Hypoglycaemia risk in the first eight weeks of titration with insulin glargine 100 U/mL in previously insulin-naive people with type 2 diabetes mellitus

Brian M. Frier, MD[1], Wolfgang Landgraf, PhD[2], Mei Zhang, PhD[3], Geremia B. Bolli, MD[4], David R. Owens, MD[5]

[1]BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

[2]Sanofi, Frankfurt, Germany

[3]Sanofi US Inc., Bridgewater, NJ, USA

[4]University of Perugia Department of Medicine, Perugia, Italy

[5]University of Swansea, Diabetes Research Group Cymru, College of Medicine, Swansea, UK

Running title: Hypoglycaemia during insulin initiation in type 2 diabetes mellitus

Corresponding author: Brian M. Frier, BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, The University of Edinburgh, Edinburgh EH16 4TJ, UK; email: brian.frier@ed.ac.uk

Abstract: **180**/180

Main text: 1826/1800

Tables/Figures: 2/2

References: 14/15

Supplementary Appendix: 4 Tables/2 Figures

ABSTRACT

Patient characteristics associated with hypoglycaemia frequency during insulin glargine 100 U/mL (Gla-100) titration and clinical outcomes at Week 24 were examined using participant-level data from 16 treat-to-target trials of people with type 2 diabetes mellitus inadequately controlled with oral antidiabetes drugs initiating Gla-100 (n=3549). Hypoglycaemia (plasma glucose <3.9 mmol/L or severe) during the first 8 weeks of titration was stratified by number of events (0, 1-3, and ≥4), resulting in 72.5%, 20.6%, and 6.9% of participants in each group, respectively. Glycaemic, body weight, and insulin dose changes from baseline to Weeks 12 and 24 were analysed. Hypoglycaemia was more common in participants with lower BMI and fasting C-peptide, and with sulfonylurea treatment. Glycaemic outcomes at Week 24 were similar in each hypoglycaemia group, despite the Week 24 mean daily dose and dose increase for Gla-100 being highest in participants without hypoglycaemia, and lowest in those experiencing ≥4 events. Hypoglycaemia risk during Gla-100 titration mainly depends on patient characteristics and sulfonylurea use and may delay dose titration, but apparently has little effect on short-term glycaemic control in a clinical trial setting.

KEYWORDS

Type 2 diabetes mellitus, hypoglycaemia, insulin initiation, insulin glargine, C-peptide, clinical trial

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is usually treated with diet and lifestyle modification followed by oral antidiabetes drugs (OADs), but many patients eventually require basal insulin to control blood glucose and reach glycaemic targets.[1] Early initiation of basal insulin is more clinically beneficial and cost-effective than delaying until failure of three OADs[2,3] and is recommended by international guidelines—especially in people with severe hyperglycaemia.[1]

Insulin secretagogues and all forms of insulin therapy increase the risk of hypoglycaemia. Clinical outcomes and hypoglycaemia risk following initiation of basal insulin therapy vary depending on a patient's pre-existing OAD regimen.[4,5] Therefore, when initiating basal insulin therapy, greater insight into how patient characteristics and concurrent OADs may influence treatment efficacy and risk of hypoglycaemia would have clinical utility. The objective of this post-hoc, participant-level analysis was to compare baseline patient characteristics and clinical outcomes at Weeks 12 and 24, relative to the number of hypoglycaemia events reported during the first 8 weeks of forced insulin glargine 100 U/mL (Gla-100) titration when added to OAD therapy as a treat-to-target concept for ≥24 weeks in people with T2DM.

METHODS

Study design and patient selection

Participant-level data were collected from randomised controlled trials of ≥24-weeks' duration including insulin-naive people with T2DM inadequately controlled on OADs. All trials were conducted by Sanofi between 2000 and 2015. Studies using a forced titration algorithm (predominantly once-weekly dose adjustment by 2-8 U/day based on patient's self-measured blood glucose) targeting fasting plasma glucose (FPG) ≤5.6 mmol/L

(≤100 mg/dL) and with at least one arm initiating Gla-100 (starting dose 10 U/day or 0.2 U/kg) were considered; 16 studies fulfilled these criteria.[6]

Endpoints

As hypoglycaemia risk is generally low in insulin-naive people with T2DM, hypoglycaemia groups were classified as 0, 1-3, or ≥4 events per patient during the first 8 weeks of treatment with Gla-100 (forced titration period). Hypoglycaemia was defined as 'confirmed' by a plasma glucose level of <3.9 mmol/L (<70 mg/dL), or 'severe' as hypoglycaemia requiring external assistance. Efficacy endpoints included change in glycated haemoglobin A1c (HbA1c), FPG, insulin dose, weight, and BMI from baseline to Weeks 12 and 24. Results were analysed for all patients and by concomitant OAD use (metformin, sulfonylurea, and metformin plus sulfonylurea).

Statistical analysis

Standardised, patient-level data were pooled from the studies. Analyses used descriptive statistics, and results are shown as mean (standard deviation) unless stated otherwise. All differences are numerical; statistical significance testing was not performed.

RESULTS

Patient characteristics

Of 3549 participants (metformin: n=623; sulfonylurea: n=906; metformin plus sulfonylurea: n=1624; other: n=396), 2573 (72.5%) had no hypoglycaemia, 732 (20.6%) reported 1-3 hypoglycaemia events, and 244 (6.9%) reported ≥4 hypoglycaemia events during the first 8 weeks. **Supplementary Table S1** shows baseline patient characteristics, stratified by hypoglycaemia frequency.

Patients without hypoglycaemia had the highest HbA1c at baseline. Patients experiencing ≥4 hypoglycaemia events had lower mean weight and C-peptide levels at baseline vs those experiencing ≤3 events. The number of hypoglycaemia events in the first 8 weeks diminished in all OAD subgroups with increasing baseline BMI and fasting C-peptide (**Supplementary Tables S2** and **S3**).

Clinical Outcomes

Discontinuation rates

Overall, 129 study participants (3.6%) discontinued treatment during the first 8 weeks, and another 232 (6.5%) later in the course of the study. For each study period, discontinuation rate was not found to be associated with the number of hypoglycaemia events during titration.

Efficacy outcomes by hypoglycaemia events

Changes in mean HbA1c and FPG from baseline to Week 24 were similar across all hypoglycaemia subgroups (**Figure 1** and **S2A**). A higher proportion of patients experiencing ≥1 hypoglycaemia event during titration reached target HbA1c <7.0% (<53 mmol/mol) or target FPG (≤5.6 mmol/L) levels at Weeks 12 and 24 vs those experiencing no hypoglycaemia events (**Figure S1** and **S2B**).

Glycaemic outcomes by concomitant OAD therapy are provided in **Table S4**. More people with T2DM in each OAD subgroup reached the target HbA1c <7.0% relative to an increasing number of hypoglycaemia events during titration, with the exception of those receiving metformin, of whom fewer reported ≥4 hypoglycaemia events (38.5%) vs 0 and 1-3 events (55.3% and 69.3%, respectively); an outcome which might have been

influenced by the small size of this group, who had the lowest BMI and were likely to be more insulin sensitive.

Basal insulin titration

At similar baseline Gla-100 doses, dose increment over time differed when analysed by hypoglycaemia frequency (**Figure 2A**). Gla-100 dose increments were lower, and slower to rise, among participants experiencing hypoglycaemia vs those who did not. The mean daily Gla-100 dose at Week 24 was highest in those with no hypoglycaemia (0.47 [0.26] U/kg) and lowest in people experiencing ≥4 hypoglycaemia events (0.29 [0.14] U/kg) (**Figure 2B**). Analysed by OAD subgroup, study participants experiencing ≥4 hypoglycaemia events recorded the smallest increase in insulin dose, regardless of the concomitant OAD (**Table S4**).

Severe and non-severe hypoglycaemia

During titration (Weeks 0-8) and throughout the continuing study period (Weeks 9-24) 0.9% and 1.2% of participants, respectively, reported a severe hypoglycaemia event. Participants with no non-severe hypoglycaemia during titration also reported no severe hypoglycaemia during this period; only 0.7% of this group reported a severe event and 19.5% a non-severe event in Weeks 9-24 (**Table S4**). A higher incidence and event rate of severe hypoglycaemia was observed in participants with 1-3 or ≥4 non-severe hypoglycaemia events both during titration and later in the course of the study. Similarly, event rates for non-severe hypoglycaemia were highest in participants with ≥4 non-severe hypoglycaemia during titration both during first 8 weeks and later in the course of the study (**Table S4**).

Body weight and BMI

Mean body weight and BMI at baseline differed considerably between hypoglycaemia groups (**Table S1**): mean weight change from baseline to Week 24 was 1.8 (3.7) kg in those not experiencing hypoglycaemia, 2.2 (3.5) kg in those experiencing 1-3 hypoglycaemia events, and 1.9 (3.4) kg in those experiencing ≥4 hypoglycaemia events. Weight change in each group did not appear to be associated with the final Gla-100 dose, but was associated with concomitant OAD therapy (**Table S4**). Weight gain ranged from 0.7 kg with metformin and no hypoglycaemia, to 3.9 kg with sulfonylurea and ≥4 hypoglycaemia events.

DISCUSSION

In recognition of the heterogeneity of the T2DM population at insulin initiation, this post-hoc analysis was undertaken to identify patient characteristics that might influence the response to basal insulin in terms of hypoglycaemia risk during titration.

Incidence of hypoglycaemia in this population of insulin-naive people with T2DM was within expected boundaries, with 27.5% of participants reporting hypoglycaemia (non-severe or severe); only 6.9% of those had ≥4 events during the 8-week titration period. Higher risk of hypoglycaemia during titration was also associated with a continued higher risk of non-severe and severe events throughout the later study period, indicating the importance of avoiding or reducing hypoglycaemia early during titration to minimise long-term risk. Our analysis has identified patient characteristics that may predispose to an increased risk of hypoglycaemia during insulin titration. These are a lower body weight and BMI at the time of insulin initiation, and low levels of fasting C-peptide, characterising an insulin-sensitive group who may require a lower dose of basal insulin to reach glycaemic targets, and therefore might need a more tailored titration strategy

and/or more vigilance regarding hypoglycaemia events. Since glutamic-acid-decarboxylase antibodies were not measured in these studies, it is also possible that the lean, more C-peptide-deficient subgroup included a subpopulation with latent autoimmune diabetes in adults (LADA), subsumed within the heterogeneous T2DM population.[7] Our results add to the existing evidence of the increased risk of hypoglycaemia with concomitant sulfonylurea use,[4,8] here shown specifically for the titration period. In addition, it shows that people with greater insulin resistance may benefit from the addition of Gla-100 to an oral regimen consisting of metformin, while avoiding sulfonylurea-based regimens and/or withdrawing sulfonylurea when basal insulin is initiated. This finding supports the timely introduction of basal insulin to metformin monotherapy, particularly for patients with higher HbA1c levels on this therapy, and indirectly suggests that additional drugs (which may include another injectable) may be needed in some individuals to reach target HbA1c.

The number of hypoglycaemia events during the 8-week titration period had little effect on short-term glycaemic outcomes (24 weeks); however it affected overall insulin-dose titration as expected. At Week 24, the difference in mean HbA1c across the three hypoglycaemia-frequency groups was <0.2%, but final mean basal insulin doses ranged from 0.29 (0.14) to 0.47 (0.26) U/kg. The analysis of all groups by number of hypoglycaemia events during titration or concomitant OAD showed that, in general, the highest percentages of people who reached the target of HbA1c <7.0% at Week 24 were those who received metformin (without sulfonylurea) and who had increasing hypoglycaemia risk during the first 8 weeks with Gla-100. This finding suggests that early occurrence of hypoglycaemia during titration does not necessarily prevent patients from achieving short- or longer-term glycaemic targets; however, these outcomes have been observed in a clinical research setting, where participants received a monitored forced insulin titration to achieve the predefined FPG target. As reported previously,[9] it is

also uncertain whether early hypoglycaemia during Gla-100 titration and recurrent hypoglycaemia later in the course of the studies induce a negative effect on treatment satisfaction or quality-of-life as such data were not systematically measured. Our findings, however, showed that people with hypoglycaemia during titration continue to experience considerably more severe and non-severe hypoglycaemia events than those who have no hypoglycaemia during titration. In addition, it is unclear how these results transfer to real-world use, as in daily practice a forced insulin titration period is not standard practice, and daily insulin doses are generally lower than in clinical trials. Therefore, in real-world practice, early and recurrent hypoglycaemia after insulin initiation might have a significant negative impact on mid- and long-term glycaemic control as fear of (and experienced) hypoglycaemia often associates with insufficient insulin titration, reduced adherence and compliance to insulin treatment, and higher discontinuation rates of insulin treatment than observed in randomized controlled trials.[10-13]

A limitation of this post-hoc analysis is that it describes observations associated with retrospectively defined hypoglycaemia subgroups and by necessity has used a descriptive analysis; it therefore cannot demonstrate any causality of these associations. Confounding factors other than BMI, weight, or fasting C-peptide level may also have contributed to the difference in hypoglycaemia risk during Gla-100 titration.

In summary, the present retrospective analysis of hypoglycaemia risk in a large sample of people with T2DM initiating Gla-100 after inadequate glycaemic control on oral therapy has identified people who required or received different insulin doses to reach a similar level of glycaemic control, but who also differed considerably in characteristics associated with hypoglycaemia risk during titration. Hypoglycaemia events (PG <3.9

mmol/L or severe) were more likely to occur when Gla-100 was added to concomitant sulfonylurea (without metformin) and in people with low body weight/BMI or low levels of fasting C-peptide before commencing basal insulin.

Further prospective studies in a real-world setting are required to examine whether the patient characteristics identified in the present analysis can be confirmed.

ACKNOWLEDGMENTS

The authors received writing/editorial support in the preparation of this manuscript provided by Michael van der Veer, PhD, of Excerpta Medica, funded by Sanofi.

FUNDING

This study was funded by Sanofi.

AUTHOR CONTRIBUTIONS

BMF was involved in designing the study, data analysis and interpretation, critical revision, and final approval of the manuscript. **WL** was involved in designing the study, data acquisition, data analysis and interpretation, critical revision, and final approval of the manuscript. **MZ** was involved in data acquisition, data analysis and interpretation, critical revision, and final approval of the manuscript. **GBB** was involved in data analysis and interpretation, critical revision, and final approval of the manuscript. **DRO** was involved in designing the study, data analysis and interpretation, critical revision, and final approval of the manuscript. All authors take responsibility for the accuracy and integrity of the data presented in this manuscript.

CONFLICT OF INTEREST

BMF has served on advisory panels for Eli Lilly, and Novo Nordisk, and on a speakers bureau for Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Merck, Sanofi, Roche Diagnostics, and Takeda. **WL** is an employee of Sanofi, Germany, and a Sanofi shareholder. **MZ** is an employee of Sanofi Inc., US. **GBB** is a consultant for Sanofi and Eli Lilly, has received research support from Sanofi, and is on the speakers bureau for Eli Lilly, Menarini, and Sanofi. **DRO** has received honoraria for lecturing and consulting from Boehringer Ingelheim, Eli Lilly, Roche Diagnostics, Sanofi, and Takeda.

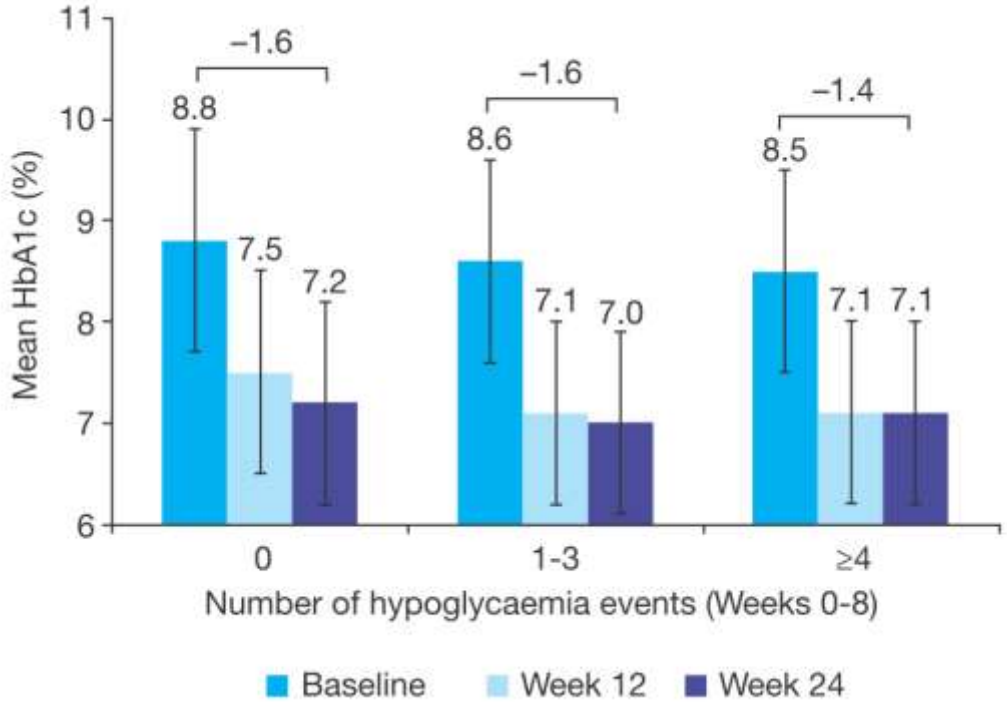
REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-149.
2. Levin PA, Zhou S, Gill J, Wei W. Health outcomes associated with initiation of basal insulin after 1, 2, or ≥3 oral antidiabetes drug(s) among managed care patients with type 2 diabetes. J Manag Care Spec Pharm 2015;21:1172-1181.
3. Levin P, Zhou S, Durden E, Farr AM, Gill J, Wei W. Clinical and economic outcomes associated with the timing of initiation of basal insulin in patients with type 2 diabetes mellitus previously treated with oral antidiabetes drugs. Clin Ther 2016;38:110-121.
4. DeVries JH, Meneghini L, Barnett AH, et al. A patient-level analysis of efficacy and hypoglycaemia outcomes across treat-to-target trials with insulin glargine added to oral antidiabetes agents in people with type 2 diabetes. Eur Endocrinol 2014;10:23-30.
5. Owens DR, Traylor L, Dain M-P, Landgraf W. Efficacy and safety of basal insulin glargine 12 and 24 weeks after initiation in persons with type 2 diabetes: a pooled analysis of data from treatment arms of 15 treat-to-target randomised controlled trials. Diabetes Res Clin Pract 2014;106:264-274.
6. Owens DR, Bolli GB, Charbonnel B, et al. Effects of age, gender, and body mass index on efficacy and hypoglycaemia outcomes across treat-to-target trials with insulin glargine 100 U/mL added to oral antidiabetes agents in type 2 diabetes. Diabetes Obes Metab 2017;19:1546-1554.
7. Adebayo O, Willis GC. The changing face of diabetes in America. Emerg Med Clin N Am 2014;32:319-327.

8. Bolen S, Feldman L, Vassy J, et. al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386-399.
9. Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycaemia on quality of life and related patient-reported outcomes in type 2 diabetes: a narrative review. Diabet Med 2012;29:293-302
10. Dalal MR, Kazemi M, Ye F, Xie L. Hypoglycemia after initiation of basal insulin in patients with type 2 diabetes in the United States: implications for treatment discontinuation and healthcare costs and utilization. Adv Ther 2017;34:2083-2092.
11. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of patients and physicians in insulin therapy study. Diabet Med 2012;29:682-689.
12. Peyrot M, Perez-Nieves M, Ivanova J, et al. Correlates of basal insulin persistence among insulin-naïve people with type 2 diabetes: results from a multinational survey. Curr Med Res Opinion 2017;33:1843-1851.
13. Mauricio D, Meneghini L, Seufert J, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. Diabetes Obes Metab. 2017;19:1155-1164.

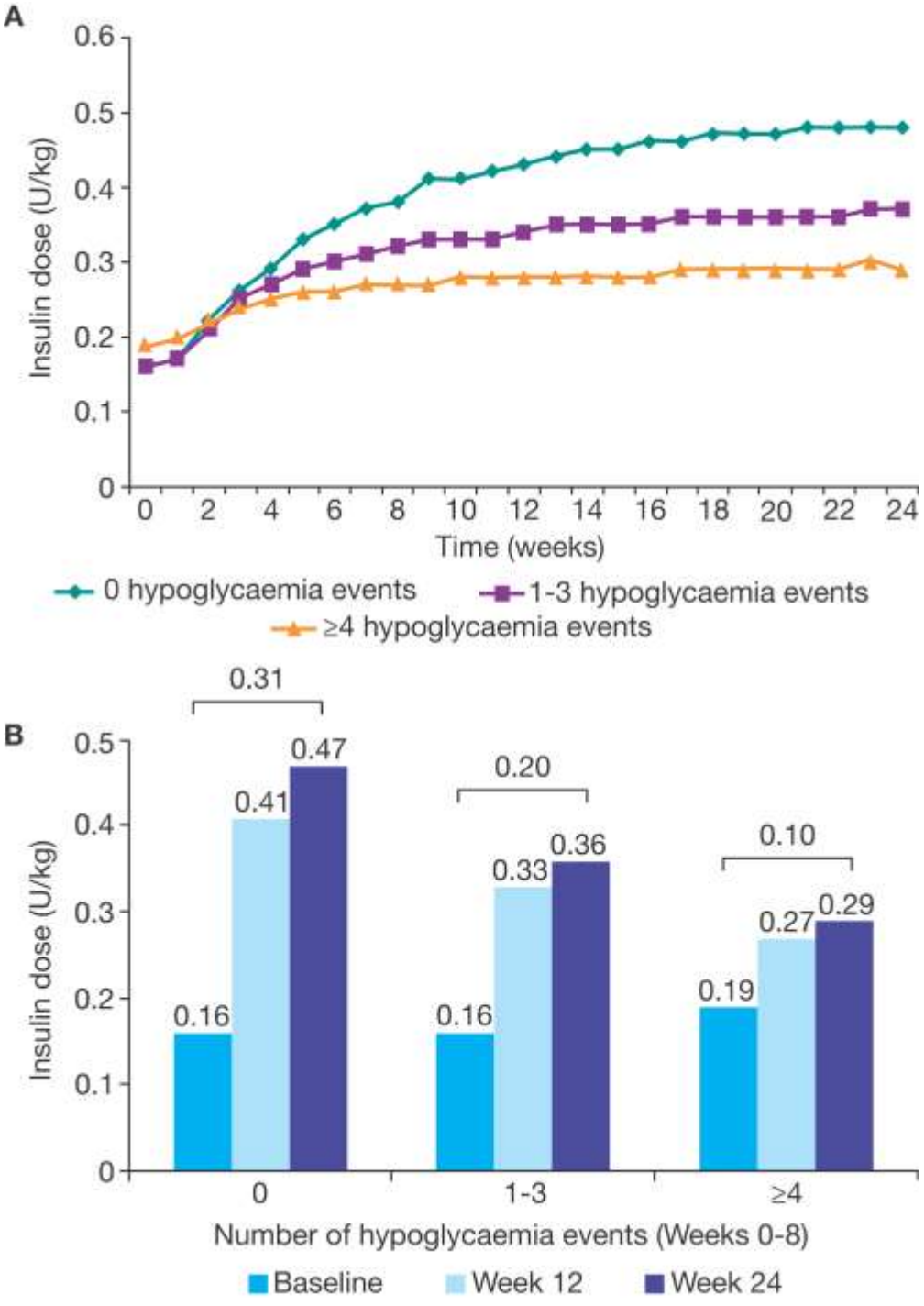
Tables and Figures:

Figure 1. Mean HbA1c at baseline and Weeks 12 and 24 after Gla-100 initiation.



Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin A1c.

Figure 2. (A.) Change in Gla-100 dose over study duration and (B.) mean dose at baseline and Weeks 12 and 24, stratified by number of hypoglycaemia events occurring during forced Gla-100 titration (Weeks 0-8).



Gla-100, insulin glargine 100 U/mL.

SUPPLEMENTARY INFORMATION

Table S1. Sociodemographic and baseline characteristics of participants with T2DM stratified by number of hypoglycaemia events during Gla-100 titration (Weeks 0-8).

Characteristic	Overall population		
	Number of hypoglycaemia events, weeks 0-8†		
	0 n=2,573	1-3 n=732	≥4 n=244
Age, years‡	57.7 (19.6-86.2)	58.3 (26.7-84.7)	59.1 (31.2-77.0)
Male, n (%)	1,385 (53.8)	384 (52.5)	125 (51.2)
T2DM duration, years‡	7.0 (0.0-50.0)	8.3 (0.5-45.0)	8.0 (0.8-40.0)
Weight, kg	87.7 (18.5)	83.3 (17.4)	77.6 (14.7)
BMI, kg/m^2	31.0 (5.3)	29.6 (4.9)	28.4 (4.5)
HbA1c, %	8.8 (1.1)	8.6 (1.0)	8.5 (1.0)
HbA1c, mmol/mol	72.7 (9.1)	70.5 (8.2)	69.4 (8.2)
FPG, mmol/L	10.8 (3.0)	10.4 (2.9)	10.3 (3.4)
FPG, mg/dL	194 (54)	187 (52)	185 (61)
Insulin dose day 1, U/kg	0.16 (0.07)	0.16 (0.08)	0.19 (0.11)
Insulin dose, U/day	13.3 (5.7)	13.0 (5.8)	14.4 (8.3)
Fasting C-peptide, nmol/L	1.21 (0.64)	1.04 (0.56)	0.95 (0.54)

† Hypoglycaemia events were defined as confirmed (PG <3.9 mmol/L [<70 mg/dL]) or severe (any event requiring third-party assistance). ‡Age and diabetes duration are presented as median (range).

Other data are presented as mean (SD).

FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin A1c; PG, plasma glucose; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Table S2. Baseline BMI by number of hypoglycaemia events during Gla-100 titration (Weeks 0-8) and concomitant OAD use.

OAD group	Baseline BMI (kg/m^2) by number of hypoglycaemia events during weeks 0-8		
	0	1-3	≥4
MET	31.8 (5.7)	29.3 (4.9)	26.7 (4.6)
SU	29.6 (5.2)	27.7 (4.6)	26.6 (3.9)
MET+SU	31.4 (5.0)	30.4 (4.8)	29.1 (4.4)

Data are shown as mean (SD).

Gla-100, insulin glargine 100 U/mL; MET, metformin; OAD, oral antidiabetes drug; SD, standard deviation; SU, sulfonylurea.

Table S3: Baseline C-peptide level by number of hypoglycaemia events during Gla-100 titration (Weeks 0-8) with concomitant OAD use.

OAD group	Baseline C-peptide (nmol/L) by number of hypoglycaemia events during weeks 0-8		
	0	1-3	≥4
MET	1.11 (0.47)	0.75 (0.33)	0.46 (0.24)
SU	1.26 (0.77)	1.03 (0.63)	0.88 (0.88)
MET+SU	1.20 (0.57)	1.08 (0.53)	1.00 (0.51)

Data are shown as mean (SD).

Gla-100, insulin glargine 100 U/mL; MET, metformin; OAD, oral antidiabetes drug; SD, standard deviation; SU, sulfonylurea.

Table S4: Clinical outcomes stratified by number of hypoglycaemia events during Gla-100 titration (Weeks 0-8) and concomitant OAD use.

Outcome	Concomitant OAD	Number of hypoglycaemia events during weeks 0-8		
		0	1-3	≥4
HbA1c Week 12, %	MET	7.3 (1.0)	6.9 (0.9)	7.4 (0.9)
	MET+SU	7.4 (0.9)	7.1 (0.8)	7.0 (0.7)
	SU	7.8 (1.2)	7.5 (1.1)	7.4 (1.2)
HbA1c Week 24, %	MET	7.0 (1.0)	6.8 (1.0)	7.5 (1.0)
	MET+SU	7.1 (0.9)	6.9 (0.8)	6.9 (0.7)
	SU	7.6 (1.2)	7.4 (1.1)	7.4 (1.2)
Patients with HbA1c <7.0% Week 24, n (%)	MET	284 (55.3)	52 (69.3)	5 (38.5)
	MET+SU	457 (45.2)	220 (54.2)	92 (59.4)
	SU	196 (30.1)	61 (37.2)	21 (38.9)
FPG Week 12, mmol/L	MET	6.7 (2.1)	5.9 (2.4)	5.3 (1.1)
	MET+SU	6.9 (2.1)	6.4 (1.8)	6.2 (2.1)
	SU	7.0 (2.2)	6.2 (2.0)	6.0 (2.3)
FPG Week 24, mmol/L	MET	6.3 (1.9)	6.0 (2.5)	6.4 (2.4)
	MET+SU	6.7 (2.1)	6.4 (1.9)	6.1 (1.9)
	SU	6.9 (2.3)	6.2 (1.9)	6.0 (1.5)
Patients with FPG ≤5.6 mmol/L Week 24, n (%)	MET	200 (40.5)	39 (54.2)	5 (38.5)
	MET+SU	295 (29.8)	151 (37.4)	66 (45.8)
	SU	289 (28.4)	73 (44.0)	25 (45.5)
Insulin dose Week 12, U/kg	MET	0.46 (0.22)	0.37 (0.16)	0.26 (0.13)
	MET+SU	0.39 (0.20)	0.31 (0.16)	0.25 (0.13)
	SU	0.40 (0.20)	0.35 (0.19)	0.33 (0.11)
Insulin dose Week 24, U/kg	MET	0.53 (0.28)	0.38 (0.19)	0.27 (0.08)
	MET+SU	0.45 (0.26)	0.35 (0.18)	0.28 (0.15)
	SU	0.45 (0.24)	0.37 (0.21)	0.32 (0.13)
Weight change Baseline to Week 24, kg	MET	0.7 (3.9)	1.2 (3.6)	2.1 (2.6)
	MET+SU	1.8 (3.3)	1.9 (3.2)	1.4 (2.9)
	SU	2.5 (3.8)	3.3 (3.8)	3.9 (4.0)
Non-severe hypoglycaemia[†]	All OADs			
Week 0-8, % people		0.0	20.6	6.9
Week 9-24, % people		19.5	13.1	6.1
Week 0-8, events/patient-year[§]		0.0	10.4 (0.3)	43.7 (1.4)
Week 9-24, events/patient-year[§]		2.7 (0.1)	10.1 (0.6)	26.8 (1.7)
Severe hypoglycaemia	All OADs			

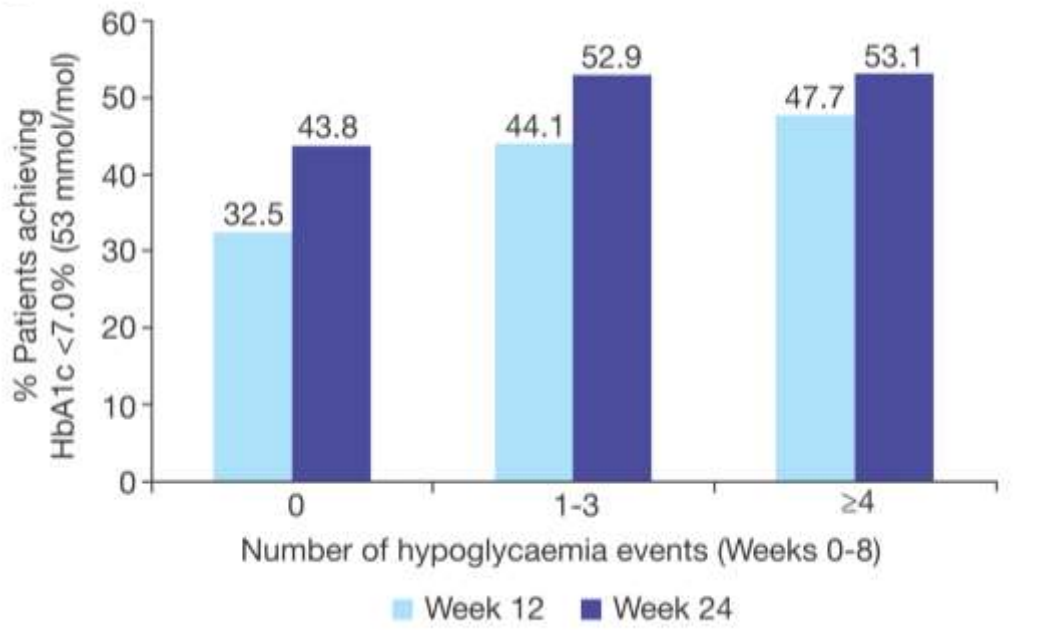
Outcome	Concomitant OAD	Number of hypoglycaemia events during weeks 0-8		
		0	1-3	≥4
Week 0-8, % people		0.0	3.4	3.3
Week 9-24, % people		0.7	2.3	3.3
Week 0-8, events/patient-year[§]		0.0	0.24 (0.07)	0.46 (0.21)
Week 9-24, events/patient-year[§]		0.03 (0.01)	0.10 (0.03)	0.51 (0.21)

[†] plasma glucose <3.9 mmol/L (<70 mg/dL). [§] Mean (SE).

Data are shown as mean (SD) unless otherwise specified.

FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; MET, metformin; OAD, oral antidiabetes drug; PG, plasma glucose; SD, standard deviation; SU, sulfonylurea.

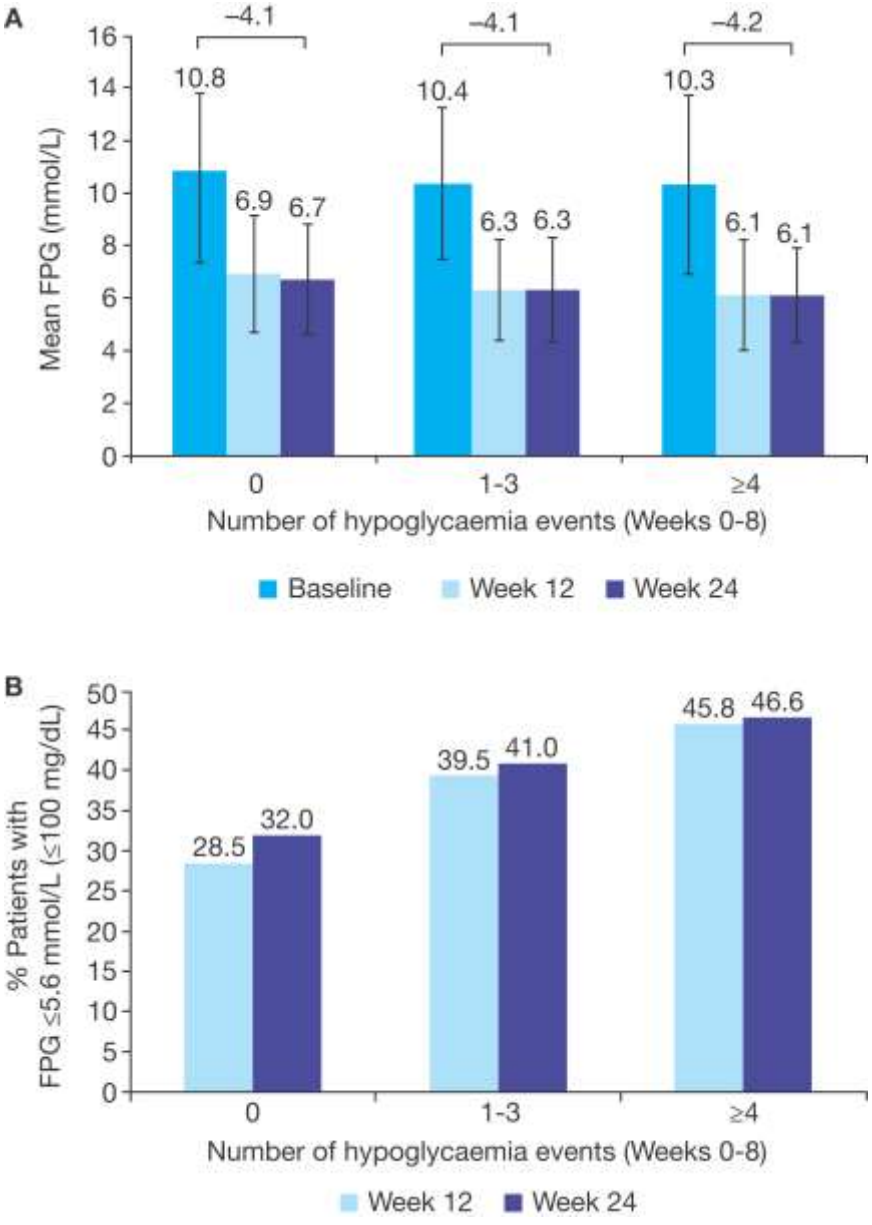
Figure S1: Percentage of people with T2DM and at target HbA1c 7.0% (53 mmol/mol), stratified by number of hypoglycaemia (PG <3.9 mmol/L [<70 mg/dL] or severe[†]) events during forced Gla-100 titration (Weeks 0-8).



[†] Hypoglycaemia events were defined as confirmed (PG <3.9 mmol/L) or severe (any event requiring third-party assistance).

HbA1c, glycated haemoglobin A1c; PG, plasma glucose; T2DM, type 2 diabetes mellitus.

FIGURE S2. (A). Mean FPG at baseline, Weeks 12 and 24 and (B.) percentage of people with T2DM at target FPG 5.6 mmol/L (100 mg/dL) stratified by number of hypoglycaemia events (PG <3.9 mmol/L [<70 mg/dL] or severe[†]) during forced Gla-100 titration (Weeks 0-8).



[†] Hypoglycaemia events were defined as confirmed (PG <3.9 mmol/L) or severe (any event requiring third-party assistance).

FPG, fasting plasma glucose; PG, plasma glucose; T2DM, type 2 diabetes mellitus.