


ORIGINAL ARTICLE

Higher versus standard starting dose of insulin glargine 100 U/mL in overweight or obese Chinese patients with type 2 diabetes: Results of a multicentre, open-label, randomized controlled trial (BEYOND VII)

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Funding information

This study was funded by Sanofi China.

Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.13967>.

Abstract

Aim: To determine the safety of a higher starting dose of basal insulin in overweight/obese patients with type 2 diabetes (T2D).

Materials and methods: This 16-week, randomized, multicentre, open-label trial enrolled adults with T2D (body mass index 25–40 kg/m²) and suboptimal glycaemic control (glycated haemoglobin [HbA1c] 7.5–11.0% [58–97 mmol/mol] and fasting plasma glucose [FPG] >9.0 mmol/L) with two to three oral anti-hyperglycaemic drugs at 51 centres in China. Patients were randomized (1:1) to a higher (0.3 U/kg) or standard (0.2 U/kg) starting dose of insulin glargine 100 U/mL, which was then titrated to achieve a self-monitored fasting blood glucose (FBG) of 4.4 to 5.6 mmol/L. The primary endpoint was the percentage of patients with ≥ 1 episode of overall confirmed hypoglycaemia (≤ 3.9 mmol/L or severe).

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Results: At the end of study (n = 866), 11.0% patients treated with the 0.3 U/kg starting insulin dose experienced overall confirmed hypoglycaemia versus 8.6% of patients treated with 0.2 U/kg (estimated difference 2.1%, 95% confidence interval – 1.68, 5.89). The proportions of patients with symptomatic (9.8% vs 7.0%; $P = 0.128$) and nocturnal hypoglycaemia (2.7% vs 1.2%; $P = 0.102$) were similar in the two groups. There were no events of severe hypoglycaemia or FBG <3.0 mmol/L during the 16-week treatment, and achievement of HbA1c <7.0% (53 mmol/mol) (37.1% vs 37.1%) or FPG <5.6 mmol/L (15.9% vs 16.3%), <6.1 mmol/L (27.6% vs 26.1%), or < 7.0 mmol/L (48.8% vs 48.3%) without hypoglycaemia were comparable in the two groups. Moreover, the mean time was shorter (4.53, 3.95 and 2.74 weeks vs 5.51, 5.21 and 3.64 weeks) and number of titrations was lower (3.5, 3.0 and 2.0 vs 4.3, 4.0 and 2.8) to achieve self-monitored FBG targets of <5.6, <6.1 and <7.0 mmol/L in the higher versus the standard insulin dose group (all $P < 0.01$).

Conclusions: Among overweight/obese patients with T2D, a higher insulin starting dose was as safe as the standard starting dose, and self-monitored FBG targets were achieved earlier with the higher versus the standard dose.

KEYWORDS

fasting plasma glucose, glycated haemoglobin, hypoglycaemia, insulin glargine, oral antidiabetic drugs, self-monitored fasting glucose, type 2 diabetes

1 | INTRODUCTION

With the failure of oral antidiabetic drugs (OADs) to achieve adequate glycaemic control in the daily management of type 2 diabetes (T2D), insulin therapy is often required to control hyperglycaemia.^{1,2} Currently 23% to 44% of patients with T2D worldwide receive insulin treatment,³⁻⁵ of whom only 16% to 30% actually achieve the recommended glycaemic target of glycosylated haemoglobin (HbA1c) <7% (53 mmol/mol).⁶⁻⁸

Insufficient dose titration largely undermines the efficacy of insulin, and is a key component associated with therapeutic inertia. ORBIT was the largest observational study of basal insulin utility in China, which showed that the dose of basal insulin among patients with uncontrolled T2D increased by only 0.034 U/kg/d during 6 months after treatment initiation, with a mean starting dose of 0.18 ± 0.07 U/kg/d.⁹ Observational studies from other countries^{10,11} have also reported that, 1 year after treatment initiation, basal insulin only increased by 0.1 U/kg/d.

Achieving appropriate insulin titration in clinical practice is challenging for several reasons. A recent study identified, from the perspective of the patient, that frustration with reaching the titration goal is a more important barrier to achieving their glycaemic target than their fear of hypoglycaemia,¹² suggesting the clinical need for balancing hypoglycaemia risk and time required to reach the target. Using a higher starting dose of insulin may be beneficial in reducing the titration time without increasing the risk of hypoglycaemia, and may therefore be a preferred option for patients.

Being overweight and/or obese is another barrier to achieving glycaemic targets.¹³ The International Diabetes Management Practices Study reported that the median body mass index (BMI) of patients with T2D increased from 26 kg/m² to 29 kg/m² between 2005 and 2017, while the proportion of insulin-treated patients who achieved the target HbA1c of <7% (53 mmol/mol) decreased from 28% to 16% over the same period,¹⁴ suggesting that achieving the glycaemic target is an additional challenge with increasing BMI. Overweight and obese patients currently form the majority of patients with T2D worldwide, and ~60% of patients with T2D in China have a BMI of ≥ 25 kg/m², corresponding to ~69 million Chinese adults.^{4,15} However, no specific insulin dosing algorithm has been determined in this population.

The current American Association of Clinical Endocrinologists consensus statement,¹⁶ and the American Diabetes Association and the European Association for the Study of Diabetes guidelines for the management of T2D² recommend that the initial starting dose of basal insulin should be based on patient's baseline HbA1c levels, while the Chinese guidelines recommend a general initial basal insulin dose of 0.1 to 0.3 U/kg.¹⁷ However, none of these guidelines include recommendations for the starting dose of insulin based on BMI. Given that the starting insulin dose is one of the most powerful predictors of HbA1c change,^{18,19} and the fact that overweight and obese patients with T2D usually require a higher insulin dose than patients with normal BMI due to greater insulin resistance, using a higher starting dose of basal insulin may be a simple and practical approach in these patients.²⁰⁻²² However, limited evidence is currently available on the safety of this approach, especially in Asian populations.

This was the first randomized controlled trial to compare the safety and efficacy of a higher starting dose (0.3 U/kg) of insulin glargine 100 U/mL (Gla-100) with its standard starting dose (0.2 U/kg) in overweight or obese Chinese patients with T2D who were inadequately controlled with OADs.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a 16-week, randomized, multicentre, open-label, parallel group, phase IV trial, conducted between October 2016 and April 2018 at 51 sites in mainland China (NCT02836704). The study design and methods have been reported previously.²³ Briefly, the study comprised a 2-week screening period, a 3-day run-in period, a 16-week randomized treatment period and 1-week follow-up period. Patients were required to cease any ongoing treatment with sulphonylureas or glinides during the run-in period, but were allowed to continue treatment with other OADs at the same dose and frequency. Use of dipeptidyl peptidase-4 inhibitors was also prohibited during the study, as these drugs were not approved as an add-on therapy to insulin in China at the time of the study. Patients with fasting plasma glucose (FPG) >16.7 mmol/L during the run-in period had to discontinue the study and received appropriate treatment in accordance with clinical guidelines.

2.2 | Patients

Eligible patients at screening included adults aged 18 to 70 years, with a BMI 25 to 40 kg/m², a confirmed diagnosis of T2D for ≥2 years, HbA1c values 7.5% to 11% (58–97 mmol/mol) and FPG levels >9 mmol/L, who were receiving two to three OADs (including metformin ≥1.5 g/d or at the maximum tolerated dose). In addition, patients had to be willing to perform self-monitoring of blood glucose using the sponsor-provided blood glucose meter (Roche Diagnostics GmbH, Accu-chek® Performa, Mannheim, Germany). Key exclusion criteria included: use of insulin, thiazolidinediones, glucagon-like peptide-1 receptor agonists, or pharmacological treatments for weight loss during the 3 months prior to screening; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; history of hypoglycaemia unawareness or unexplained hypoglycaemia in the past 6 months; and pregnancy, breastfeeding, or not using an acceptable method of birth control.

The study protocol was approved by the local institutional review board at each study site, and the study was conducted in accordance with the ethical standards of the institutional and/or national research committees at each centre and with the 1964 Declaration of Helsinki, as revised in 2013. All authors confirm that the study was strictly conducted as per the Good Clinical Practice guidelines²⁴ and the manuscript complies with Good Publication Practice guidelines. All patients included in the study provided written informed consent before initiating the trial.

2.3 | Treatment and procedures

All patients who met the eligibility criteria at the end of the run-in period were randomly assigned (1:1) using an interactive voice and web-response system to receive once-daily subcutaneous injection of Gla-100 (Lantus SoloSTAR®, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) at a standard starting dose (0.2 U/kg) or a higher starting dose (0.3 U/kg). Randomization was stratified by baseline sulphonylurea or glinide use to minimize bias due to a possibly short washout period duration (the 3-day run-in period). Patients were advised to administer the insulin dose at the same time each day, preferably at dinner time. While patients, investigators and site staff remained unmasked to treatment, the statistician and sponsor remained masked until after database lock and completion of analyses.

All patients were required to measure and record the values of their four-point self-monitoring of blood glucose (before breakfast and 2 hours after breakfast, lunch, and dinner) on the last day of the run-in period and ≥3 consecutive days within the week prior to each visit during the treatment period. Patients were instructed to adjust the insulin doses at each visit based on their median self-monitored fasting blood glucose (FBG) levels prior to the visit, to achieve a self-monitored FBG target of 4.4 to 5.6 mmol/L (80–100 mg/dL) using the same titration algorithm (Table S1).

Patients attended their scheduled clinic visits during the screening, run-in and randomization periods, then at weeks 2, 6, 12 and 16 during the treatment period. In addition, telephone follow-ups were conducted at 1, 3, 4, 5, 8 and 10 weeks after randomization, and 1 week after the end of treatment. The self-monitoring of blood glucose values and daily insulin dose were also recorded at each study visit, and additional assessments (HbA1c, body weight) were conducted at week 16. Adverse events (AEs) and hypoglycaemia events were recorded throughout the study, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) 20.1.

2.4 | Outcomes

The primary endpoint was the incidence proportion of patients with overall confirmed hypoglycaemia (≤3.9 mmol/L or severe) during the 16-week treatment in the two treatment arms. The secondary safety endpoints included: assessment of annualized event rates (events per patient-years of exposure) of overall confirmed hypoglycaemia, symptomatic hypoglycaemia, nocturnal hypoglycaemia, severe hypoglycaemia and FBG <3.0 mmol/L (Table S2); clinical laboratory assessments; and non-hypoglycaemia treatment-emergent AEs (TEAEs), that is, non-hypoglycaemia AEs that developed or worsened during the 16-week treatment period. The secondary efficacy endpoints included: the proportion of patients who achieved the HbA1c targets of <6.5%, <7.0% and <7.5% and FPG targets of <5.6, <6.1 and <7.0 mmol/L without hypoglycaemia at week 16; the change from baseline in HbA1c and FPG at week 16; and the change in body weight from baseline to week 16. The exploratory endpoint was the

time and the mean number of dose titrations required to first achieve self-monitored FBG targets.

2.5 | Statistical analysis

The study sample size was calculated to test the non-inferiority of the difference between the two treatment groups using an estimated non-inferiority margin of 10%²⁵ (absolute value) and a one-sided α -value of 0.025, with an estimated control group incidence of hypoglycaemia of 32.65% based on pooled data from 15 treat-to-target randomized controlled trials, conducted over 24 weeks.²⁶ Based on these calculations, 440 patients were required in each group to achieve a power of 85%, assuming a 10% dropout rate.

Efficacy was assessed in the modified intention-to-treat (ITT) population of all randomized patients who received ≥ 1 dose of Gla-100 and had ≥ 1 post-treatment efficacy measurement. Analyses were repeated in the per-protocol (PP) population of all ITT patients with no major protocol violations. Safety analyses included all patients who were randomized and received ≥ 1 dose of Gla-100.

For analysis of the primary endpoint, the number and percentage of patients with confirmed or severe hypoglycaemia were determined for each treatment arm, and an adjusted estimate of the group difference was obtained from a log-binomial regression after adjusting the stratification factor (sulphonylureas/glinides intake or not at run-in), with its 95% confidence intervals (CIs) obtained using the normal approximation to the binomial. The non-inferiority of the higher versus standard starting dose (0.3 U/kg vs 0.2 U/kg) of insulin for the incidence proportion of overall confirmed hypoglycaemia (≤ 3.9 mmol/L or severe) was confirmed if the upper limit of the 95% CI was $< 10\%$. For the analysis of secondary safety endpoints, *P* values for between-group differences were determined using logistic regression, adjusted for the stratification factor; in the event rate of hypoglycaemia, *P* values for between-group differences were determined using Poisson regression. For the analysis of secondary efficacy endpoints, the percentages of patients who achieved HbA1c and FPG targets were analysed using the same method as that used for the primary endpoint, with *P* values for differences between treatment groups determined using log-binomial regression after adjusting for baseline HbA1c or FPG, respectively. Changes in endpoints from baseline to post-baseline visits were estimated using either ANCOVA (HbA1c, body weight) or mixed models for repeated measures (FPG), using the end-of-treatment measurements as the dependent variable, treatment as a fixed effect, baseline measurements as a covariate, and patient/visit as a repeated measure indicator. Other continuous variables were summarized using descriptive statistics. The time and mean number of dose titrations required to achieve the self-monitored FBG target were summarized (mean, SD, median, range) in the two treatment arms and analysed using the *t*-test and Wilcoxon's test. Adjustment for multiplicity was not applied for secondary endpoints, and was considered exploratory. All statistical analyses were conducted using SAS (version 7.1).

3 | RESULTS

3.1 | Participants

Of the 1073 patients screened, 892 were randomized. Of these, 866 (97.1%) received ≥ 1 dose of insulin and were included in the modified ITT population, and 814 patients (91.2%) completed the study (Figure 1). The PP and safety analyses included 814 and 887 patients, respectively.

Baseline patient demographics and clinical characteristics were well balanced between treatment groups (Table 1). The mean \pm SD age was 52.5 ± 9.7 years, with slightly more men (59.0%) than women. The majority of patients (81.3%) had a BMI of 25 to < 30 kg/m² (mean \pm SD 27.8 ± 2.6 kg/m²), and the mean \pm SD duration of diabetes was 7.6 ± 4.5 years. The majority of patients (87.9%) received two OADs; metformin (100%) and α -glucosidase inhibitors (AGIs; 51.3%) were the most common concomitant OADs, with 51.3% and 52.7% patients receiving AGIs in the 0.3 and 0.2 U/kg insulin groups, respectively.

3.2 | Primary endpoint

Overall, 11.0% of patients treated with the higher starting dose of Gla-100 (0.3 U/kg) and 8.6% of patients treated with the standard starting dose (0.2 U/kg) reported overall confirmed hypoglycaemia. The higher starting dose of Gla-100 was non-inferior to the standard starting dose with regard to the incidence proportion of overall confirmed hypoglycaemia, with an estimated between-group difference of 2.1% (95% CI $-1.68, 5.89$). Similar results were observed in the PP populations (Figure 2). The number of overall confirmed hypoglycaemia episodes at each study visit was numerically higher in patients treated with the higher starting dose of Gla-100 versus the standard dose (Table S3); however, no statistical analyses were performed due to low frequency of overall confirmed hypoglycaemia in the two arms.

3.3 | Secondary endpoints

3.3.1 | Safety

The incidence and numbers of symptomatic (9.8% vs 7.0%; *P* = 0.128) and nocturnal (2.7% vs 1.2%; *P* = 0.102) hypoglycaemia episodes at 16 weeks were similar with 0.3 versus 0.2 U/kg starting doses of Gla-100 (Table 2); however, the observed number of overall confirmed hypoglycaemia episodes at week 2 in patients treated with 0.3 U/kg was higher versus the 0.2 U/kg starting dose of Gla-100 (Table S3). There were no events of severe hypoglycaemia or FBG < 3.0 mmol/L during the 16-week treatment (Table 2).

In patients receiving 0.3 versus 0.2 U/kg starting doses of Gla-100, the annualized rates of overall confirmed (0.593 vs 0.476 events per patient-year; *P* = 0.194) and symptomatic (0.483

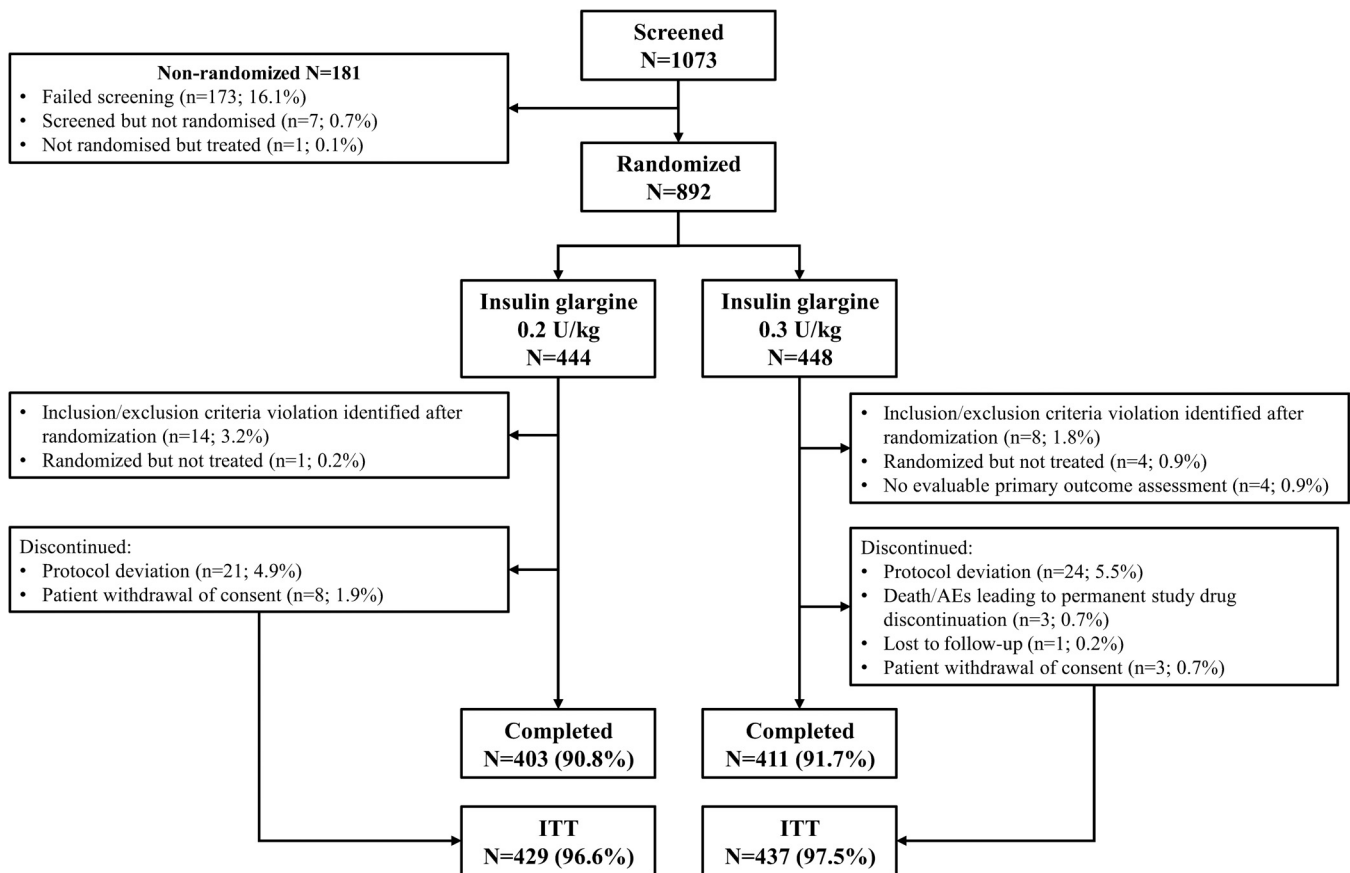


FIGURE 1 Patient disposition. AEs, adverse events; ITT, intention-to-treat

vs 0.335 events per patient-year; $P = 0.059$) hypoglycaemia episodes were similar (Table 2). However, despite no statistically significant difference in the incidence of nocturnal hypoglycaemia between the two groups, the annualized rate of nocturnal hypoglycaemia was higher in the 0.3 U/kg versus the 0.2 U/kg treatment group (0.124 vs 0.045 events per patient-year; $P = 0.030$; Table 2) owing to one patient who reported five episodes of hypoglycaemia not confirmed by blood glucose measurements on 5 consecutive nights. An analysis excluding this patient showed no significant difference in the annualized rate of nocturnal hypoglycaemia between the treatment groups (0.045 vs 0.088 events per patient-year; $P = 0.176$ using Poisson regression [Table 2]).

The frequency of any serious non-hypoglycaemia TEAEs was numerically higher in the 0.2 U/kg group versus the 0.3 U/kg group, with 13 patients (2.9%) in the 0.2 U/kg group and 11 patients (2.5%) in the 0.3 U/kg group reporting serious non-hypoglycaemia TEAEs (Table 3). A total of three patients (0.7%) in the 0.3 U/kg group discontinued the study because of non-hypoglycaemia TEAEs, compared with no patients in the 0.2 U/kg group. The main reasons for treatment discontinuation in the 0.3 U/kg group were: allergic reaction ($n = 1$); diabetic ketoacidosis ($n = 1$); and hyperglycaemia ($n = 1$). Except for the patient who experienced an allergic reaction, which was considered to be treatment-related, the other two patients had

uncontrolled hyperglycaemia as they did not adhere to their insulin glargine regimen and were additionally taking herbal supplements without obtaining consent from the study investigator. The most frequent non-hypoglycaemia TEAEs reported in $\geq 3\%$ of patients were infections and infestations, and gastrointestinal disorders (Table 3).

3.3.2 | Efficacy

The adjusted mean change in HbA1c from baseline to week 16 was similar in the higher and standard starting dose groups (-1.5% vs -1.5% ; $P = 0.463$ [Table S5]). The proportions of patients who achieved HbA1c targets of $<6.5\%$, $<7.0\%$ and $<7.5\%$ at week 16 (Figure S1A), and those who achieved HbA1c targets without confirmed hypoglycaemia at week 16 (Figure S1B) were also similar in the two groups.

Mean changes in FPG (-4.3 vs -4.3 mmol/L; $P = 0.924$) from baseline to week 16 were similar in the higher and standard starting dose groups (Table S5). The proportions of patients who achieved FPG targets of <5.6 , <6.1 and <7.0 mmol/L at week 16 (Figure S1C), and those who achieved FPG targets without confirmed hypoglycaemia at week 16 (Figure S1D) were also similar in the two treatment arms. Although the adjusted mean change from

baseline in FPG was greater in patients in the 0.3 U/kg arm at week 2 compared with the 0.2 U/kg arm (−3.38 vs −2.77 mmol/L; $P < 0.001$ [Figure 3]), no statistically significant difference in the

reduction of FPG levels was observed at the end of the treatment period.

The mean times to first achieve a self-monitored FBG of <5.6, <6.1 and <7.0 mmol/L were significantly shorter with the higher versus the standard Gla-100 starting dose (Figure S2A) and the mean number of dose titrations required to achieve these targets was lower with the higher dose (Figure S2B). While the change in insulin dose was greater among patients who received the standard starting dose of Gla-100, the final dose of insulin at week 16 was 0.4 U/kg and 0.36 U/kg in the 0.3 and 0.2 U/kg groups, respectively. The mean titration dose of Gla-100 during the 16-week treatment was 0.10 U/kg and 0.16 U/kg in the 0.3 and 0.2 U/kg groups, respectively.

TABLE 1 Baseline patient demographics and clinical characteristics (intention-to-treat population)

	Gla-100 starting dose	
	0.2 U/kg (N = 429)	0.3 U/kg (N = 437)
Age, years	53.2 (9.6)	51.7 (9.7)
Male, n (%)	242 (56.4)	269 (61.6)
Body weight, kg	76.7 (11.3)	77.5 (11.2)
BMI, kg/m ²	27.8 (2.7)	27.8 (2.6)
BMI category, n (%)		
≥25 to <30 kg/m ²	349 (81.4)	355 (81.2)
≥30 kg/m ²	80 (18.6)	82 (18.8)
Duration of type 2 diabetes, years	7.9 (4.5)	7.3 (4.4)
Diabetic complications, n (%)		
Neuropathy	31 (7.2)	42 (9.6)
Nephropathy	13 (3.0)	24 (5.5)
Retinopathy	14 (3.3)	15 (3.4)
Microangiopathy	12 (2.8)	13 (3.0)
Other vascular disorders	12 (2.8)	13 (3.0)
Foot syndrome	0	0
Other	3 (0.7)	3 (0.7)
HbA1c, %	8.8 (1.04)	8.8 (0.96)
FPG, mmol/L	11.6 (2.74)	11.5 (2.79)
Number of concomitant medications, n (%)		
1 OAD	193 (45.0)	206 (47.1)
2 OADs	234 (54.5)	229 (52.4)
3 OADs	2 (0.5)	2 (0.5)

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug.

Data are mean (SD), unless otherwise indicated.

TABLE 2 Hypoglycaemia outcomes at 16 weeks

	Gla-100 starting dose		P
	0.2 U/kg (N = 429)	0.3 U/kg (N = 437)	
Patients with hypoglycaemia, n (%)			
Symptomatic	30 (7.0)	43 (9.8)	0.128
Nocturnal	5 (1.2)	12 (2.7)	0.102
Severe	0	0	–
FBG <3.0 mmol/L	0	0	–
Hypoglycaemia annualized rate, events/PYE			
Overall confirmed	64/134.5 (0.476)	81/136.7 (0.593)	0.194
Symptomatic	45/134.5 (0.335)	66/136.7 (0.483)	0.059
Nocturnal	6/134.5 (0.045)	17/136.7 (0.124)	0.030
Nocturnal ^a	6/134.5 (0.045)	12/136.7 (0.088)	0.176
Severe	0	0	–
FBG <3.0 mmol/L	0	0	–

Abbreviations: FBG, fasting blood glucose; Gla-100, insulin glargine 100 U/mL; PYE, patient-years of exposure.

^aExcluding one patient who reported hypoglycaemia on 5 consecutive nights occurring at the same time each night but without an associated confirmatory self-monitored blood glucose measurement.

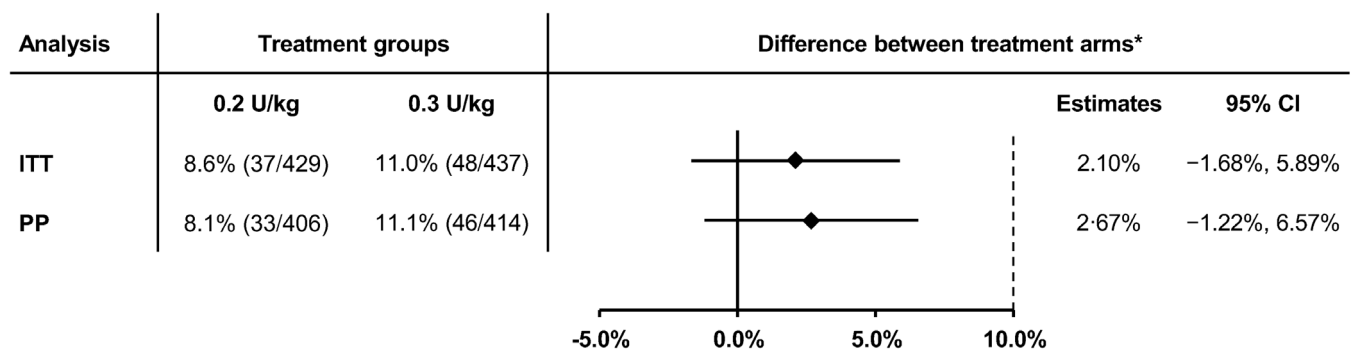


FIGURE 2 Forest plot for the incidence proportion of overall confirmed hypoglycaemia in the intention-to-treat (ITT; n = 866) and per-protocol (PP; n = 820) populations. Vertical dotted line = non-inferiority margin 10%. CI, confidence interval

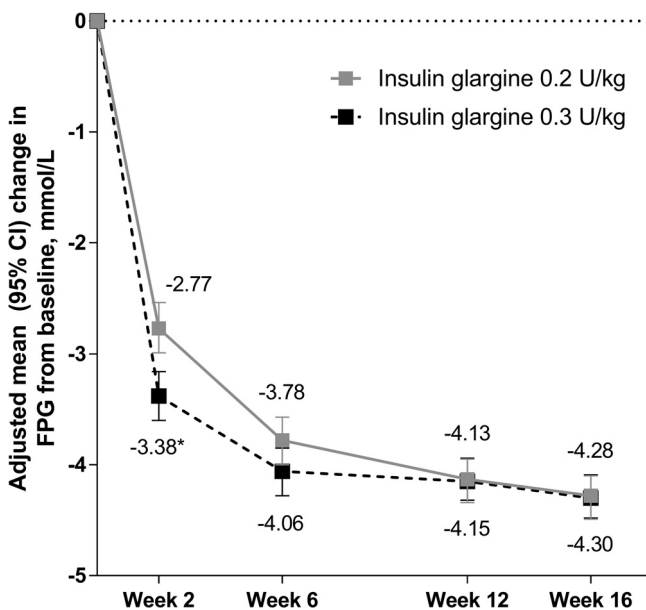
TABLE 3 Non-hypoglycaemia treatment-emergent adverse events during the 16-week treatment period

Other safety outcomes, n (%)	0.2 U/kg N = 444	0.3 U/kg N = 443
Any non-hypoglycaemia TEAE ^a	135 (30.4)	99 (22.3)
Serious non-hypoglycaemia TEAEs ^a	13 (2.9)	11 (2.5)
Non-hypoglycaemia TEAEs ^a leading to discontinuation	0	3 (0.7)
Non-hypoglycaemia TEAEs ^a leading to death	0	0
Non-hypoglycaemia TEAEs ^a occurring in ≥3% of patients		
Infections and infestations	57 (12.8)	45 (10.2)
Gastrointestinal disorders	20 (4.5)	12 (2.7)
Any possibly related non-hypoglycaemia TEAE ^b	6 (1.4)	6 (1.4)
Possibly related serious non-hypoglycaemia TEAEs ^b	0	0
Possibly related non-hypoglycaemia TEAEs ^b leading to discontinuation	0	1 (0.2)
Possibly related non-hypoglycaemia TEAEs ^b leading to death	0	0

Abbreviations: TEAE, treatment-emergent adverse event.

^aDefined as any adverse event that developed or worsened during the on-treatment period (time from first dose of study medication up to week 16).

^bDefined as a TEAE that possibly related to study medication.

**FIGURE 3** Change in fasting plasma glucose (FPG) from baseline to week 16. Intention-to-treat analysis (n = 866). * $P < 0.001$ vs insulin glargine 0.2 U/kg. CI, confidence interval

The mean change in body weight from baseline to week 16 was significantly greater (+0.4 kg) in the 0.3 U/kg group than in the 0.2 U/kg group (0 kg; $P = 0.012$ [Table S5]).

4 | DISCUSSION

To our knowledge, this is the first randomized controlled trial to focus on the optimization of basal insulin in overweight and obese patients with T2D in China. This prospective trial showed that a higher starting dose of Gla-100 (0.3 U/kg) resulted in comparable glycaemic control and treatment-associated hypoglycaemia, with shorter time to achieve FBG targets, compared with the standard starting dose (0.2 U/kg) in overweight and obese patients with T2D.

Treatment-associated hypoglycaemia is the main safety concern in patients with T2D receiving insulin treatment. In clinical practice, physicians generally prefer to initiate basal insulin from a conservative starting dose (usually 0.1–0.2 U/kg), and slowly uptitrate until satisfactory glycaemic control is achieved. The present study showed that a higher starting dose of 0.3 U/kg was non-inferior to the standard starting dose (0.2 U/kg), with similar incidence of overall confirmed hypoglycaemia and no statistically significant difference in the incidence of symptomatic or nocturnal hypoglycaemia during the 16-week treatment period. Moreover, no severe cases of hypoglycaemia or hypoglycaemic events ≤ 3.0 mmol/L were reported, indicating that Gla-100 was well tolerated at a higher starting dose of 0.3 U/kg in overweight and obese Chinese patients with T2D.

Initiating Gla-100 at a starting dose of 0.3 U/kg is not only safe but also contributes to improving glycaemic control. A recent study reported a non-linear relationship between basal insulin doses and glycaemic control, with the efficacy inflection point at 0.3 U/kg, and a plateauing effect at 0.5 U/kg.²⁷ A starting dose of 0.3 U/kg of insulin glargine may therefore reduce the gap between the initial and final dose required, thus reducing the titration period. In the present study, patients using a starting Gla-100 dose of 0.3 U/kg showed significantly greater change from baseline in FPG at week 2 versus patients using a starting dose of 0.2 U/kg, although the change in FPG in the two treatment arms eventually converged over the treatment period due to the treat-to-target titration algorithm. Furthermore, the time to achieve FBG targets in the 0.3 U/kg group was much shorter than in the 0.2 U/kg group, and fewer dose titrations were required to achieve FBG targets in the 0.3 U/kg group versus the 0.2 U/kg group. Considering that frustration at the time taken to reach HbA1c targets was reported as one of the main barriers to insulin titration,¹² these findings indicate that a higher starting dose of 0.3 U/kg could be a simple and practical way to overcome titration inertia, and consequently improve glycaemic control in the treated patients.

The slightly increased mean change in body weight from baseline to week 16 observed in the 0.3 U/kg group was unexpected (+0.4 kg vs 0 kg; $P = 0.012$) and should be considered within the context of continuous titration during the study which may have been the result of slightly aggressive titration. It should also be noted that the proportion of patients who achieved the HbA1c target < 6.5 (19.4% vs 17.0%; $P = 0.287$) without hypoglycaemia (18.0% vs 15.4%; $P = 0.245$) was numerically higher in the 0.3 U/kg versus the 0.2 U/kg treatment arm, and the final insulin dose used was also numerically higher in the 0.3 U/kg group versus the 0.2 U/kg group (0.4 U/kg vs 0.36 U/kg).

Although numerous insulin titration algorithms have been published in the past two decades, titration inertia is still a major challenge in clinical practice because of a lack of effective patient education and adequate physician–patient communication.¹² Unlike previous treat-to-target trials which focused on titration algorithm optimization (and consisted of a 12–16-week titration period and a 12–16-week maintenance period),^{28–31} the present study focused on the optimization of the starting dose (and included a 16-week titration period as the impact of starting dose weakened over time).

Two interesting observations regarding the baseline characteristics of participants were noted. One was that the mean BMI of patients included in this study was 27.8 kg/m², which was lower than the average BMI of patients with T2D in Western countries. As lower BMI is generally associated with an increased risk of hypoglycaemia,³² these results may be more relevant to the worldwide overweight and obese T2D population with high BMI values; however, real-world studies are required to confirm these results in Western populations. Another observation was that 51.3% of patients included in the study were concomitantly treated with AGIs during the study. This was mainly because AGIs are widely used in the management of Asian T2D patients as glycaemic control with AGIs is comparable to metformin, with a similar hypoglycaemia risk.³³ Furthermore, AGIs are also recommended by the Chinese guidelines for the management of T2D.¹⁷

The present study has some limitations. Firstly, a potential bias introduced by the open-label nature of the study, wherein the enrolled patients were educated regarding hypoglycaemia risk monitoring, cannot be ruled out. Secondly, the study strictly followed the “treat-to-target” titration algorithm to determine the risk of hypoglycaemia, which may have blunted the difference in efficacy between the two treatment arms.

In conclusion, compared with the standard starting dose (0.2 U/kg), a higher starting dose of basal insulin (0.3 U/kg) showed similar safety (hypoglycaemia risk) and efficacy in achieving glycaemic control in overweight and obese patients with T2D in China who had uncontrolled hyperglycaemia despite treatment with OADs. The higher starting dose was also associated with fewer dose titrations versus the standard starting dose, suggesting that using a higher starting dose of basal insulin (0.3 U/kg) may be a simple and practical approach to overcoming clinical inertia in overweight and obese patients with T2D receiving basal insulin treatment.

ACKNOWLEDGMENTS

This study was supported by Sanofi. We thank the patients, principal investigators (see Supporting Information), and their staff for participating in the study. We would also like to thank Andrea Bothwell, on behalf of inScience Communications, Springer Healthcare, Julian Martins of inScience Communications, Springer Healthcare, and Nishad Parkar, PhD, of Springer Healthcare communications, who provided medical writing assistance, which was funded by Sanofi China.

CONFLICTS OF INTEREST

L.J. reports receiving consulting and lecture fees from Eli Lilly, Bristol-Myers Squibb, Novartis, Novo Nordisk, Merck, Bayer, Takeda, Sanofi,

Roche and Boehringer Ingelheim and research grants from Roche and Sanofi. H.W., B.W., X.W., J.W., R.B., W.P., J.T., Y.W., F.B. and Z.G. have no conflicts of interests. A.C., W.F., X.Z. and N.C. are employees of Sanofi.

AUTHOR CONTRIBUTIONS

L.J., A.C. and N.C. participated in the trial design. H.W., B.W., X.W., J.W., R.B., W.P., J.T., Y.W., F.B. and Z.G. contributed to the conduct of the trial and the data collection. W.F. and X.Z. contributed to the data analysis. All authors interpreted the data and participated in writing the report, with the support of medical writing services provided by the funder. All authors read and approved the submitted version of the report.

DATA SHARING

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.clinicalstudydatarequest.com>.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Ji L, Wan H, Wen B, et al. Higher versus standard starting dose of insulin glargine 100 U/mL in overweight or obese Chinese patients with type 2 diabetes: Results of a multicentre, open-label, randomized controlled trial (BEYOND VII). *Diabetes Obes Metab*. 2020;22:838-846. <https://doi.org/10.1111/dom.13967>