E D I T I O N investigational new insulin U300

every day in the life of patients with diabetes

An investigational new insulin glargine U300: glucose control and hypoglycaemia in people with type 2 diabetes using basal and mealtime Insulin (EDITION I)

Matthew Riddle[1], Geremia B Bolli[2], Monika Ziemen[3], Isabel Muehlen-Bartmer[3], Florence Bizet[4], Phillip Home[5]

[1]Oregon Health & Science University, Portland, OR, USA; [2]University of Perugia, Perugia, Italy; [3]Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany; [4]Sanofi, Paris, France; [5]Newcastle University, Newcastle upon Tyne, UK

INTRODUCTION

- Introduction of long-acting (basal) insulin analogues has done much to improve management of diabetes over the last decade.
- The first such analogue indicated for once-daily injection was insulin glargine 100 U.mL^{-1} (Gla-100),[1,2] which has a well-established efficacy and safety profile and is widely recommended.[3,4]
- An opportunity for the further improvement of basal insulins exists, notably with regard to the further reduction in the risk of hypoglycaemia and more convenient dosing.[1,4,5]
- Investigational new insulin glargine U300 (Gla-300) has demonstrated an even flatter, more stable and prolonged PK and PD profile compared with Gla-100.[6,7]
- The different PK and PD profile of Gla-300 may offer treatment optimisation with once-daily injection and potentially a lower risk of hypoglycaemia.
- The phase 3a EDITION programme is assessing the efficacy and safety of Gla-300 compared with Gla-100 in various patient populations. EDITION I is the first of these studies to be completed.

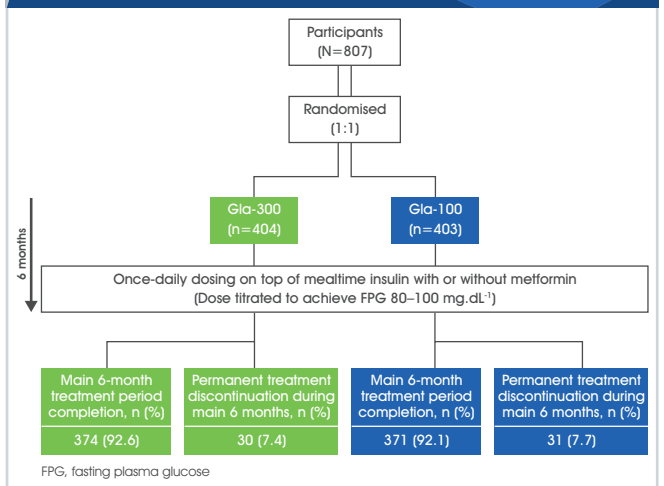
MAIN OBJECTIVE

To compare the efficacy and safety of Gla-300 with Gla-100 in people with T2DM previously using both basal and mealtime insulin.

METHODS

- **Design (Figure 1):** Multicentre randomised, open-label, two-arm, parallel-group, phase 3a study in 13 countries (Canada, Czech Republic, Estonia, Finland, France, Germany, Hungary, Latvia, Mexico, the Netherlands, Romania, South Africa, USA).

Figure 1: Trial schematic diagram



FPG, fasting plasma glucose

- **Participants:** Males and females, aged ≥18 years, with T2DM (as defined by the World Health Organization) but otherwise healthy with HbA_{1c} 7.0–10.0 % and established treatment with basal insulin (glargine or NPH) at dosage ≥42 U daily together with mealtime insulin ± oral therapies.
- **Treatment:** Randomised (1:1) to Gla-300 or Gla-100 administered once daily in the evening, with systematic titration seeking self-monitored plasma glucose (SMPG) 80–100 mg.dL^{-1} for 6 months.
- **Informed consent:** Local ethics committees approved the protocol and it was conducted according to Good Clinical Practice and the Declaration of Helsinki.
- **Study endpoints:**

Primary efficacy endpoint:

— HbA_{1c} change, baseline to endpoint (month 6).

1st main secondary efficacy endpoint:

— Percentage of participants with ≥1 confirmed or severe (≤70 mg.dL^{-1}) nocturnal (24:00–05:59) hypoglycaemia from month 3 to 6.

Other secondary efficacy endpoints:

— Fasting plasma glucose (FPG), 8-point SMPG profile.

Hypoglycaemic events

Safety and tolerability

- **Data analysis and statistics:** To assess non-inferiority with regards to the primary endpoint, the upper bound of the two-sided 95% confidence interval (CI; estimated within the framework of ANCOVA) was compared to a predefined non-inferiority margin (<0.4 % for HbA_{1c}). If non-inferiority was demonstrated for HbA_{1c}, the superiority of Gla-300 vs Gla-100 was tested for nocturnal hypoglycaemia according to a hierarchical testing procedure.

RESULTS

- **Baseline demographics (Table 1):** The treatment groups were similar in age, gender, body mass index (BMI), duration of diabetes, prior insulin dose and glycaemic control (HbA_{1c} and FPG).

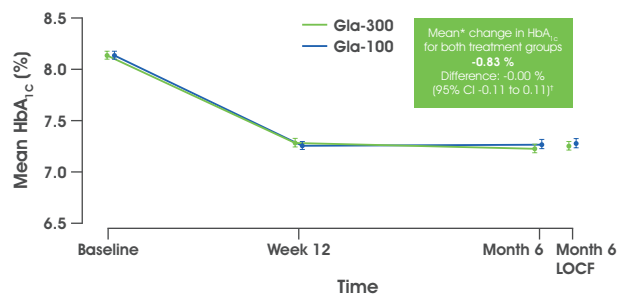
Table 1: Baseline demographics (Randomised population)

Mean (SD)	Gla-300 (n=404)	Gla-100 (n=403)	Overall (N=807)
Age (years)	60.1 (8.5)	59.8 (8.7)	60.0 (8.6)
BMI (kg.m^{-2})	36.6 (6.8)	36.6 (6.1)	36.6 (6.4)
Years of T2DM	15.6 (7.2)	16.1 (7.8)	15.8 (7.5)
Years of basal insulin use	6.7 (4.7)	6.5 (4.8)	6.6 (4.8)
Basal insulin dose (U.kg^{-1}.day^{-1})	0.67 (0.26)	0.67 (0.24)	0.67 (0.25)
Total insulin dose (U.kg^{-1}.day^{-1})	1.19 (0.48)	1.20 (0.45)	1.20 (0.47)
HbA_{1c} (%)	8.15 (0.8)	8.16 (0.8)	8.15 (0.8)

SD, standard deviation

- **Primary efficacy endpoint:** At the end of the 6-month treatment period, HbA_{1c} had decreased similarly in both treatment groups (least squares [LS] mean change -0.83 [0.06] % in both groups; difference -0.00 % [95% CI -0.11 to 0.11]) (**Figure 2**).

Figure 2: Change in HbA_{1c}



*Least squares mean; †The upper bound lower than the predefined non-inferiority margin of 0.4 %; LOCF, last observation carried forward

- **Main secondary efficacy endpoint (nocturnal hypoglycaemia):** Treatment with Gla-300 was associated with a significant reduction in percentage of patients reporting at least one confirmed or severe nocturnal hypoglycaemic event from month 3 to 6 (Gla-300, 36.1%; Gla-100, 46.0%; relative risk [RR] 0.79 [95% CI 0.67 to 0.93]; p=0.0045; modified Intent-to-Treat [mITT] population) (**Table 2**).
- **Other categories of hypoglycaemia (Gla-300 vs Gla-100):** A lower risk of confirmed or severe nocturnal hypoglycaemia and confirmed or severe hypoglycaemia at any time of the day (24-hour) was observed consistently across the entire study period (**Table 2**).

Table 2: Confirmed or severe hypoglycaemia events (Safety population)

Participants (%)	Gla-300 (n=404)	Gla-100 (n=402)	Relative risk (RR) RR	CI
Confirmed or severe nocturnal hypoglycemia*				
Baseline to month 6	44.6	57.5	0.78	0.68 to 0.89
Baseline to week 8	26.2	33.3	0.79	0.63 to 0.98
Week 9 to month 6†	36.1	46.0	0.79	0.67 to 0.93
Confirmed or severe hypoglycaemia at any time of the day (24-hour)				
Baseline to month 6	81.9	87.8	0.93	0.88 to 0.98
Baseline to week 8	64.4	75.1	0.86	0.79 to 0.93
Week 9 to month 6	74.8	77.6	0.96	0.89 to 1.04

*Defined as: confirmed or severe by plasma glucose ≤70 mg.dL^{-1} which occurred between 24:00 and 5:59 hours; †First main secondary endpoint (mITT population); CI, confidence interval

During the 6-month study period:

— Any hypoglycaemia was reported by 83.4% of Gla-300- and 88.6% of Gla-100-treated participants (RR 0.94; 95% CI 0.89 to 0.99).

— Any nocturnal hypoglycaemia was 45.3% for Gla-300 and 59.7% for Gla-100 (RR 0.76; 95% CI 0.66 to 0.87).

— Any daytime hypoglycaemia was 81.2% for Gla-300 and 85.8% for Gla-100.

— Severe hypoglycaemia was 5.0% for Gla-300 and 5.7% for Gla-100.

- **Other secondary efficacy endpoints:** At the end of the 6-month treatment period, FPG and glucose measurements of the 8-point profile had decreased similarly in the Gla-300 and Gla-100 groups.
- **Adverse events:** In the Gla-300- and Gla-100-treated participants, 56.4% and 54.2% had treatment emergent adverse events (TEAEs), 1.5% and 1.7% had an event leading to discontinuation, while 6.4% and 5.2% had a serious adverse event, respectively. Injection site reactions were reported by 2.2% and 1.5%, respectively. One person receiving Gla-300 and two receiving Gla-100 had a TEAE with fatal outcome.

SUMMARY

EDITION I study comparing the efficacy and safety of Gla-300 and Gla-100 in people with advanced T2DM, high BMI and need for both basal and mealtime insulin demonstrated:

- Similar improvement in glycaemic control.
- A significant 21% reduction in confirmed or severe nocturnal hypoglycaemia from month 3 to 6.
- Consistently, similar or lower percentages of patients with hypoglycaemia at any time of the day (24-hour) throughout the study.

CONCLUSION

Gla-300 is as effective in improving glycaemic control as Gla-100 glargine with significantly less nocturnal hypoglycaemia.

Disclosures: Matthew C Riddle — **Research grant support:** Amylin, Eli Lilly and Sanofi; **Honoraria for consulting and/or speaking:** Amylin, Elcelyx, Eli Lilly, Hoffmann-La Roche, Sanofi and Valeritas. Geremia B Bolli — **Honoraria for advising and lecturing:** Sanofi, Eli Lilly and Novartis. Monika Ziemen, Isabel Muehlen-Bartmer and Florence Bizet are employees of Sanofi. Philip D Home — **Funding for affiliated institutions:** AstraZeneca/BMS Alliance, Eli Lilly, GlaxoSmithKline, Janssen/J&J, Merck (MSD), Novo Nordisk, Roche Diagnostics, Roche Pharma, Sanofi, SkyePharma and Takeda.

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Contact details: Dr Matthew C. Riddle; Oregon Health & Science University, L-345, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, USA; riddlem@ohsu.edu.

Funding: This study is funded by SANOFI. The authors received editorial/writing support in the preparation of this poster provided by Spela Ferjancic, PhD, of Fishawack Communications Ltd, funded by SANOFI.

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