breakfast SMPG was similar between age subgroups and treatment groups; mean (standard deviation; SD): 130 (29) mg/dL versus 128 (25) mg/dL for the <75 years subgroup and 129 (27) mg/dL versus 125 (24) mg/dL for the ≥75 years subgroup for Gla-300 and Gla-100, respectively.

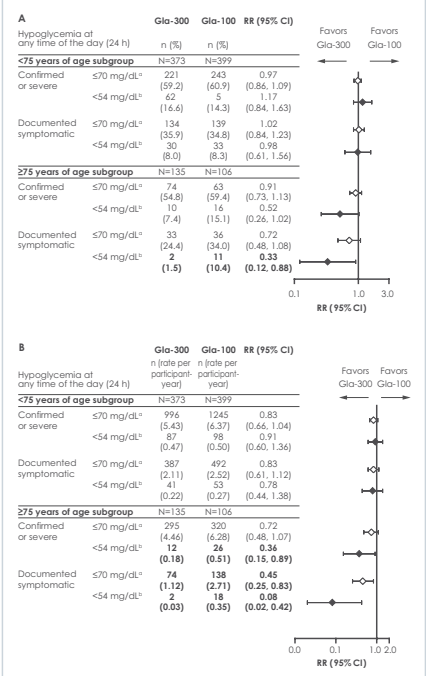
Figure 1: Change in mean HbA_{1c} in A) <75 years and B) ≥75 years subgroups (ITT population)



BL, baseline; ITT, intent-to-treat; SE, standard error; W, week

- **Hypoglycemia incidence**
  - The incidence of confirmed or severe hypoglycemia at either threshold was comparable for Gla-300 versus Gla-100 and consistent between <75 and ≥75 years subgroups (**Figure 2A**).
  - Incidence of documented symptomatic hypoglycemia was comparable for Gla-300 and Gla-100 in the <75 years group, but fewer participants had an event with Gla-300 versus Gla-100 in the ≥75 years group at the <54 mg/dL (<3.0 mmol/L) threshold (**Figure 2A**).
- **Hypoglycemic event rates:**
  - Annualized event rates of confirmed or severe hypoglycemia were lower for Gla-300 versus Gla-100 in the ≥75 years subgroup at the <54 mg/dL (<3.0 mmol/L) threshold (**Figure 2B**).
  - Annualized rates of documented symptomatic hypoglycemia at both glycemic thresholds were lower with Gla-300 versus Gla-100 in the ≥75 years subgroup, but were comparable between treatments in the <75 years subgroup (**Figure 2B**).
- **Treatment-emergent adverse events (TEAEs):**
  - Incidence of any TEAE was similar across all subgroups and between treatment groups (54.7%–61.7%).
  - Incidence of any cardiovascular TEAE (0.5%–2.2%) and falls/fractures (0%–3.8%) were low.

Figure 2: A) Percentage of participants with ≥1 hypoglycemic event and B) annualized hypoglycemic event rates in the <75 and ≥75 years subgroups (safety population)



RR data adjusted by randomization strata of: HbA_{1c} levels at screening (<8.0 or ≥8.0 %); previous use of insulin (Yes/No); and use of sulfonylureas or meglitinides at screening (Yes/No).
[a] ≤3.9 mmol/L; [b] <3.0 mmol/L; CI, confidence interval; RR, relative risk (for percentage of participants with ≥1 event) or rate ratio (for annualized rates of hypoglycemia).

SUMMARY

- Gla-300 was effectively and safely titrated in older people (≥65 years of age) with T2DM, with comparable reductions in HbA_{1c} observed between treatment groups in both the <75 years and ≥75 years subgroups.
- There was a consistent trend towards a lower incidence of hypoglycemia with Gla-300 in the ≥75 years subgroup, which achieved significance for documented symptomatic hypoglycemia at the <54 mg/dL (<3.0 mmol/L) threshold (indicative of clinically significant hypoglycemia).[3]
- Significant reductions in annualized event rates for documented symptomatic hypoglycemia and for confirmed or severe hypoglycemia (<54 mg/dL [<3.0 mmol/L]) were achieved with Gla-300 versus Gla-100 in the older subgroup (≥75 years of age).

CONCLUSIONS

- **Gla-300 demonstrated comparable efficacy to Gla-100 in <75 and ≥75 years subgroups, with consistently lower rates and incidence of documented symptomatic hypoglycemia observed in participants ≥75 years of age.**
- **Gla-300 may offer treatment benefits in the understudied and potentially vulnerable elderly population (≥75 years of age), who are at high risk of hypoglycemia.**

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