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Clinical Perspectives from the BEGIN and EDITION Programs: Trial-Level Meta-Analyses Outcomes with Either Degludec or Glargine 300 U/mL vs Glargine 100 U/mL in T2DM

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INTRODUCTION

- Efficacy and safety of insulin degludec (IDeg) and insulin glargine 300 U/mL (Gla-300) have been compared with that of insulin glargine 100 U/mL (Gla-100) in the BEGIN and EDITION clinical trial programs, respectively.
- IDeg and Gla-300 are longer acting than Gla-100, and have more stable pharmacokinetic and pharmacodynamic profiles.[1,2] In treat-to-target clinical trials, both IDeg and Gla-300 were confirmed to be non-inferior to Gla-100 in terms of HbA_{1c} reduction, while resulting in less hypoglycemia.[3,4]
- Trial-level meta-analyses enable better understanding of results across multiple individual trials, facilitating the interpretation of clinical importance.

OBJECTIVE

To explore comparative glycemic control and hypoglycemia incidence with IDeg or Gla-300 vs Gla-100 in two trial-level meta-analyses of people with type 2 diabetes (T2DM) from the BEGIN and EDITION programs.

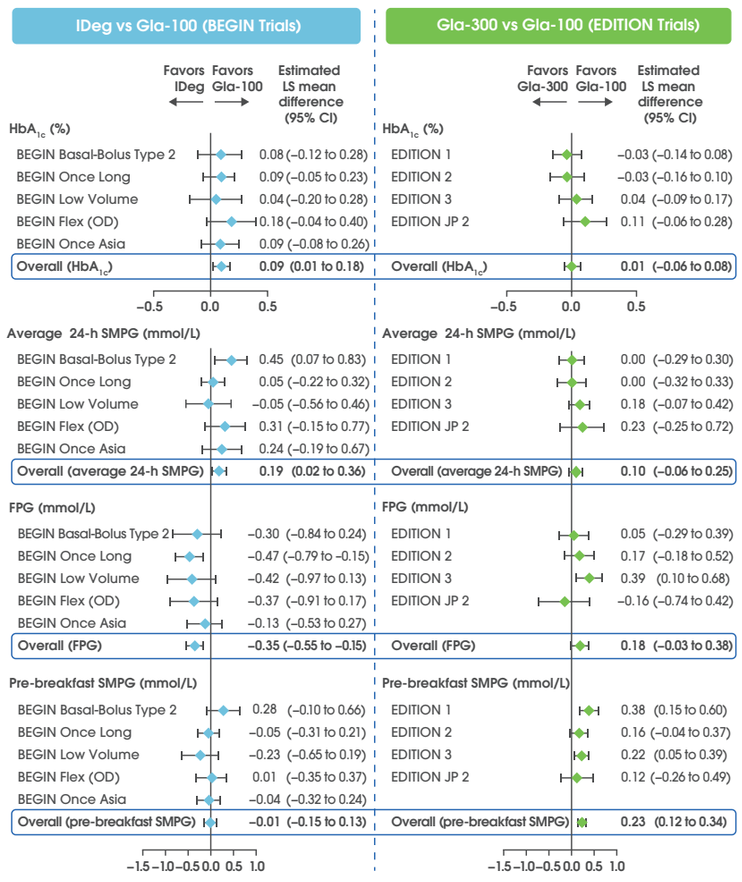
METHODS

- **Design:** All BEGIN and EDITION trials included in the analyses were randomized, open-label, phase 3a, treat-to-target trials.
- **Participants:** People aged ≥18 years with T2DM; details are presented in **Table 1**.
- **Treatment:** Randomized to IDeg vs Gla-100 (BEGIN) and Gla-300 vs Gla-100 (EDITION). Titrated to fasting plasma glucose target:
  - BEGIN, 70–90 mg/dL (3.9–5.0 mmol/L).
  - EDITION, 80–100 mg/dL (4.4–5.6 mmol/L).
- **Outcomes:**
  - HbA_{1c} (primary endpoint), fasting plasma glucose (FPG), average 24-h self-measured plasma glucose (SMPG) based on 9-point (BEGIN) or 8-point (EDITION) SMPG profiles, pre-breakfast SMPG.
  - Percentage of participants with ≥1 confirmed (BEGIN, <56 mg/dL (<3.1 mmol/L); EDITION, <54 mg/dL (<3.0 mmol/L)) or severe hypoglycemic event, or documented symptomatic (≤70 mg/dL (≤3.9 mmol/L)) hypoglycemic event, during the night (BEGIN, 00:01–05:59 h; EDITION, 00:00–05:59 h) and at any time of day (24 h), or with ≥1 severe hypoglycemic event at any time of day.
- **Data Sources:** Trial-level meta-analyses for the EDITION program were performed using data on file. Data from the BEGIN trials included in the trial-level meta-analyses were extracted from the relevant FDA briefing document[14] and clinical study reports.[15]
- **Data Analysis and Statistics:** Meta-analyses were performed using R v3.2.2, with the META and RMETA packages. For HbA_{1c} and FPG, change from baseline to study end was analyzed. Owing to data availability, average 24-h SMPG and pre-breakfast SMPG at study end were analyzed, and between-treatment differences were adjusted on baseline data. A random effects model was used (inverse variance method), and heterogeneity between individual studies within each meta-analysis was assessed using Q statistics. Relative risk of experiencing ≥1 hypoglycemic event with IDeg or Gla-300 vs Gla-100 was calculated from incidence data.

RESULTS

- **Glycemic Control:**
  - In the BEGIN meta-analysis, HbA_{1c} and average 24-h SMPG reduction was significantly better for Gla-100 vs IDeg (p=0.024 and p=0.032, respectively) despite IDeg lowering FPG significantly more than Gla-100 (p<0.001) (**Figure 1**). Reduction in pre-breakfast SMPG was comparable with IDeg and Gla-100 (p=nonsignificant (NS)).
  - In the EDITION meta-analysis, HbA_{1c}, FPG and average 24-h SMPG reduction was comparable with Gla-300 and Gla-100 (p=NS) (**Figure 1**). Reduction in pre-breakfast SMPG was significantly better for Gla-100 vs Gla-300 (p<0.001).
  - No significant heterogeneity of treatment effect across individual trials was observed in either trial-level meta-analysis for any glycemic control measure (p=NS).

Figure 1: Differences in HbA_{1c}, FPG, Average 24-h SMPG and Pre-breakfast SMPG Reduction in BEGIN and EDITION Clinical Trials in People with T2DM

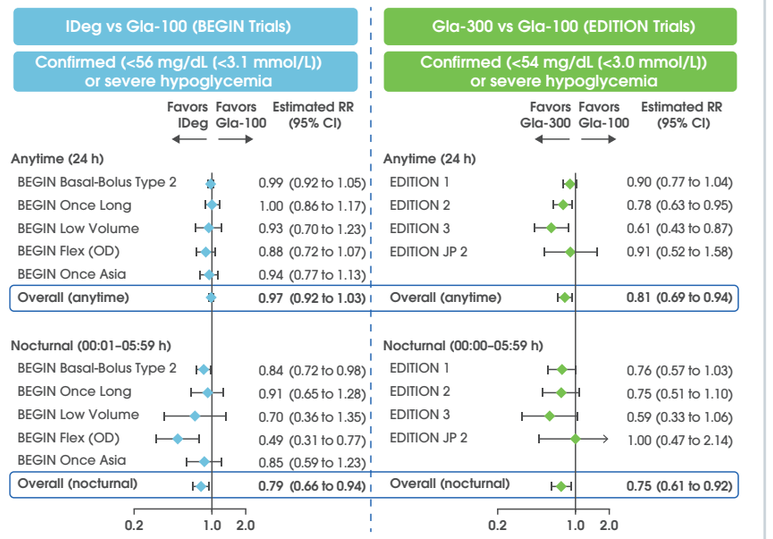


From the BEGIN Flex trial only the 'OD' arm was included in these trial-level meta-analyses; participants in the 'OD Flex' arm received IDeg at intervals of 8–40 h,[8] therefore these data were not included.

CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; OD, once daily; SMPG, self-measured plasma glucose

- **Hypoglycemia:**
  - Risk of ≥1 confirmed (<56 mg/dL (<3.1 mmol/L)) or severe hypoglycemic event in the BEGIN trials was lower with IDeg vs Gla-100 at night (00:01–05:59 h) (p=0.008) but comparable at any time of day (24 h) (p=NS) (**Figure 2**).
  - The risk of ≥1 confirmed (<54 mg/dL (<3.0 mmol/L)) or severe hypoglycemic event in the EDITION trials was consistently lower with Gla-300 vs Gla-100 both at night (00:00–05:59 h) (p=0.007) and also at any time of day (24 h) (p=0.007) (**Figure 2**).
  - Risk of ≥1 documented symptomatic (≤70 mg/dL (≤3.9 mmol/L)) hypoglycemic event closely reflected that of confirmed or severe events:
    - BEGIN (IDeg vs Gla-100): relative risk 0.87 (95% CI: 0.78 to 0.96) for nocturnal events (p=0.007) and 1.02 (0.97 to 1.06) for anytime (24 h) events (p=NS).

Figure 2: Relative Risk of ≥1 Hypoglycemic Event in BEGIN and EDITION Clinical Trials in People with T2DM



The percentage of participants experiencing ≥1 confirmed or severe hypoglycemic event was: BEGIN (IDeg vs Gla-100) 22.2 vs 23.6% (nocturnal (00:01–05:59 h) events), 56.5 vs 52.9% (anytime (24 h) events); EDITION (Gla-300 vs Gla-100) 9.7 vs 13.0% (nocturnal (00:00–05:59 h) events), 26.0 vs 32.0% (anytime (24 h) events). From the BEGIN Flex trial only the 'OD' arm was included in these trial-level meta-analyses; participants in the 'OD Flex' arm received IDeg at intervals of 8–40 h,[8] therefore these data were not included.

CI, confidence interval; OD, once daily; RR, relative risk of ≥1 hypoglycemic event

  - EDITION (Gla-300 vs Gla-100): relative risk 0.74 (95% CI: 0.65 to 0.83) for nocturnal events (p<0.001) and 0.89 (0.83 to 0.95) for anytime (24 h) events (p<0.001).
  - In the BEGIN and EDITION trials, the risk of experiencing ≥1 severe hypoglycemic event was comparable with IDeg or Gla-300 vs Gla-100:
    - BEGIN, relative risk 0.51 (95% CI: 0.16 to 1.60) (p=NS).
    - EDITION, relative risk 0.87 (95% CI: 0.54 to 1.41) (p=NS).
  - No significant heterogeneity of treatment effect across individual trials was observed for any presented hypoglycemia definition in either trial-level meta-analysis (p=NS).

DISCUSSION

These trial-level meta-analyses allowed the exploration of outcomes of interest without the need to access patient-level data, although the summary nature of such an analysis technique may be a limitation.

When assessing hypoglycemia risk it is important to consider glycemic control, since basal insulin therapy can result in a compromise between achieving glycemic targets and avoiding hypoglycemia. These meta-analyses investigated measures of overall glycemic control (HbA_{1c} and average 24-h SMPG) as well as those that reflect glucose levels at a particular time of day (FPG and pre-breakfast SMPG). HbA_{1c} is regarded as the "gold standard" for assessing the efficacy of diabetes interventions and reflects average glycemia over several months,[16] with other measures being used as supportive evidence.

- In the trial-level meta-analysis of BEGIN studies in T2DM:
  - ➔ Gla-100 reduced HbA_{1c} and average 24-h SMPG more than IDeg, despite IDeg lowering FPG more than Gla-100 and having a comparable effect on pre-breakfast SMPG.
  - ➔ Risk of ≥1 confirmed (<56 mg/dL (<3.1 mmol/L)) or severe hypoglycemic event, and ≥1 documented symptomatic (≤70 mg/dL (≤3.9 mmol/L)) hypoglycemic event, with IDeg vs Gla-100 was lower for nocturnal (00:01–05:59 h) but not anytime (24 h) events.
- In the trial-level meta-analysis of EDITION studies in T2DM:
  - ➔ Improvements in glycemic control were consistently comparable between Gla-300 and Gla-100 for HbA_{1c}, FPG and average 24-h SMPG. Pre-breakfast SMPG reduction was greater with Gla-100.
  - ➔ Risk of both nocturnal (00:00–05:59 h) hypoglycemia and anytime (24 h) hypoglycemia, using both definitions, was lower for Gla-300 vs Gla-100.

Table 1: Summary of BEGIN and EDITION Trials in People with T2DM

	BEGIN Development Program					EDITION Development Program			
Trial Description and Treatment	**BEGIN Basal-Bolus Type 2[5]**	**BEGIN Once Long[6]**	**BEGIN Low Volume[7]**	**BEGIN Flex (OD)[8]**	**BEGIN Once Asia[9]**	**EDITION 1[10]**	**EDITION 2[11]**	**EDITION 3[12]**	**EDITION JP 2[13]**
Number of Participants[a]	IDeg, 755 Gla-100, 251	IDeg, 773 Gla-100, 257	IDeg, 228 Gla-100, 229	IDeg, 228 Gla-100, 230	IDeg, 289 Gla-100, 146	Gla-300, 404 Gla-100, 403	Gla-300, 404 Gla-100, 407	Gla-300, 439 Gla-100, 439	Gla-300, 121 Gla-100, 120
Study Duration, Weeks	52	52	26	26	26	26	26	26	26
Glucose-Lowering Therapy at Screening	Basal ± mealtime insulin ± OADs	Insulin naïve + OADs	Insulin naïve + OADs	Insulin naïve + OADs or basal insulin ± OADs	Insulin naïve + OADs	Basal + mealtime insulin ± Met	Basal insulin + OADs	Insulin naïve + OADs	Basal insulin + OADs
Inclusion Criteria									
HbA_{1c}	≥7–≤10 %	≥7–≤10 %	≥7–≤10 %	≥7.0–≤11[b] or ≤10[c] %	≥7–≤10 %	≥7–≤10 %	≥7–≤10 %	≥7–≤11 %	≥7–≤10 %
Age	≥18 years	≥18 years	≥18 years	≥18 years	≥18 years[d]	≥18 years	≥18 years	≥18 years	≥18 years
BMI	≤40 kg/m²	≤40 kg/m²	≤45 kg/m²	≤40 kg/m²	≤35 kg/m²	N/A	N/A	N/A	<35 kg/m²

From the BEGIN Flex trial only the 'OD' arm was included in these trial-level meta-analyses; participants in the 'OD Flex' arm received IDeg at intervals of 8–40 h,[8] therefore these data were not included.
[a]Full analysis set for BEGIN trials and randomized population for EDITION trials. [b]Insulin-naïve participants. [c]Participants on basal insulin. [d]≥20 years in Japan.
BMI, body mass index; Met, metformin; N/A, not applicable; OAD, oral antihyperglycemic drug; OD, once daily

CONCLUSION

- **For IDeg vs Gla-100, the hypoglycemia benefit was only seen for nocturnal events, not those at any time, and was achieved in the context of slightly but significantly less improvement in HbA_{1c}.**
- **For Gla-300 vs Gla-100, there was comparable HbA_{1c} improvement alongside a hypoglycemia benefit both at night and at any time.**
- **The differences in results observed between glycemic measures analyzed is of interest and is worthy of further investigation to better refine their relative contributions to overall efficacy.**
- **The findings of these trial-level meta-analyses in T2DM could support informed clinical evaluations; however, head-to-head trials of IDeg vs Gla-300 are warranted to allow direct comparisons between these insulins.**

The data were presented previously at the 52nd Annual Meeting of the European Association for the Study of Diabetes, 12–16 September, 2016, Munich, Germany.

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