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Glycemic control and hypoglycemia benefits with insulin glargine 300 U/mL (Gla-300) extend to people with type 2 diabetes (T2DM) and mild-to-moderate renal impairment

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INTRODUCTION

- Insulin glargine 300 U/mL (Gla-300) is a long-acting basal insulin for the treatment of both type 1 diabetes (T1DM) and type 2 diabetes (T2DM).
- Pharmacokinetic and pharmacodynamic studies have shown that, following injection, Gla-300 releases more gradually from the subcutaneous tissue than insulin glargine 100 U/mL (Gla-100), giving a more constant pharmacokinetic profile with a prolonged duration of action beyond 24 hours.
- EDITION 1, 2 and 3 showed that over 6 months Gla-300 provided comparable glycemic control to Gla-100, with less hypoglycemia in people with T2DM.[1–3]
  - Post hoc analyses have shown these benefits were maintained regardless of age, BMI and diabetes duration.[4]
- Renal impairment increases the risk of hypoglycemia in people with T2DM[5–6], and may limit glucose-lowering-therapy options.[7]
  - Therefore, it may be more challenging to manage diabetes in this population than in people with normal renal function.

OBJECTIVE

To investigate the impact of renal function on HbA_{1c} reduction and hypoglycemia in a post hoc patient-level meta-analysis of people with T2DM treated with Gla-300 or Gla-100 for 6 months in the EDITION 1,2 and 3 studies.

METHODS

Design:

- Post hoc patient-level meta-analysis of EDITION 1, 2 and 3 (NCT01499082, NCT01499095, NCT01676220) at 6 months.
- EDITION 1, 2 and 3 were multicenter randomized (1:1), open-label, two-arm, parallel-group, phase 3a studies.[1–3]

Participants:

- Adult patients (≥18 years of age) with previous diagnosis of T2DM:
  - EDITION 1: on basal (≥42 U/day) and prandial insulin therapy ± metformin for ≥1 year;
  - EDITION 2: on basal insulin therapy (≥42 U/day) in combination with oral antihyperglycemic drugs (OADs) for ≥1 year;
  - EDITION 3: insulin naïve on OADs for ≥6 months.
- People with severe, unstable or end-stage renal disease (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2) were excluded from the EDITION trials.

Treatment:

- Once-daily evening injection of Gla-300 or Gla-100 titrated to a fasting self-monitored plasma glucose (SMPG) of 80–100 mg/dL (4.4–5.6 mmol/L).

Subgroups:

- The effects of Gla-300 vs Gla-100 were assessed in renal function subgroups based on baseline eGFR (mL/min/1.73 m^2):
  - ≥30 to <60 (moderate renal impairment)
  - ≥60 to <90 (mild renal impairment)
  - ≥90 (normal renal function).
- Participants with baseline eGFR <30 mL/min/1.73 m^2 (severe renal impairment) were excluded from this post hoc analysis (pooled randomized population: Gla-300, n=7; Gla-100, n=13).

Outcomes:

- Mean change from baseline HbA_{1c} was assessed together with the percentage of participants achieving HbA_{1c} target <7.0 % and <7.5 % at month 6.
- Hypoglycemia was assessed according to the following guidelines:
  - Cumulative number of events, relative risk (≥1 event) and rate per participant-year of confirmed (≤70 or <54 mg/dL (≤3.9 or <3.0 mmol/L)) or severe nocturnal (00:00–05:59 h) or at anytime (24 h) hypoglycemia.

Statistical analyses:

- Change in HbA_{1c} was analyzed using Mixed effect Model Repeat Measurement (MMRM).
- Relative risk of hypoglycemia was analyzed using the Cochran–Mantel–Haenszel method.
- Hypoglycemic events per participant-year were analyzed using an overdispersed Poisson regression model.
- For HbA_{1c} and annualized rates of hypoglycemia, the homogeneity of the treatment effect among subgroups was assessed using subgroup-by-treatment interaction.
- Differences of treatment effect across subgroups are only relevant if significant heterogeneity was observed (p<0.05).

RESULTS

Patient characteristics:

- Data were available for 2476 participants (randomized population: EDITION 1, 401; EDITION 2, 1390; EDITION 3, 685).
- Most participants (56%) had baseline eGFR ≥60 to <90 mL/min/1.73 m^2.
- The distribution of subjects according to each study is shown in **Table 1**.

Table 1: Baseline eGFR (by study and pooled population)

		≥30 to <60		≥60 to <90		≥90	
		Gla-300 (N=201)	Gla-100 (N=200)	Gla-300 (N=703)	Gla-100 (N=687)	Gla-300 (N=336)	Gla-100 (N=349)
EDITION 1	N	93	83	234	221	75	89
	Mean (SD)	49.2 (7.7)	48.7 (8.1)	74.7 (8.3)	75.6 (8.2)	102.1 (10.0)	103.0 (10.0)
EDITION 2	N	55	55	213	218	134	132
	Mean (SD)	50.4 (7.0)	50.0 (7.0)	75.8 (8.3)	74.4 (8.1)	105.7 (14.5)	104.1 (12.9)
EDITION 3	N	53	62	256	248	127	128
	Mean (SD)	50.5 (6.9)	51.2 (6.7)	76.9 (8.5)	76.4 (8.6)	104.3 (11.1)	103.8 (13.2)
Pooled population	N	201	200	703	687	336	349
	Mean (SD)	49.9 (7.3)	49.8 (7.5)	75.9 (8.4)	75.5 (8.4)	104.4 (12.4)	103.7 (12.3)

Pooled randomized population. eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); SD, standard deviation

- Baseline patient characteristics are shown in **Table 2**.

Table 2: Baseline demographic and disease characteristics by renal function subgroups

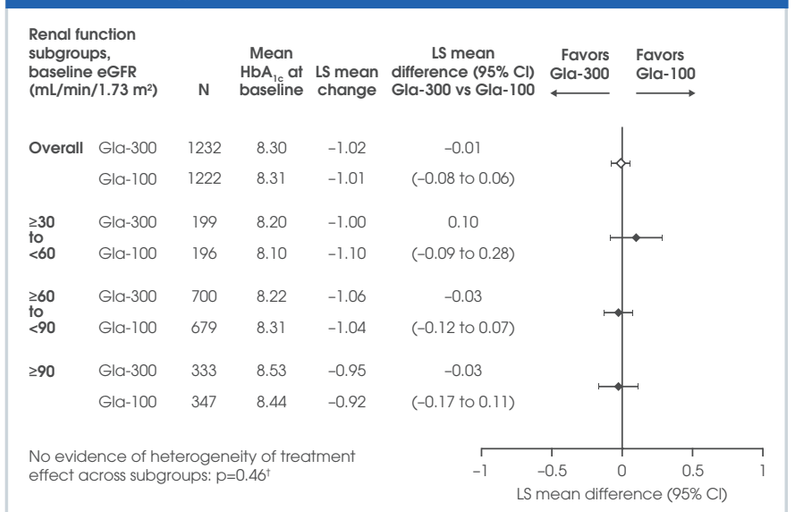
	≥30 to <60		≥60 to <90		≥90	
	Gla-300 (N=201)	Gla-100 (N=200)	Gla-300 (N=703)	Gla-100 (N=687)	Gla-300 (N=336)	Gla-100 (N=349)
Age, years	65.0 (7.9)	65.0 (7.6)	59.7 (7.9)	59.0 (8.4)	52.7 (9.3)	53.5 (10.0)
Gender, male, n (%)	105 (52.2)	96 (48.0)	381 (54.2)	373 (54.3)	167 (49.7)	175 (50.1)
BMI, kg/m^2	35.6 (7.0)	35.3 (6.4)	34.5 (6.9)	34.8 (6.0)	34.7 (7.2)	34.6 (7.2)
eGFR, mL/min/1.73 m^2	49.9 (7.3)	49.8 (7.5)	75.9 (8.4)	75.5 (8.4)	104.4 (12.4)	103.7 (12.3)
Duration of T2DM, years	15.7 (7.9)	15.7 (7.9)	12.8 (7.2)	12.7 (7.5)	10.7 (6.2)	10.6 (6.5)
Duration of basal insulin treatment, years†	5.7 (4.9)	6.0 (4.6)	5.5 (4.8)	5.4 (4.5)	4.3 (3.5)	4.1 (3.7)

Data are mean (SD) unless otherwise indicated. Pooled randomized population (EDITION 1, 2 and 3). †EDITION 1 and 2 only. BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; T2DM, type 2 diabetes

Efficacy:

- HbA_{1c} change from baseline to month 6 was comparable between Gla-300 and Gla-100 for the overall population and remained comparable regardless of renal function (**Figure 1**).
- There was no evidence of heterogeneity of treatment effect across subgroups (p=0.46).

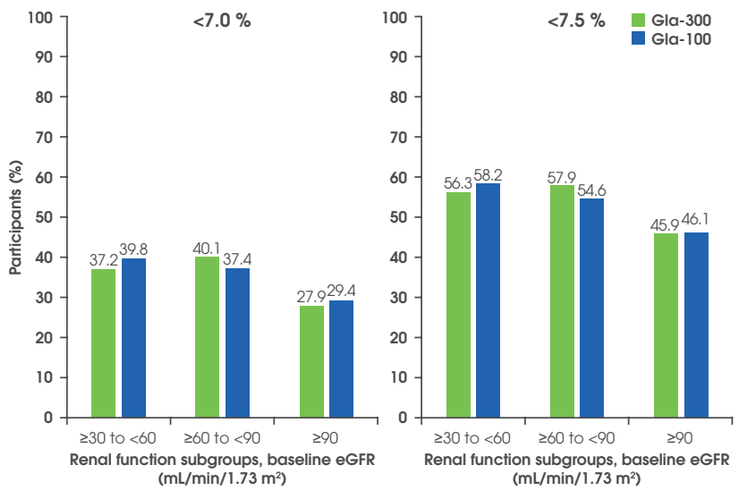
Figure 1: HbA_{1c} Reduction from baseline to month 6



Pooled mITT population, †p<0.05 corresponds to significant heterogeneity of treatment effect. CI, confidence interval; LS, least squares; mITT, modified intent-to-treat

- No significant difference was seen between Gla-300 and Gla-100 treatment arms in proportion of participants at HbA_{1c} targets (**Figure 2**).

Figure 2: Percentage of Subjects Achieving HbA_{1c} <7.0 % and <7.5 %



eGFR, estimated glomerular filtration rate

Safety:

- Risk of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia was significantly lower for nocturnal (00:00–05:59 h) events and comparable or lower for anytime (24 h) events for Gla-300 vs Gla-100 across subgroups (**Table 3**).
- Renal function did not affect the lower rate of nocturnal or anytime hypoglycemia (no evidence of heterogeneity of treatment effect across subgroups: p=0.73, p=0.27).
- Severe hypoglycemia was rare and renal function did not affect the rate of severe events.

Figure 3: Cumulative mean number of events of confirmed (≤3.9 mmol/L (≤70 mg/dL)) or severe hypoglycemia

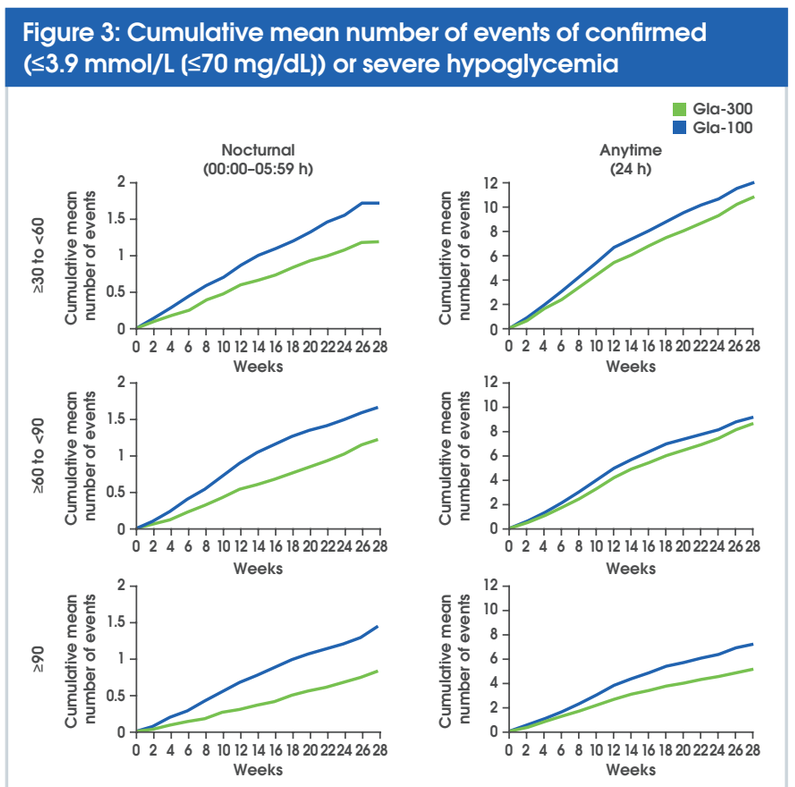


Table 3: Participants with ≥1 confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemic events

		Nocturnal (00:00–05:59 h) Participants with ≥1 event, n (%)		Anytime (24 h) Participants with ≥1 event, n (%)	
Renal function subgroups, baseline eGFR (mL/min/1.73m²)	N	Gla-300	Gla-100	Gla-300	Gla-100
Overall	2468	371 (30.0)	490 (39.7)	812 (65.7)	884 (71.7)
≥30 to <60	399	79 (39.5)	102 (51.3)	159 (79.5)	160 (80.4)
≥60 to <90	1386	225 (32.1)	274 (40.0)	470 (67.0)	489 (71.4)
≥90	683	67 (20.1)	114 (32.7)	183 (54.8)	235 (67.3)

Pooled safety population. eGFR, estimated glomerular filtration rate

Table 4: Rate of confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemic events

		Nocturnal (00:00–05:59 h) Number of events (rate per participant-year)		Anytime (24 h) Number of events (rate per participant-year)	
Renal function subgroups, baseline eGFR (mL/min/1.73m²)	N	Gla-300	Gla-100	Gla-300	Gla-100
Overall	2468	1234 (2.1)	1769 (3.1)	8925 (15.3)	10,066 (17.4)
≥30 to <60	399	221 (2.3)	309 (3.3)	1961 (20.7)	2158 (23.2)
≥60 to <90	1386	769 (2.3)	1022 (3.2)	5411 (16.2)	5606 (17.5)
≥90	683	244 (1.5)	438 (2.7)	1553 (9.9)	2302 (13.9)

Pooled safety population, treatment effect. eGFR, estimated glomerular filtration rate

SUMMARY

This patient-level meta-analysis of pooled 6-month data from the EDITION 1, 2 and 3 studies of participants with T2DM by eGFR subgroups (normal (n=683), mild (n=1386) and moderate (n=399) renal impairment) at baseline demonstrated:

- Consistent and comparable HbA_{1c} reductions for both the Gla-300 and Gla-100 groups, regardless of renal function subgroups.
- Hypoglycemia rates at night and at any time were consistently lower for participants treated with Gla-300 vs Gla-100 and were not affected by eGFR subgroups at baseline.

CONCLUSION

Gla-300 provided comparable glycemic control and consistently reduced the risk of nocturnal hypoglycemia vs Gla-100 in participants with T2DM regardless of renal function, with no increase in anytime hypoglycemia.

The data were presented previously at the 19th Annual Meeting of the Canadian Diabetes Association, October 26–29, 2016, Ottawa, Ontario, Canada, and as an oral presentation at the 76th Scientific Sessions of the American Diabetes Association, June 10–14, 2016, New Orleans, LA, USA.

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