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Insulin glargine 300 U/mL versus 100 U/mL in older people with T2DM: results from a randomized trial

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INTRODUCTION

- An estimated 94 million people aged 65–79 years had diabetes in 2015.[1]
- Older people with diabetes are more prone to hypoglycemia compared with younger people because of a reduced knowledge and awareness of its warning symptoms and diminished psychomotor performance.[2]
- Hypoglycemic events in older people with diabetes have been linked to an increased incidence of acute cardiovascular events, falls and fractures, impaired cognitive function, dementia, hospitalizations, and mortality.[3–10]
- The American Diabetes Association (ADA) guidelines recommend an individualized approach to setting glycemic targets in older populations.[11]
- Insulin glargine 300 U/mL (Gla-300) provides more stable and prolonged steady-state pharmacokinetic and pharmacodynamic profiles than insulin glargine 100 U/mL (Gla-100).[12]
- A post hoc analysis of data pooled from the EDITION 1, 2, and 3 trials confirmed comparable glycemic control and hypoglycemia benefit for Gla-300 versus Gla-100 in people with type 2 diabetes (T2DM) ≥65 years of age.[13]
- The SENIOR study was the first prospectively designed clinical trial to address the efficacy and safety of insulin glargine in older people (≥65 years of age) with T2DM. The study was also designed such that approximately 20% of the people enrolled would be ≥75 years of age.

OBJECTIVE

To compare the efficacy and safety of Gla-300 with Gla-100 in older people with T2DM.

METHODS

- **Design:** SENIOR (NCT02320721) was a phase 3b international, multicenter, active-controlled, randomized, open-label, 2-arm, parallel- group study. The study consisted of 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 (SU) or meglitinide use at screening (Yes/No). Insulin was titrated to the ADA-recommended glycemic target for healthy older people (fasting self-monitored plasma glucose [SMPG]: 90–130 mg/dL 5.0–7.2 mmol/L]), a higher glycemic target than utilized previously in randomized controlled trials of Gla-300 versus Gla-100 in adults. Gla-300 and Gla-100 were self-administered once daily at the same time (preferably in the evening) within ±3 hours.
- **Key inclusion criteria:** Age ≥65 years, receiving an antihyperglycemic regimen including no insulin or basal insulin only, HbA_{1c} 7.5–11.0 % (for insulin-naïve participants) or 7.0–10.0 % (for participants using basal insulin).
- **Primary endpoint:** Change in HbA_{1c} from baseline to week 26.
- **Secondary endpoints:**
  - Percentage of participants with ≥1 confirmed (≤70 mg/dL [≤3.9 mmol/L]) and/or severe hypoglycemic event occurring at any time of day (24 h) over 26 weeks of treatment.
  - Percentage of participants with ≥1 nocturnal (00:00–05:59 h) confirmed (≤70 mg/dL [≤3.9 mmol/L]) and/or severe hypoglycemic event over 26 weeks of treatment.
  - Documented symptomatic hypoglycemia, adverse events (AEs), and serious AEs (SAEs).
- **Data analysis and statistics:**
  - Change in HbA_{1c} from baseline to week 26 was assessed using an analysis of covariance (ANCOVA) 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. Analysis of the ≥75 years subpopulation was prespecified only for the primary endpoint.
  - A stepwise closed testing approach was used to assess non-inferiority and superiority for the primary endpoint. Tests were performed one- sided at level α=0.025.
  - Superiority testing for the main secondary efficacy endpoints was analyzed using the Cochran-Mantel-Haenszel (CMH) method with treatment group as a factor and stratified by randomization strata. Tests for superiority were performed 2-sided at level α=0.05.

RESULTS

- **Study participants:**
  - Of a total of 1014 participants (**Table 1**), 241 (23.8%) were ≥75 years of age and 331 (32.6%) were insulin-naïve.

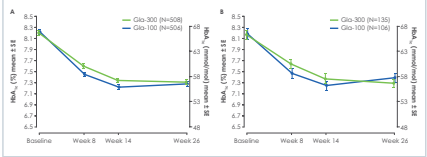
Table 1: Demographic and baseline characteristics (randomized population)

	Overall study population		Participants ≥75 years of age	
	Gla-300 (N=508)	Gla-100 (N=506)	Gla-300 (N=135)	Gla-100 (N=106)
Age, years	71.1 (4.9)	70.8 (4.8)	78.0 (2.7)	78.1 (3.5)
Gender, male, n (%)	250 (49.2)	277 (54.7)	76 (56.3)	61 (57.5)
Race, n (%)				
Caucasian/white	417 (82.1)	422 (83.4)	111 (82.2)	85 (80.2)
Black	17 (3.3)	12 (2.4)	5 (3.7)	2 (1.9)
Asian/Oriental	40 (7.9)	32 (6.3)	8 (5.9)	6 (5.7)
Other	34 (6.7)	40 (7.9)	11 (8.1)	13 (12.3)
BMI, kg/m²	30.9 (5.5)	31.2 (5.7)	29.7 (5.0)	29.5 (5.1)
eGFR, mL/min/1.73 m²	75.4 (23.0)	75.4 (22.6)	66.9 (19.9)	67.0 (23.1)
Duration of diabetes, years	15.3 (8.2)	15.4 (7.7)	16.9 (9.1)	18.0 (8.4)
Previous insulin daily dose, U/kg	0.42 (0.26)	0.41 (0.24)	0.40 (0.26)	0.36 (0.22)
Prior use of SU or meglitinides, n (%)	249 (49.0)	249 (49.2)	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

- **Change in HbA_{1c}:**
  - Mean HbA_{1c} decreased from baseline to week 26 in both treatment groups (**Figure 1**). The proportion of participants who reached HbA_{1c} <7.5 % at week 26 was 60.6% and 58.9% for Gla-300 vs Gla-100, respectively, overall, and 62.2% and 53.8%, respectively, for the ≥75 years subpopulation.

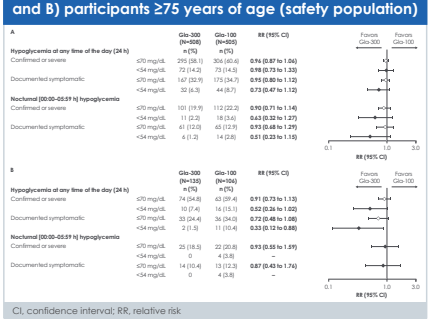
Figure 1: Mean change in HbA_{1c} by visit during the 26-week treatment period in A) the overall study population and B) participants ≥75 years of age (ITT population)



ITT, intent to treat

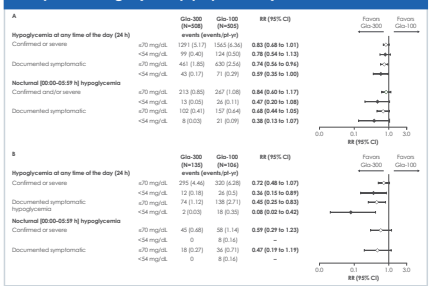
  - The primary objective was met. Gla-300 was non-inferior versus Gla-100 for change in HbA_{1c} from baseline to week 26 (LS mean change [standard error (SE)]: Gla-300, −0.89 [0.04] %; Gla-100, −0.91 [0.04] %; LS mean difference [95% CI] Gla-300 vs Gla-100: 0.02 [−0.09, 0.13] %). For the ≥75 years subpopulation, LS mean (SE) change in HbA_{1c} was −0.91 (0.07) % and −0.80 (0.09) % for Gla-300 versus Gla-100, respectively; LS mean difference: −0.11 (95% CI: −0.33, 0.11) %. Similar results were obtained in subgroup analyses according to the randomization strata.
- **Confirmed and/or severe hypoglycemia:**
  - Comparable proportions of participants from both treatment groups experienced ≥1 confirmed and/or severe hypoglycemic event, for both glycemic thresholds examined, at any time of day (24 h) and at night (00:00–05:59 h); this was observed for the overall population (**Figure 2A**) and for participants ≥75 years of age (**Figure 2B**).
  - Overall, annualized event rates for confirmed (≤70 mg/dL [≤3.9 mmol/L]) and/or severe hypoglycemia were similar, both at any time of day and at night (00:00–05:59 h), but a trend towards lower rates with Gla-300 versus Gla-100 was observed at the lower threshold of <54 mg/dL (<3.0 mmol/L) (**Figure 3A**); for participants ≥75 years of age, reductions in annualized rates of anytime (24 h) hypoglycemia with Gla-300 versus Gla-100 were observed (**Figure 3B**).

Figure 2: Number (%) of participants experiencing ≥1 hypoglycemic event in A) the overall study population and B) participants ≥75 years of age (safety population)



CI, confidence interval; RR, relative risk

Figure 3: Annualized event rates of hypoglycemia in A) the overall study population and B) participants ≥75 years of age (safety population)



CI, confidence interval; pt-yr, participant-year; RR, rate ratio

- **Documented symptomatic hypoglycemia:**
  - For the overall population, the incidence of documented symptomatic (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia at anytime (24 h) and at night (00:00–05:59 h) was comparable between treatment groups (**Figure 2A**); the incidence of anytime (24 h) documented symptomatic (<54 mg/dL [<3.0 mmol/L]) hypoglycemia was lower with Gla-300 than Gla-100 in participants ≥75 years of age (**Figure 2B**).
  - The annualized rates of documented symptomatic (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia at any time of day (24 h) were lower with Gla-300 versus Gla-100, both in the overall study population and in the ≥75 years subpopulation (**Figure 3A** and **3B**).
- **Adverse events:**
  - The incidence of treatment-emergent AEs (TEAEs) was similar in the Gla-300 and Gla-100 groups (**Table 2**).

Table 2: Adverse events (safety population)

	Gla-300 (N=508)	Gla-100 (N=505)
Participants with any TEAE	299 (58.9)	304 (60.2)
Participants with any treatment-emergent SAE	41 (8.1)	34 (6.7)
Participants with any TEAE leading to death	3 (0.6)	2 (0.4)
Participants with any TEAE leading to permanent treatment discontinuation	6 (1.2)	5 (1.0)
Cardiac disorders	24 (4.7)	16 (3.2)
Any cardiovascular death	2 (0.4)	1 (0.2)
Infections and infestations	131(25.8)	150 (29.7)
Any hypersensitivity reaction	28 (5.5)	21 (4.2)
Injection-site reaction	5 (1.0)	9 (1.8)
Headaches	22 (4.3)	13 (2.6)
Osteoporosis	1 (0.2)	0
Osteoarthropathies	6 (1.2)	6 (1.2)
Any fracture	4 (0.8)	8 (1.6)
Hepatobiliary disorders	8 (1.6)	2 (0.4)

Data shown are the number (%) of events for the overall population. TEAE, treatment-emergent adverse event; SAE, serious adverse event

DISCUSSION

- HbA_{1c} reductions observed in SENIOR were consistent with those reported in EDITION 1, 2, and 3,[14–16] despite the less stringent glycemic target set for SENIOR (90–130 mg/dL) than EDITION (80–100 mg/dL).
- Overall, slight reductions in hypoglycemia were observed for Gla-300 versus Gla-100. The incidence of confirmed (≤70 mg/dL [≤3.9 mmol/L]) and/or severe hypoglycemia was lower than expected, possibly owing to the higher glycemic treatment target set in SENIOR compared with the EDITION trials.
- Gla-300 was associated with consistently lower annualized event rates and number (%) of participants with documented symptomatic (<54 mg/dL [<3.0 mmol/L]) hypoglycemia in the ≥75 years subpopulation, indicating that Gla-300 may help this subpopulation avoid the complications associated with these more serious hypoglycemic events such as seizure, fall, confusion, coma, and cardiac arrhythmias.[5]
- Reduced hypoglycemic risk for Gla-300 versus Gla-100 was more pronounced in participants ≥75 years of age. Further analysis is required to elucidate the reason behind the greater reduction in hypoglycemia risk in this subpopulation.

CONCLUSIONS

Results of the SENIOR study indicate that Gla-300 was effective in older people with T2DM, with a good safety profile, resulting in comparable reductions in HbA_{1c} and lower rates of documented symptomatic hypoglycemia versus Gla-100.

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References: 1. International Diabetes Federation. Managing Older People With Type 2 Diabetes: Global Guideline. 2013; 2. Viljoen A, *et al. Med Clin North Am* 2011; 95: 615–29, xi-ii; 3. Kirkman MS, *et al. Diabetes Care* 2012; 35: 2650–64; 4. Sinclair A, *et al. J Am Med Dir Assoc* 2012; 13: 497–502; 5. Abdelhafiz AH, *et al. Aging Dis* 2015; 6: 156–67; 6. Whitmer RA, *et al. JAMA* 2009; 301: 1565–72; 7. Geller AI, *et al. JAMA Intern Med* 2014; 174: 678–86; 8. Kagansky N, *et al. Arch Intern Med* 2003; 163: 1825–9; 9. Majumdar SR, *et al. Diabetes Care* 2013; 36: 3585–90; 10. Stepka M, *et al. Aging* (Milano) 1993; 5: 117–21; 11. ADA. *Diabetes Care* 2017; 40: S99–S104; 12. Becker RH, *et al. Diabetes Care* 2015; 38: 637–43; 13. Yale J-F, *et al. Diabetes* 2015; 64 (Suppl 1): Abstract 991-P; 14. Riddle MC, *et al. Diabetes Care* 2014; 37: 2755–62; 15. Yki-Jarvinen H, *et al. Diabetes Care* 2014; 37: 3235–43; 16. Bolli GB, *et al. Diabetes Obes Metab* 2015; 17: 386–94.

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