



ORIGINAL ARTICLE

Efficacy and safety of a basal insulin + 2-3 oral antihyperglycaemic drugs regimen versus a twice-daily premixed insulin + metformin regimen after short-term intensive insulin therapy in individuals with type 2 diabetes: The multicentre, open-label, randomized controlled BEYOND-V trial

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Abstract

Aim: To compare the efficacy and safety of basal insulin glargine 100 units/ml (Gla) + 2-3 oral antihyperglycaemic drugs (OADs) with twice-daily premixed insulin aspart 70/30 (Asp30) + metformin (MET) after short-term intensive insulin therapy in adults with type 2 diabetes in China.

Materials and Methods: This open-label trial enrolled insulin-naïve adults with type 2 diabetes and an HbA1c of 7.5%-11.0% (58-97 mmol/mol) despite treatment with 2-3 OADs. All participants stopped previous OADs except MET, then received short-term intensive insulin therapy during the run-in period, when those with a fasting plasma glucose of less than 7.0 mmol/L and 2-hour postprandial glucose of less than 10.0 mmol/L were randomized to Gla + MET + a dipeptidyl peptidase-4 inhibitor or twice-daily Asp30 + MET. If HbA1c was more than 7.0% (>53 mmol/mol) at week 12, participants in the Gla group were added repaglinide or acarbose, at the physician's discretion, and participants in the Asp30 group continued to titrate insulin dose. The change in HbA1c from baseline to week 24 was assessed in the per protocol (PP) population (primary endpoint).

Results: There were 384 enrollees (192 each to Gla and Asp30); 367 were included in the PP analysis. The threshold for non-inferiority of Gla + OADs versus Asp30 + MET was met, with a least squares mean change from baseline in HbA1c of -1.72% and -1.70% (-42.2 and -42.1 mmol/mol), respectively (estimated difference -0.01%; 95% CI -0.20%, 0.17% [-0.1 mmol/mol; 95% CI -2.2, 1.9]). Achievement of

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HbA1c less than 7.0% (<53 mmol/mol) was comparable between the groups (60% vs. 57%). The proportion of participants with any (24% vs. 38%; $P = .003$), symptomatic (19% vs. 31%; $P = .007$) or confirmed hypoglycaemia (18% vs. 33%; $P < .001$) was lower in the Gla + OADs group.

Conclusions: Compared with Asp30 + MET, Gla + 2-3 OADs showed similar efficacy but a lower hypoglycaemia risk in Chinese individuals with type 2 diabetes who had undergone short-term intensive insulin therapy.

KEYWORDS

basal insulin, efficacy and safety, premixed insulin, short-term intensive insulin therapy, type 2 diabetes

1 | INTRODUCTION

As the prevalence of diabetes has increased considerably over the last few decades, China has become an epicentre of the disease, with ~25% of the 463 million people with diabetes worldwide residing in China.¹ As such, the management of diabetes is of great importance in China.

Current treatment strategies for type 2 diabetes aim to achieve intensive glycaemic control, as hyperglycaemia is a major risk factor for the development of many of the long-term complications of diabetes.²⁻⁴ In China, 74% of individuals receiving insulin treatment do not achieve the glycaemic target of HbA1c less than 7.0% (<53 mmol/mol). Furthermore, the burden of hypoglycaemia with insulin treatment is high, with ~16% of Chinese individuals receiving insulin treatment requiring a visit to a clinic because of hypoglycaemia.⁵ As such, there is an urgent need to improve the use of insulin in China to optimize the balance of efficacy and hypoglycaemic risk.

Compared with Caucasians, people of Chinese descent typically have a disease that is characterized primarily by reduced beta cell function rather than insulin resistance.⁶ Because of this pathological difference, Chinese physicians typically use short-term intensive insulin treatment, which has been shown to improve beta cell function.⁷

In China, nearly 50% of individuals with type 2 diabetes start their insulin treatment in hospital.⁸ However, there is little guidance on how to transition individuals with type 2 diabetes initiating insulin treatment from inpatient to outpatient care, and the most appropriate insulin regimen after short-term intensive insulin treatment has not been elucidated. In China, individuals typically switch to premixed insulin after discharge from hospital. However, the use of a basal insulin in combination with oral antihyperglycaemic drugs (OADs) may be associated with a lower risk of hypoglycaemia and similar efficacy compared with premixed insulin.⁹

The aim of this study was to compare the efficacy and safety of basal insulin glargine 100 U/ml (Gla) plus 2-3 OADs with twice-daily premixed insulin plus metformin (MET) in Chinese individuals with type 2 diabetes who have received short-term intensive insulin

therapy. To the best of our knowledge, this is the first clinical trial to compare these two treatment regimens in individuals with type 2 diabetes after short-term intensive insulin treatment.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomized, open-label, parallel group, multicentre, non-inferiority phase IV trial. The trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT03359837. The study design and methods have been reported previously,¹⁰ and a full list of the study investigators is provided in the Appendix. The study consisted of a 2-week screening period, a 7- to 10-day run-in period and a 24-week randomized treatment period.

2.2 | Participants

Eligible participants at screening included individuals aged 18-70 years with poorly controlled type 2 diabetes (defined as an HbA1c of 7.5%-11.0% [58-97 mmol/mol]) despite receiving 2-3 OADs (Table S1) for more than 8 weeks. In addition, participants had to be willing and able to perform self-monitored blood glucose (SMBG) using the sponsor-provided blood glucose monitor and have a fasting plasma glucose (FPG) of more than 7.0 mmol/L, a fasting C-peptide of more than 3 nmol/L (>1 ng/ml) and a body mass index (BMI) of 20 kg/m² or higher and less than 40 kg/m². Key exclusion criteria were use of insulin in the 6 months prior to screening; a history of diabetic ketoacidosis, lactic acidosis or hyperosmolar non-ketotic coma in the past 12 months; a history of hypoglycaemia unawareness; recurrent or severe hypoglycaemia in the past 12 months; and pregnancy, breastfeeding or not using an acceptable method of birth control.

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. The study protocol was approved by the local institutional review board at each study site, and written informed consent was collected from all participants before initiating the trial.

2.3 | Randomization and masking

During the run-in period, participants were hospitalized, and stopped previous OADs except for MET (no changed dosage), then received short-term intensive insulin therapy with Gla (Lantus; Sanofi) and bolus insulin glulisine (Apidra; Sanofi). All participants who had an FPG of less than 7.0 mmol/L and 2-hour postprandial glucose (PPG) of less than 10.0 mmol/L in the last 2 consecutive days of the run-in period were discharged from hospital and randomly assigned (1:1) to receive once-daily basal insulin glargine in combination with a dipeptidyl peptidase-4 inhibitor (DPP4i; either sitagliptin [Januvia; MSD, Beijing, China] or vildagliptin [Galvus; Novartis, Beijing, China]) or twice-daily premixed insulin aspart (Asp30; Novolog Mix 70/30; Novo Nordisk, Tianjin, China). All participants continued to receive their background MET. Randomization was performed using centralized interactive response technology and was stratified by baseline sulphonylurea/glinide use and HbA1c level at screening ($>9.0\%$ or $\leq 9.0\%$ [>75 or ≤ 75 mmol/mol]). While participants, investigators and site staff remained unmasked to treatment, the statistician and sponsor were masked to the treatment assignment until after database lock and completion of analyses.

2.4 | Procedures

All participants were required to measure and record the values of their fasting and predinner SMBG on the last day of the run-in period and at least 3 consecutive days within the week prior to each visit during the treatment period. Participants were instructed to titrate insulin doses at each visit based on their median fasting blood glucose or premeal SMBG levels prior to the visit, to achieve a target of 4.4–6.1 mmol/L (Table S2).

Participants attended clinic visits during the screening and randomization periods, then at weeks 2, 8, 12, 16 and 24 during the treatment period. In addition, telephone follow-ups were conducted at weeks 1, 3 and 20 postrandomization. The SMBG values and daily insulin dose were recorded at each study visit, and additional assessments (HbA1c, FPG) were conducted at weeks 12 and 24. If HbA1c was more than 7.0% (>53 mmol/mol) at week 12, participants in the Gla + OADs group were administered repaglinide (1 mg thrice daily) or acarbose (50 mg thrice daily), at the physician's discretion, and participants in the Asp30 + MET group continued to titrate insulin dose. Treatment-emergent adverse events (TEAEs) and hypoglycaemia events were recorded throughout the study, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

2.5 | Outcomes

The primary endpoint was the change in HbA1c from baseline (end of run-in period) at 24 weeks after randomization. Secondary endpoints included changes in FPG, daily blood glucose variations (including standard deviation [SD], coefficient of variation [CV], mean amplitude of glucose excursions [MAGE], low blood glucose index [LBGI] and high blood glucose index [HBGI] scores) and total daily insulin dose from baseline to week 12 and week 24, as well as the change in HbA1c from baseline to week 12. The proportion of individuals achieving an HbA1c of less than 7.0% (<53 mmol/mol) and an FPG of less than 7.0 mmol/L at weeks 12 and 24, as well as the proportion of individuals achieving these glycaemic targets with no hypoglycaemia, were also assessed as secondary endpoints. Patient quality of life and health with treatment was assessed using the European Quality of Life-5 Dimensions (EQ-5D) questionnaire and the EQ visual analogue scale (VAS), respectively. Safety endpoints included the incidence and frequency of hypoglycaemia, as well as the frequency of non-hypoglycaemia TEAEs and the change in bodyweight from baseline to week 24. Hypoglycaemia categories included any hypoglycaemia, symptomatic hypoglycaemia, confirmed hypoglycaemia (blood glucose ≤ 3.9 mmol/L with/without hypoglycaemia-related symptoms), confirmed hypoglycaemia with a blood glucose of less than 3.0 mmol/L and severe hypoglycaemia.

2.6 | 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 0.4% (4 mmol/mol) for HbA1c and a one-sided alpha of .025.¹⁰ Based on these calculations, 160 participants were required in each group to achieve a power of 90%, assuming a 20% dropout rate.

The primary efficacy endpoint was assessed in the per protocol (PP) population, which included all randomized participants who received at least one dose of study medication, had at least one post-treatment efficacy assessment and had no major protocol deviations. Secondary efficacy endpoints were assessed in the intent-to-treat (ITT) population, which included all randomized participants who received at least one dose of study medication and had at least one post-treatment efficacy assessment. Safety analyses included all participants who received at least one dose of study medication.

For analysis of the primary endpoint, the mean and SD HbA1c values at baseline and week 24 were determined for each treatment arm. In each treatment arm, the last observation carried forward least squares mean (LSM) and standard error (SE) values for the change from baseline to week 24 were estimated through an analysis of covariance model, with treatment and sulphonylurea/glinide usage (yes vs. no) as fixed effects and baseline HbA1c as a covariate. The LSM difference in HbA1c change and 95% CI between the two treatment groups were also estimated, with the non-inferiority of

Gla + OADs versus Asp30 + MET of HbA1c change confirmed if the upper limit of the 95% CI was less than 0.4% (<4 mmol/mol).

For the analysis of secondary efficacy endpoints, changes from baseline to week 24 in FPG were analysed using the same method as that used for the primary endpoint, whereas the numbers and percentages of participants who achieved HbA1c and FPG targets were determined for each treatment arm, and a crude estimate of the difference with 95% CIs was determined using normal approximation to the binomial. Changes in daily variations in blood glucose from baseline to week 24 were modelled through the mixed model for repeated measures, including fixed categorical effects of treatment, visit, treatment-by-visit interaction and randomization strata of sulphonylurea/glinide use (yes vs. no) and HbA1c level at screening (>9% vs. ≤9% [>75 vs. ≤ 75 mmol/mol]). Blood glucose variation at each visit was the dependent variable. All other demographics, secondary efficacy and safety outcomes were summarized using descriptive statistics, including mean and SD for continuous variables and number and proportion of participants for categorical variables. Adjustments for multiplicity were not applied for secondary endpoints, which should be considered exploratory.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. SAS/STAT, Cary, NC). A CONSORT checklist is available in Table S3.

3 | RESULTS

3.1 | Participants

From 20 January 2018 to 29 June 2020, 466 individuals were screened for study enrolment at 30 centres in mainland China. Of these, 397 entered the run-in period and 384 were randomized. Of these, 382 received at least one dose of study medication and were included in the safety analysis; 375 individuals (97.7%) were included in the ITT analysis and 372 participants (96.9%) completed the study (Figure S1). The PP analysis included 367 participants.

Baseline characteristics were balanced across the treatment groups (Table 1). The mean (SD) age was 54.2 (8.8) years, with slightly more male (59.6%) than female participants. Participants had a mean (SD) BMI of 26.0 (3.1) kg/m², a duration of diabetes of 6.8 (3.0) years and the majority (90.4%) were receiving two OADs prior to insulin initiation.

3.2 | Efficacy

Gla + OADs was as effective as Asp30 + MET in reducing HbA1c after 24 weeks of treatment (Figure 1). The LSM (SE) change in HbA1c from baseline to week 24 in the PP analysis was -1.72% (0.07%) (-42.2 [0.7] mmol/mol) with Gla + OADs and -1.70% (0.07%) (-42.1 [0.7] mmol/mol) with Asp30 + MET, giving an LSM between-group difference that met the prespecified non-inferiority criterion (-0.01% ; 95% CI -0.20% , 0.17% [-0.1 mmol/mol; 95% CI

TABLE 1 Baseline demographics and clinical characteristics

	Gla + OADs group (n = 192)	Asp30 + MET group (n = 192)
Age, y	54.3 (8.7)	54.0 (8.9)
Male, n (%)	116 (60.4)	113 (58.9)
Bodyweight, kg	74.3 (12.3)	72.6 (11.1)
BMI, kg/m ²	26.3 (3.1)	25.8 (3.1)
BMI category, n (%)		
<25 kg/m ²	70 (36.6)	81 (42.2)
≥25 to <30 kg/m ²	105 (55.0)	95 (49.5)
≥30 kg/m ²	16 (8.4)	16 (8.3)
Missing	0	1
Duration of type 2 diabetes, y	6.6 (3.0)	7.0 (3.0)
HbA1c, %	8.6 (1.14)	8.6 (1.07)
HbA1c, mmol/mol	70.2 (12.5)	70.6 (11.7)
FPG, mmol/L	6.1 (1.42)	5.9 (1.54)
Diabetes complications, n (%)	150 (78.1)	146 (76.0)
Number of OADs at screening, n (%)		
2	172 (89.6)	175 (91.1)
3	20 (10.4)	17 (8.9)

Note: Data are mean (SD) unless stated otherwise.

Abbreviations: Asp30, premixed insulin aspart 70/30; BMI, body mass index; FPG, fasting plasma glucose; Gla, basal insulin glargine; MET, metformin; OADs, oral antihyperglycaemic drugs; SD, standard deviation.

-2.2 , 1.9]). This result was confirmed in the ITT analysis; the LSM (SE) change from baseline at week 24 in HbA1c was -1.69% (0.07%) (-42.0 [0.7] mmol/mol) and -1.70% (0.07%) (-42.1 [0.7] mmol/mol) in the Gla + OADs and Asp30 + MET groups, respectively. Again, the LSM between-group difference (0.01%; 95% CI -0.17% , 0.20% [0.1 mmol/mol; 95% CI -1.9 , 2.1]) met the prespecified non-inferiority criterion. This effect was observed as early as week 12, with the LSM between-group difference (0.03%; 95% CI -0.14% , 0.20% [0.3 mmol/mol; 95% CI -1.6 , 2.2]) in the ITT analysis also meeting the prespecified non-inferiority criterion (Table S3).

The proportions of participants who achieved an HbA1c of less than 7.0% [<53 mmol/mol] at weeks 12 and 24 were similar in the Gla + OADs and Asp30 + MET groups (Figure 2A). However, significantly more participants in the Gla + OADs group achieved the HbA1c target without confirmed hypoglycaemia at weeks 12 and 24 ($P = .009$ and $P = .002$, respectively) compared with participants in the Asp30 + MET group (Figure 2B).

LSM increases in FPG (0.89 vs. 1.85 mmol/L) from baseline to week 24 were significantly lower in the Gla + OADs group versus the Asp30 + MET group (LSM difference -0.96 mmol/L; 95% CI -1.38 , -0.55 ; $P < .001$). The difference between treatment groups was apparent at week 12 (Table S4). Furthermore, the proportions of participants who achieved an FPG of less than 7.0 mmol/L at weeks 12 and 24 (Figure 2C), and those who achieved these FPG targets

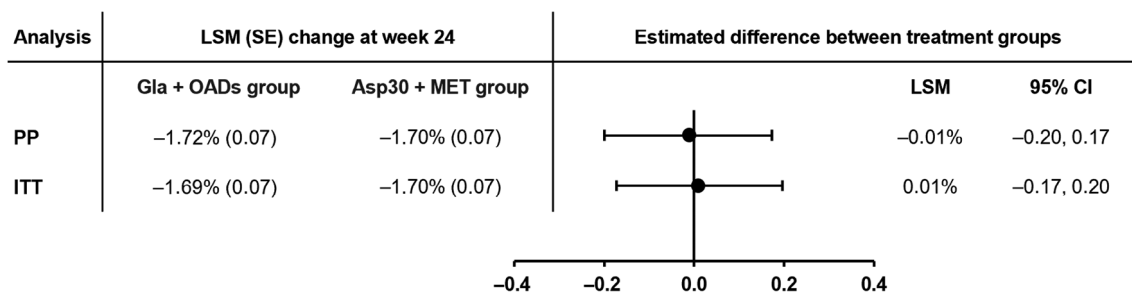


FIGURE 1 Forest plot for the change from baseline in HbA1c at week 24 in the per protocol (PP; n = 367) and intent-to-treat (ITT; n = 375) populations. Vertical dotted line = non-inferiority margin 0.4%. Asp30, premixed insulin aspart 70/30; CI, confidence interval; Gla, basal insulin glargine; LSM, least squares mean; MET, metformin; OADs, oral antihyperglycaemic drugs; SE, standard error

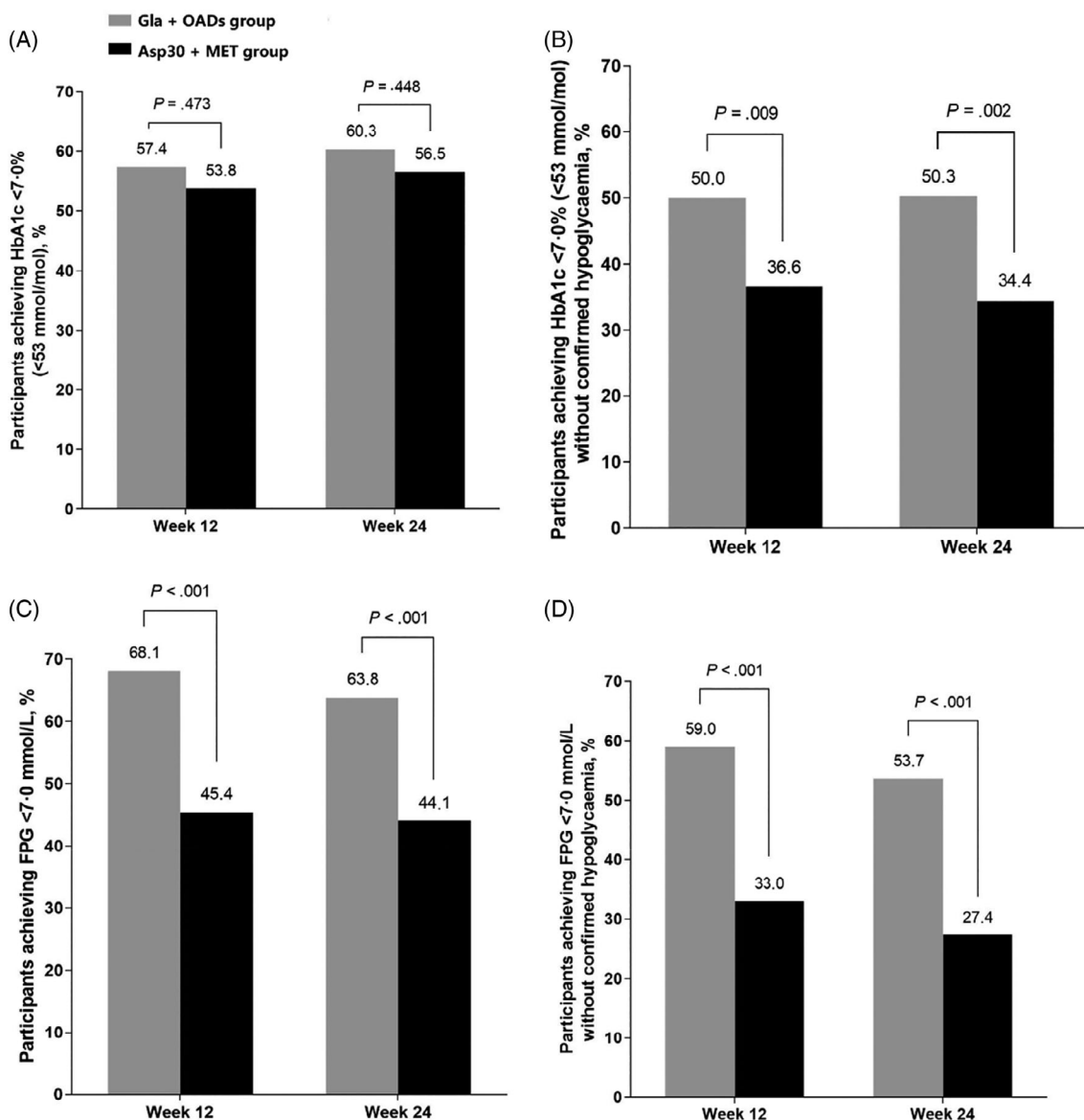


FIGURE 2 Last observation carried forward A, Proportion of participants in the intent-to-treat population (n = 375) who achieved HbA1c levels of <7.0% (<53 mmol/mol) at weeks 12 and 24 overall, and B, Without confirmed hypoglycaemia; and C, Proportion of participants who achieved fasting plasma glucose (FPG) levels of <7.0 mmol/L at weeks 12 and 24 overall, and D, Without confirmed hypoglycaemia. Asp30, premixed insulin aspart 70/30; Gla, basal insulin glargine; MET, metformin; OADs, oral antihyperglycaemic drugs

TABLE 2 Daily blood glucose variations in the intent-to-treat analysis

	Gla + OADs group (n = 189)	Asp30 + MET group (n = 186)
Standard deviation, mmol/L		
Baseline	1.65 (0.76)	1.84 (1.01)
Week 24	1.51 (0.73)	1.68 (1.32)
Week 24 LSM (95% CI) difference	−0.14 (−0.36, 0.08)	
P value	.205	
Coefficient of variation, %		
Baseline	23.43 (10.11)	25.65 (11.08)
Week 24	18.61 (6.65)	20.74 (12.28)
Week 24 LSM (95% CI) difference	−1.95 (−3.98, 0.08)	
P value	.060	
Mean amplitude of glucose excursion, mmol/L		
Baseline	3.15 (1.78)	3.46 (1.90)
Week 24	2.82 (1.53)	3.10 (2.45)
Week 24 LSM (95% CI) difference	−0.23 (−0.66, 0.19)	
P value	.273	
Low blood glucose index		
Baseline	0.21 (0.26)	0.22 (0.27)
Week 24	0.05 (0.08)	0.08 (0.12)
Week 24 LSM (95% CI) difference	−0.03 (−0.05, −0.005)	
P value	.016	
High blood glucose index		
Baseline	0.60 (0.53)	0.67 (0.64)
Week 24	1.08 (1.13)	1.02 (0.96)
Week 24 LSM (95% CI) difference	0.10 (−0.12, 0.31)	
P value	.377	

Note: Data are mean (SD) unless stated otherwise.

Abbreviations: Asp30, premixed insulin aspart 70/30; CI, confidence interval; Gla, basal insulin glargine; LSM, least squares mean; MET, metformin; OADs, oral antihyperglycaemic drugs; SD, standard deviation.

without confirmed hypoglycaemia (Figure 2D), were significantly greater in the Gla + OADs group (all $P < .001$).

A significant difference in LBGI between participants in the Gla + OADs group versus participants in the Asp30 + MET group was observed at week 24 ($P = .016$; Table 2). No significant difference between treatment groups in any other daily blood glucose variations (SD, CV, MAGE or HBGI scores) at week 24 was observed (Table 2). Similar changes in blood glucose variables with each treatment were seen at week 12 (Table S4).

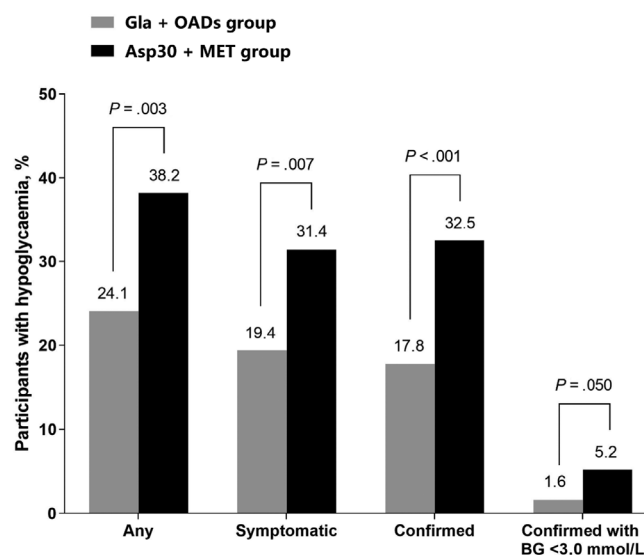


FIGURE 3 Hypoglycaemia events in the safety population (n = 382). Asp30, premixed insulin aspart 70/30; BG, blood glucose; Gla, basal insulin glargine; MET, metformin; OADs, oral antihyperglycaemic drugs

At week 24, seven-point SMBG values increased from baseline in both treatment groups (Figure S2). A significant difference between participants in the Gla + OADs group versus participants in the Asp30 + MET group was observed at week 24 in before breakfast, before lunch, 2-hour postdinner and bedtime SMBG values (all $P < .05$).

At week 24, the total daily insulin dose was lower in participants in the Gla + OADs group (mean [SD] 26.5 [9.9] U/day and 0.36 [0.12] U/kg/day) compared with the Asp30 + MET group (42.9 [15.1] U/day and 0.58 [0.20] U/kg/day), with a lower change from baseline to week 24 in total daily insulin dose also seen in the Gla + OADs group (mean [SD] change 1.7 [5.0] U/day and 0.02 [0.07] U/kg/day vs. 9.4 [12.1] U/day and 0.12 [0.17] U/kg/day). The difference in the total daily insulin dose between treatment groups was also apparent at week 12 (data not shown). Sixteen participants (8.4%) in the Gla + OADs group were treated with repaglinide, and 60 (31.4%) were treated with acarbose since week 12.

No significant changes in EQ-5D scores from baseline at week 24 were observed in either treatment group (data not shown). At week 24, the Gla + OADs group was associated with a significantly greater improvement in EQ-VAS scores from baseline compared with the Asp30 + MET group (LSM change from baseline 2.75 vs. 1.27, respectively; LSM difference 1.48; 95% CI 0.31, 2.66; $P = .013$).

3.3 | Safety

There were no events of severe hypoglycaemia during the 24-week treatment period. Fewer participants in the Gla + OADs group experienced hypoglycaemia than participants in the Asp30 + MET group (Figure 3). The relative risk of experiencing any hypoglycaemia (0.63;

95% CI 0.46, 0.86; $P = .003$), symptomatic hypoglycaemia (0.61; 95% CI 0.43, 0.88; $P = .007$), confirmed hypoglycaemia with a blood glucose of 3.9 mmol/L or less (0.55; 95% CI 0.38, 0.79; $P < .001$) and confirmed hypoglycaemia with a blood glucose of less than 3.0 mmol/L (0.30; 95% CI 0.08, 1.08; $P = .050$) was significantly lower in the Gla + OADs group than in the Asp30 + MET group. The significant difference was also seen when hypoglycaemia was analysed by events per participant-years (Table S5).

When assessed in 4-week intervals, significant differences between the treatment groups in the proportion of participants experiencing any hypoglycaemia were seen at weeks 5-8 ($P = .026$), weeks 9-12 ($P < .001$), weeks 13-16 ($P < .001$) and weeks 21-24 ($P = .042$; Figure S3).

The frequency of any non-hypoglycaemia TEAEs was numerically higher in the Gla + OADs group versus the Asp30 + MET group, with 14 participants (7.3%) in the Gla + OADs group and six participants (3.1%) in the Asp30 + MET group reporting serious non-hypoglycaemia TEAEs. Two participants (1.0%) in the Gla + OADs group discontinued the study because of non-hypoglycaemia TEAEs compared with one participant (0.5%) in the Asp30 + MET group. Among the 60 participants who used acarbose, five had gastrointestinal TEAEs, all of which were mild: four (6.7%) were acarbose-related according to investigator judgement, and one discontinued acarbose as a result of epigastric pain. Two deaths occurred, one case of abnormal hepatic function with insulin glargine + sitagliptin whose relationship to treatment could not be determined, and one case of acute myocardial infarction in the Asp30 + MET group that was considered unrelated to treatment. The most frequently reported TEAEs in the Gla + OADs group were upper respiratory tract infection, nasopharyngitis and hyperlipidaemia.

The mean change in body weight from baseline to week 24 was numerically lower in the Gla + OADs group than in the Asp30 + MET group (LSM change 0.91 vs. 1.38 kg, respectively; LSM difference -0.47 kg; 95% CI $-1.07, 0.13$).

4 | DISCUSSION

The results of this randomized, open-label, parallel group, multicentre, non-inferiority phase IV trial show that, after short-term intensive insulin therapy, treatment with a basal insulin + DPP4i regimen is as effective as a premixed insulin regimen and is associated with a lower risk of hypoglycaemia in Chinese individuals with type 2 diabetes who are also receiving MET. The reduction in HbA1c from baseline to week 24 in the Gla + OADs group was comparable with that in the Asp30 + MET group, with the LSM difference between treatment groups meeting the prespecified non-inferiority criterion (upper bound of 95% CI $<0.4\%$ [<4 mmol/mol]). In addition, the proportion of participants with hypoglycaemia was significantly lower in the Gla + OADs group. Significantly more participants in the Gla + OADs group achieved an HbA1c of less than 7.0% (<53 mmol/mol) without confirmed hypoglycaemia at weeks 12 and 24. Furthermore, the proportions of participants who achieved an

FPG of less than 7.0 mmol/L at weeks 12 and 24, and those who achieved the FPG targets without confirmed hypoglycaemia, were significantly greater in the Gla + OADs group. Finally, participants in the Gla + OADs group reported greater health, assessed using EQ-VAS scores, with treatment, than participants in the Asp30 + MET group.

To the best of our knowledge, this is the first clinical trial to compare treatment with Gla + 2-3 OADs with twice-daily Asp30 + MET in Chinese individuals with type 2 diabetes after switching from short-term intensive insulin therapy. The conventional view when selecting an appropriate follow-up treatment in Chinese individuals with type 2 diabetes who have received short-term intensive insulin treatment has been that basal insulin may not be sufficient to achieve glycaemic control, mainly because Asian individuals typically have a higher propensity to postprandial hyperglycaemia and PPG excursions,¹¹⁻¹⁵ leading Chinese physicians to typically use premixed insulin for glycaemic control.¹⁶ To reduce the risk of hypoglycaemia, individuals receiving premixed insulin need to amend their dietary habits.^{17,18}

Over the last few decades, the adoption of sedentary lifestyles and energy-dense Western diets in Chinese individuals has resulted in a shift in the blood glucose profiles of these individuals to those typically seen in Western populations.^{16,19,20} Furthermore, in some individuals, short-term intensive insulin therapy improves beta cell function,^{7,21} which may influence the choice of follow-up treatment. Basal insulin-based treatment is convenient and showed a lower risk of hypoglycaemia than premixed insulin in Chinese individuals with type 2 diabetes.^{8,22,23} Treatment with DPP4is combined with basal insulin improved glycaemic control without an increased risk of hypoglycaemia or weight gain compared with basal insulin treatment alone.²⁴ The results of this study support previous findings and show that this combination is effective and safe as a follow-up treatment after short-term intensive insulin therapy.

A strength of this study is that we included participants who had undergone short-term intensive insulin treatment and therefore the population of this study was similar to that seen in current clinical treatment in China. Previous studies comparing the efficacy and safety of a basal insulin regimen versus a premixed insulin regimen typically enrolled participants with high FPG values, and, as such, the results of those studies are not applicable to people who have undergone short-term intensive insulin treatment, who have an FPG closer to normal values and may be at greater risk of hypoglycaemia when receiving insulin treatment.^{21,25,26} There are some limitations to this study, namely, the open-label nature of drug administration, which can be associated with reporting bias, and the homogeneous study population.

In conclusion, the findings of this study indicate that, compared with Asp30 + MET, Gla + 2-3 OADs had a similar efficacy but a lower hypoglycaemia risk in Chinese individuals with type 2 diabetes. Although premixed insulin is widely used in China, the results of this trial suggest that a basal insulin regimen may be a better treatment choice for Chinese individuals with type 2 diabetes who have undergone short-term intensive insulin treatment.

AUTHOR CONTRIBUTIONS

YM, LG, QP, YL, HW, JW, BX, GW, CJ and LL were in charge of individual study centres: they recruited participants and conducted the study. WF, JL, XZ, TW and NC participated in study design and coordinated study centres. All authors contributed to the writing of the report. YM and LG are the guarantors of this article. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The manuscript was written by all the listed authors with assistance from professional medical writers (funded by Sanofi).

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CONFLICT OF INTEREST

YM has received honoraria for speakers' bureau from Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Lily Diabetes, Novo Nordisk Inc. and Sanofi. LG has served on advisory board panels and received consultancy fees from Sanofi, AstraZeneca, Novo Nordisk, Merck Sharp & Dohme Corp., Bayer Healthcare Pharmaceuticals Inc., Merck & Co., Inc., Eli Lilly and Company, BD and Novartis AG. QP, YL, HW, JW, BX, GW, CJ and LL have no conflicts of interest to disclose. WF, JL, TW, XZ and NC are employees of Sanofi and may hold shares and/or stock options in the company.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14780>.

DATA AVAILABILITY STATEMENT

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 criterion, eligible studies, and process for requesting access can be found at: <https://www.vivli.org/>

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SUPPORTING INFORMATION

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

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APPENDIX

BEYOND V STUDY GROUP

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G. Wang	Second Affiliated Hospital of Baotou Medical College
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X. Sun	Ningbo Second Hospital
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J. Kuang	Shenyang Fourth People's Hospital
Y. Wang	Chaoyang Second Hospital
C. Liu	The First Affiliated Hospital of Jinzhou Medical University
L. Zhong	Chengdu The First People's Hospital of Longquanyi District
X. Song	Shenyang Fifth People's Hospital
L. Zhu	Shandong Provincial Third Hospital
W. Li	The Second Affiliated Hospital of Guangzhou Medical University
W. Yao	Wuxi Second People's Hospital
M. An	The Second People's Hospital of Wuhu City
W. Gao	Qingdao Endocrinology and Diabetes Hospital
K. Feng	Nangang District of Heilongjiang Provincial Hospital
W. Cui	The First Affiliated Hospital of Xi'an Jiaotong University
Y. Li	Lishan District of Anshan Central Hospital
X. Wang	Tiedong District of Anshan Central Hospital
L. Guo	Beijing Hospital
R. Li	The Third People's Hospital of Yunnan Province
J. Liu	Gansu Provincial People's Hospital
W. Huang	Haidian District of Peking University Third Hospital
J. Du	The Fourth Affiliated Hospital of China Medical University
J. Hu	The Second Affiliated Hospital of Soochow University