

Wider windows for evaluating nocturnal hypoglycemia capture more events and confirm lower nocturnal hypoglycemia risk with insulin glargine 300 U/mL (Gla-300) vs 100 U/mL (Gla-100) in T2DM

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INTRODUCTION

- Insulin glargine 300 U/mL (Gla-300) has more stable and prolonged pharmacokinetic and pharmacodynamic profiles than insulin glargine 100 U/mL (Gla-100),¹ which translates into Gla-300 providing equivalent glycemic control to Gla-100 with less hypoglycemia in people with type 2 diabetes (T2DM), as shown in the EDITION treat-to-target studies.²
- The 00:00–05:59 h nocturnal window used in the EDITION studies provides a standardized assessment interval that avoids the potential confounders of food and exercise. However, this window may not capture all clinically relevant nocturnal hypoglycemic events during the true fasting period (i.e. late evening to pre-breakfast).
- The value of extending the interval when assessing nocturnal hypoglycemia was shown in a patient-level meta-analysis of EDITION 1, 2 and 3, whereby the clinically defined window from 22:00 h to just before breakfast included many more hypoglycemic events vs the 00:00–05:59 h window and confirmed a clinically relevant benefit of Gla-300.³
- It would be of value to explore the consistency of these findings using studies in which only basal insulin was used (no prandial insulin; EDITION 2, 3 and Japan (JP) 2), avoiding confounding effects of prandial insulin. In addition, including broader nocturnal windows than the predefined interval would ensure that all clinically relevant nocturnal events were captured.

OBJECTIVE

To evaluate nocturnal hypoglycemia risk for Gla-300 vs Gla-100, using four different windows to define nocturnal hypoglycemia, in a patient-level meta-analysis of people with T2DM from EDITION 2, 3 and JP 2.

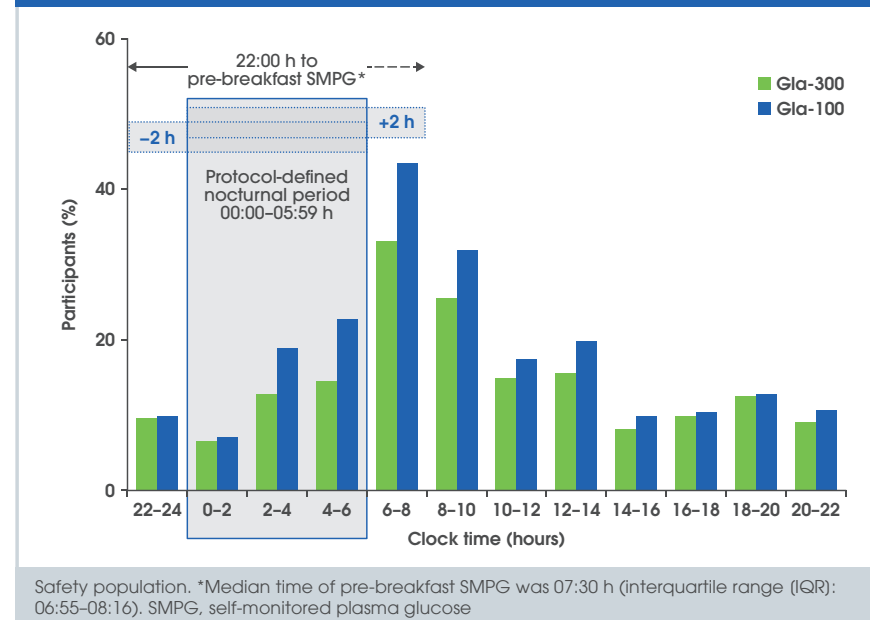
METHODS

- Design:** EDITION 2, 3 and JP 2 were multicenter, randomized, open-label, two-arm, parallel-group, phase 3a studies in different populations of people with T2DM (NCT01499095, NCT01676220, NCT01689142).^{4–6}
- Participants:** People with previously uncontrolled T2DM; ≥18 years of age; basal insulin (EDITION 2: ≥42 U/day) + oral antihyperglycemic drugs (OADs, EDITION 2 and JP 2) or insulin naïve + OADs (EDITION 3).
- Treatment:** Randomized (1:1) to receive once-daily injections of Gla-300 or Gla-100 titrated seeking a fasting self-monitored plasma glucose (SMPG) target of 80–100 mg/dL (4.4–5.6 mmol/L). Injections were to be administered in the evening, defined as the time immediately before the evening meal until bedtime, at the same time every day for each individual during the study.
- Outcomes:** Prespecified hypoglycemia endpoints were the same for each study and were based on ADA definitions.⁷ Confirmed or severe hypoglycemia was defined as any event that was documented symptomatic or asymptomatic with a plasma glucose measurement of ≤70 mg/dL (≤3.9 mmol/L) or <54 mg/dL (<3.0 mmol/L), or severe.
 - Events were reported as pattern of hypoglycemia by time of day, percentage of participants with ≥1 event and annualized rates (events per participant-year) during the main 6-month treatment period.
- Data analysis and statistics:** Hypoglycemia was assessed by study and in a patient-level meta-analysis.
 - Windows used for evaluation of nocturnal hypoglycemia:
 - Per protocol, events between 00:00 h and 05:59 h were classified as nocturnal (predefined window).
 - In this post hoc analysis, the predefined nocturnal interval was expanded by 2 h either in the late evening (22:00–05:59 h) or early morning (00:00–07:59 h).
 - An additional window was defined using a fixed start time (22:00 h) and an end time that varied by participant (based on each individual's recorded time of pre-breakfast SMPG).
 - Percentage of participants with ≥1 hypoglycemic event was estimated using the Cochran–Mantel–Haenszel method. Rates of hypoglycemia per participant-year were analyzed using an overdispersed Poisson regression model.

RESULTS

- Study participants:**
 - Data were available for 1930 participants (randomized population: EDITION 2, 811; EDITION 3, 878; EDITION JP 2, 241).
- Time of pre-breakfast SMPG and basal insulin injection:**
 - Timing of pre-breakfast SMPG and timing of basal insulin injection were comparable in all studies (data not shown). In the patient-level meta-analysis, the median times of pre-breakfast SMPG and basal insulin injection were 07:30 h (interquartile range (IQR): 06:55–08:16) and 21:17 h (IQR: 20:00–22:05), respectively.
- Pattern of hypoglycemia by time of day:**
 - At every time point, fewer participants reported confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia for Gla-300 than Gla-100.
 - Events were reported most frequently between 06:00 h and 08:00 h; these events were only captured by windows extending beyond the predefined (00:00–05:59 h) window (Figure 1).

Figure 1: Percentage of participants with ≥1 confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemic event by time of day (patient-level meta-analysis of EDITION 2, 3 and JP 2)

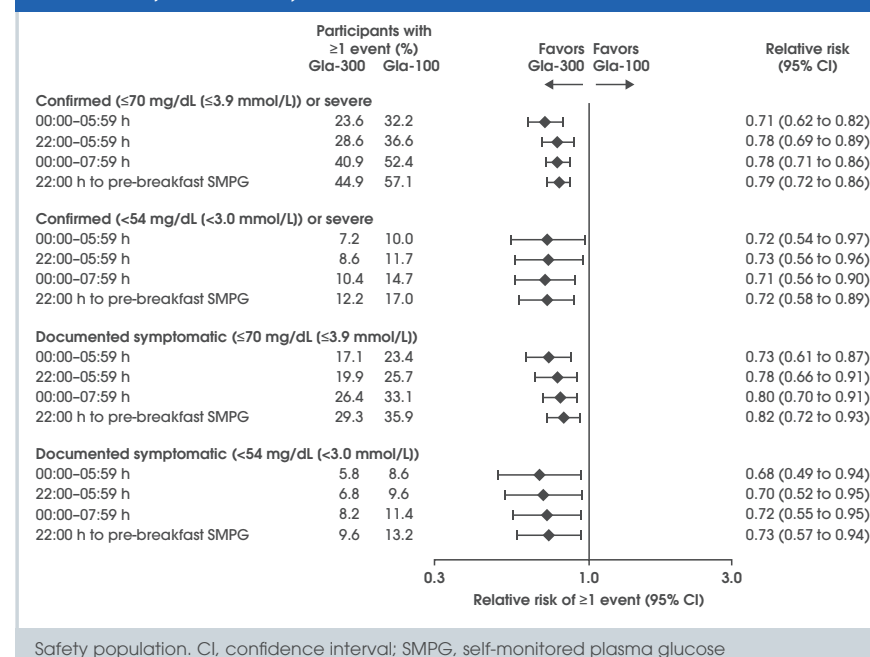


Safety population. *Median time of pre-breakfast SMPG was 07:30 h (interquartile range (IQR): 06:55–08:16). SMPG, self-monitored plasma glucose

Percentage of participants with ≥1 nocturnal hypoglycemic event:

- Risk of ≥1 confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe event was consistently lower for Gla-300 vs Gla-100 using the predefined and the extended windows (Figure 2).
- Risk was 29% lower using the predefined window and 21–22% lower using the extended windows.
- A similar pattern of lower risk for Gla-300 vs Gla-100 was seen with other hypoglycemia definitions (Figure 2).

Figure 2: Relative risk of ≥1 hypoglycemic event by nocturnal window during the 6-month treatment period (patient-level meta-analysis of EDITION 2, 3 and JP 2)



Safety population. CI, confidence interval; SMPG, self-monitored plasma glucose

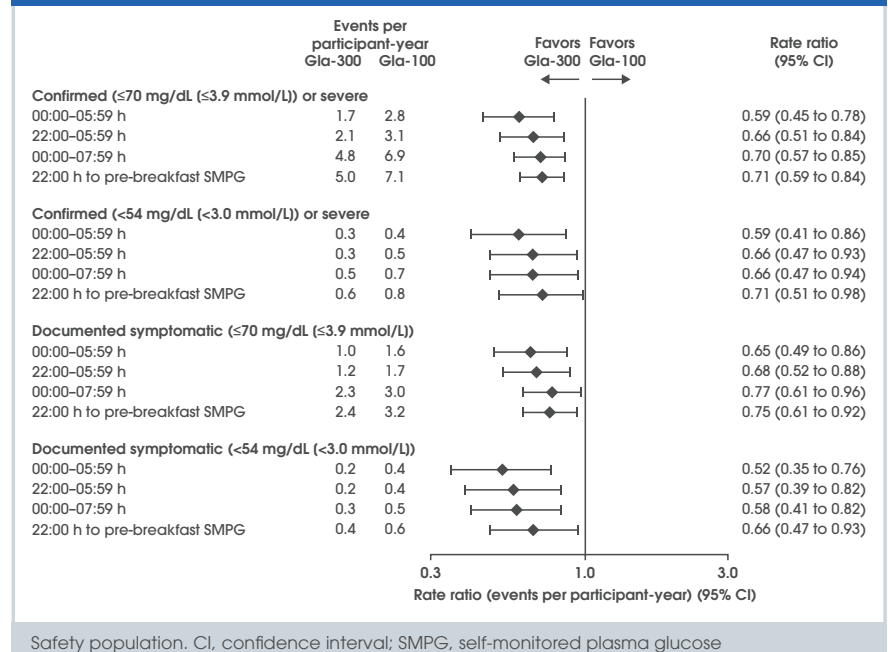
- Number of events by nocturnal window:**
 - Approximately 2–3 times more events were identified for windows extending past 05:59 h vs the predefined window, and absolute differences favored Gla-300 for all windows (Table 1).
- Annualized rates of nocturnal hypoglycemia:**
 - Annualized rates were lower with Gla-300 vs Gla-100 for all windows (Figure 3).
 - For confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe hypoglycemia, rates were 41% lower using the predefined window and 29–34% lower using the extended windows.

Table 1: Total number of nocturnal hypoglycemic events by window (patient-level meta-analysis of EDITION 2, 3 and JP 2)

Nocturnal window	00:00–05:59 h (predefined window in EDITION studies)	22:00–05:59 h	00:00–07:59 h	22:00 h to pre-breakfast SMPG
Confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe				
Gla-300	754	925	2173	2260
Gla-100	1275	1412	3132	3210
Difference*	521	487	959	950
Confirmed (<54 mg/dL (<3.0 mmol/L)) or severe				
Gla-300	112	140	209	251
Gla-100	191	214	317	357
Difference*	79	74	108	106
Documented symptomatic (≤70 mg/dL (≤3.9 mmol/L))				
Gla-300	468	529	1029	1075
Gla-100	721	782	1351	1445
Difference*	253	253	322	370
Documented symptomatic (<54 mg/dL (<3.0 mmol/L))				
Gla-300	83	100	138	178
Gla-100	162	177	239	272
Difference*	79	77	101	94

Safety population. *Gla-100 minus Gla-300. SMPG, self-monitored plasma glucose

Figure 3: Rate ratios of hypoglycemia by nocturnal window during the 6-month treatment period (patient-level meta-analysis of EDITION 2, 3 and JP 2)



Safety population. CI, confidence interval; SMPG, self-monitored plasma glucose

SUMMARY

This analysis of pooled, patient-level data from three randomized studies in people with T2DM on basal insulin + OADs used clinically relevant windows to define nocturnal hypoglycemia, which were assessed alongside the predefined 00:00–05:59 h window.

- The incidence of reported hypoglycemia was highest in the 06:00–08:00 h interval, which is outside the conventional, predefined 00:00–05:59 h window and includes the typical time of pre-breakfast glucose testing.
 - Owing to the longer fasting period, approximately 2–3 times more events were identified for windows extending past 05:59 h vs the predefined window.
- Individual risk of having ≥1 nocturnal confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe event was 21–22% lower with the extended windows and 29% lower with the predefined window for Gla-300 vs Gla-100.
- Annualized rates of nocturnal confirmed (≤70 mg/dL (≤3.9 mmol/L)) or severe events were 29–34% lower with the extended windows and 41% lower with the predefined window for Gla-300 vs Gla-100.

CONCLUSION

- Broader windows of observation for nocturnal hypoglycemia during the fasting period (extending past 05:59 h and into the waking hours) identify more affected individuals and more events, and may have additional clinical relevance vs the predefined window.**
- The lower incidence and rate of nocturnal hypoglycemia with Gla-300 vs Gla-100 was confirmed using all analyzed time windows, showing a hypoglycemic benefit of Gla-300 at times when basal insulins may not be expected to cause such events.**

The data were presented previously at the 76th Scientific Sessions of the American Diabetes Association, June 10–14, 2016, New Orleans, LA, USA.

Disclosures: Geremia B. Bolli — **Advisory panel:** Sanofi; **Consultant:** Novartis; **Speakers bureau:** Eli Lilly, Carol Wysham — **Advisory panel:** AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Sanofi; **Consultant:** AstraZeneca, Eli Lilly, Janssen, Sanofi; **Research support:** AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi; **Speakers bureau:** AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi, Miles Fisher — **Advisory panel:** AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi; **Speakers bureau:** Janssen, MSD, Soazig Chevalier — **Employee:** Sanofi; **Stock/shareholder:** Sanofi, Anna Cali — **Employee:** Sanofi; Bruno Leroy — **Employee:** Sanofi; **Stock/shareholder:** Sanofi, Matthew C. Riddle — **Consultant:** AstraZeneca, Biodel, Elcelyx, GlaxoSmithKline, Sanofi, Valeritas; **Research support:** AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi.

References: 1. Becker RHA, et al. *Diabetes Care* 2015; 38: 637–43; 2. Ritzel R, et al. *Diabetes Obes Metab* 2015; 17: 859–67; 3. Riddle MC, et al. *Diabetes* 2015; 64 (Suppl 1): A263; 4. Yki-Järvinen H, et al. *Diabetes Care* 2014; 37: 3235–43; 5. Bolli GB, et al. *Diabetes Obes Metab* 2015; 17: 386–94; 6. Terauchi Y, et al. *Diabetes Obes Metab* 2016; 18: 366–74; 7. American Diabetes Association. *Diabetes Care* 2005; 28: 1245–9.

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Funding: These studies were funded by SANOFI. NCT01499095, NCT01676220, NCT01689142. The authors received editorial/writing support in the preparation of this poster provided by Leanne Regan of Fishawack Communications Ltd, funded by SANOFI.