Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100 U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy

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Abstract [word count 247]

Aims

Evaluate efficacy and hypoglycaemia according to concomitant oral antidiabetes drug (OAD) in people with type 2 diabetes initiating insulin glargine 100 U/mL (Gla-100) or neutral protamine Hagedorn insulin (NPH) once daily.

Methods

Four studies (target fasting plasma glucose [FPG] ≤100 mg/dL [≤5.6 mmol/L]; duration ≥24 weeks) were included. Standardised data from 2091 subjects (Gla-100, n=1024; NPH, n=1067) were analysed. Endpoints included: HbA1c and FPG change; glycaemic target achievement; hypoglycaemia; weight change and insulin dose.

Results

Mean HbA1c and FPG reductions were similar with Gla-100 and NPH regardless of concomitant OAD (*P*=0.184 and *P*=0.553, respectively) and similar proportions of subjects achieved HbA1c <7.0% (*P*=0.603). There was a trend for more subjects treated with Gla-100 achieving FPG ≤100mg/dL vs NPH (RR 1.09 [95% CI 0.97-1.23]; *P*=0.135). Plasma glucose confirmed (<70 mg/dL) overall and nocturnal hypoglycaemia incidences and rates were lower with Gla-100 versus NPH (overall: RR 0.93 [95% CI 0.87-1.00]; *P*=0.041; nocturnal RR 0.73 [95% CI 0.65-0.83]; *P*<0.001). After 24 weeks, weight gain and insulin doses were higher with Gla-100 versus NPH (2.7 kg vs 2.3 kg, *P*=0.009 and 0.42 U/kg vs 0.39 U/kg; *P*=0.003, respectively). Insulin doses were higher when either insulin was added to sulfonylurea alone.

Conclusions

Pooled results from treat-to-target trials in insulin-naïve people with type 2 diabetes demonstrate a significantly lower overall and nocturnal hypoglycaemia risk across different plasma glucose definitions with Gla-100 versus NPH at similar glycaemic control. OAD therapy co-administered with Gla-100 or NPH impacts glycaemic control and overall nocturnal hypoglycaemia risk.

Keywords

Sulfonylurea

Metformin

Insulin glargine

neutral protamine Hagedorn insulin

Glycaemic control

Hypoglycaemia

1. Introduction

People diagnosed with type 2 diabetes (T2DM) usually begin treatment with an oral agent, principally metformin or, if contraindicated, a sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, or insulin sensitizer [1, 2]. However, because it is a progressive disease, over time many people with T2DM will require the addition of insulin therapy to avoid hyperglycaemia [3]. Guidelines recommend the addition of basal insulin for those not meeting their individual HbA1c targets with current therapy [1, 2]. The options for providing basal insulin supplementation include basal insulin analogues (insulin glargine 100 U/mL [Gla-100] and 300 U/mL, insulin detemir, insulin degludec) recommended for once-daily dosing, and neutral protamine Hagedorn (NPH) insulin, an intermediate-acting basal insulin that is conventionally dosed once or twice daily [4]. In general, the longer-acting basal insulin analogues are preferred over intermediate-acting NPH insulin because they provide a more physiological pattern of insulin release with less variability throughout the day, and are associated with lower rates of nocturnal and interprandial hypoglycaemia and a reduced requirement for self-monitoring of blood glucose [2, 4, 5].

Hypoglycaemia is of particular concern for people with T2DM being treated with insulin (as well as certain oral antidiabetes drugs [OADs], mainly sulfonylureas and glinides), as it undermines confidence in their treatment, contributes to lost productivity, and has been associated with increased mortality [1, 2]. Additionally, concerns about hypoglycaemia may lead clinicians, and people managing their own T2DM, to under-dose basal insulin and thus fail to achieve optimal glycaemic control [6]. Therefore, minimising the risk of hypoglycaemia is crucial in the management of T2DM, and choosing a basal insulin that provides good glycaemic control with a reduced risk of hypoglycaemia is a key principle of achieving optimal care [1, 2].

The aim of this analysis was to compare the initiation of Gla-100 or NPH insulin in people with T2DM inadequately controlled on existing OADs, using pooled, standardised subject-level data

solely derived from randomised, controlled, treat-to-target trials in order to evaluate outcomes according to concomitant OAD therapy. This may assist healthcare professionals in deciding the best course of action when initiating patients on basal insulin currently uncontrolled on various background OAD regimens. Combining subject-level data increases statistical power compared with individual studies, and is associated with less bias than the pooling of summary data from individual randomised controlled trials [7]. Data are presented for three different timeframes: the entire treatment period (Week 0–24), the titration phase (Week 0–12), and the maintenance phase (Week 12–24).

2. Methods

2.1. Study Selection

Only prospective phase IIIa/b or phase IV, randomised, controlled, treat-to-target trials comparing Gla-100 with NPH insulin, each given once-daily at bedtime, targeting FPG levels ≤100 mg/dL (≤5.6 mmol/L), and with a study duration ≥24 weeks were eligible for inclusion in this analysis. We initially identified seven studies [8–14], all of which were conducted by the manufacturer of Gla-100 (Sanofi, Paris, France and predecessor companies). Three trials were subsequently excluded because the FPG target in these trials was >100 mg/L [8, 9, 13]. Details of the studies included and excluded from the analysis are presented in Supplementary Table 1.

2.2 Outcomes

Glycaemic control was evaluated by determining mean HbA1c and FPG levels at baseline and change from baseline to Week 12 and to Week 24. The proportions of subjects achieving an HbA1c <7.0% (<53 mmol/mol) or <6.5% (<47.5 mmol/mol) or FPG <100 mg/dL (<5.6 mmol/L) at Week 12 and at Week 24 also were assessed. Both the incidence and event rates of overall, nocturnal, and severe hypoglycaemia were assessed during the entire treatment period and during titration and maintenance phases of the study. Overall hypoglycaemic events were defined as those with confirmed plasma glucose <70 mg/dL (<3.9 mmol/L) or <56 mg/dL (<3.1 mmol/L) or requiring third-party assistance. Nocturnal hypoglycaemic events were defined as those with confirmed plasma glucose <70 mg/dL or <56 mg/dL, occurring between the times of 00:01 and 05:59. Severe hypoglycaemic events were defined as those events requiring third-party assistance together with confirmed plasma glucose <36 mg/dL (<2.0 mmol/L). In addition, composite efficacy and hypoglycaemia endpoints, including the proportion of subjects achieving an HbA1c <7.0% or <6.5% or a FPG ≤100 mg/dL without hypoglycaemia, also were assessed. Insulin dose, change in body weight, and the number needed to harm (NNH; the average number of people to

be treated for one additional person to experience a hypoglycaemic event if NPH insulin is used rather than Gla-100) were also calculated.

2.3 Statistical Analysis

Data from the studies were pooled and analysed within subpopulations determined by the specified background OAD therapies; i.e. metformin plus a sulfonylurea or a sulfonylurea alone. Subjects were excluded from the analysis if they took antidiabetes treatments other than metformin or a sulfonylurea at any time during the analysis period (e.g. thiazolidinediones [TZDs], glinides, DPP-4 inhibitors, sodium-glucose cotransporter-2 [SGLT2] inhibitors, alpha-glucosidase inhibitors or another insulin which was not part of study medication). The safety population (all randomised subjects who received ≥1 dose of Gla-100 or NPH insulin and OADs within the subpopulation of interest) were included in all analyses. Continuous efficacy endpoints of HbA1c and FPG were analysed using generalised linear models with adjustments for OAD group (when applicable), study, and baseline value. For the comparative analyses, two-sided 95% confidence intervals (CIs) and *P* values were estimated for the group differences. For the outcomes of achievement of HbA1c or FPG targets, odds ratios (ORs) and 95% CIs were derived from a logistic binomial regression model, with baseline value as a covariate and treatment combination as a factor, including only those subjects not already at target at baseline (or Week 12 for the assessment of the maintenance phase).

The incidence and event rates of hypoglycaemia were adjusted for baseline subject characteristics. The proportion of subjects with ≥1 hypoglycaemic event (incidence) for Gla-100 or NPH insulin within each OAD treatment group was analysed using a generalised linear logistic regression model with fixed-effect terms for age, baseline BMI, duration of diabetes, treatment, and OAD treatment group. In addition, the overall annualised rate (event rate per patient-year) of hypoglycaemic events was estimated and analysed based on negative binomial regression, also

with age, baseline BMI, duration of diabetes treatment, and OAD treatment group included as factors. Relative risk and rate ratios (with associated 95% CIs) were obtained for the difference in incidence and event rates, respectively. Body weight and dose were analysed in a similar manner to the continuous efficacy outcomes. The NNH was calculated using the formula: 1/(proportion at risk of hypoglycaemia with NPH insulin minus proportion at risk of hypoglycaemia using Gla-100.. Predicted hypoglycaemic event rates per patient-year were obtained for HbA1c values reported at endpoint using meta-regression techniques. Regression coefficients for HbA1c (at endpoint), age, baseline BMI, and duration of diabetes were first estimated using a negative binomial regression model of event rates. Raw population averages for the treatment arm were calculated for age, BMI and duration of diabetes, which were then used as constant values in the prediction model that also included the estimated regression coefficients.

3. Results

3.1. Study Population

A total of 2091 subjects were included in the analysis. Of these, 1024 were treated with Gla-100 and 1067 with NPH insulin. Baseline characteristics are presented in Supplementary Table 2. Subjects in the overall Gla-100 and NPH insulin groups were similar in terms of age, sex, body weight, and disease characteristics. Subjects receiving a concomitant sulfonylurea in both the Gla-100 and NPH insulin groups had a longer duration of diabetes, higher HbA1c and FPG at baseline, but a lower BMI than those receiving concomitant metformin plus a sulfonylurea.

3.2. Efficacy

The addition of Gla-100 and NPH insulin to the two OAD regimens led to reductions in HbA1c and FPG from baseline to Week 24 (Table 1), with the vast majority of the effect occurring in the first 12 weeks of treatment. Reductions in mean HbA1c and FPG at Week 24 were similar with Gla-100 and NPH insulin regardless of the concomitant OAD received. Similar reductions in HbA1c and FPG were achieved with both basal insulins during the titration phase and the maintenance phase irrespective of the background OADs (Table 1). The proportion of subjects achieving HbA1c and FPG goals over the whole treatment period and the titration and maintenance phases of the study was similar with Gla-100 compared with NPH insulin, though there was a trend for more subjects treated with Gla-100 achieving FPG ≤100mg/dL (P=0.135) (Supplementary Table 3). Subjects adding Gla-100 to background metformin plus a sulfonylurea were significantly more likely to reach the FPG target than those adding NPH insulin over the whole treatment period (P=0.009), and over the maintenance phase (P=0.0037) (Supplementary Table 3). The higher proportion of subjects achieving HbA1c goals was driven by a greater proportion of subjects achieving HbA1c <7.0% and <6.5% when Gla-100 was added to background metformin plus a sulfonylurea compared with the addition of NPH insulin to metformin plus a sulfonylurea (Supplementary Table 3).

3.3 Hypoglycaemia

Adjusted incidences of overall, nocturnal, and severe hypoglycaemia in the overall treatment groups and by concomitant OAD during the whole treatment period (Fig. 1), the titration phase (Supplementary Fig. 1), and the maintenance phase (Supplementary Fig. 2) of the study are presented. Adjusted event rates of overall, nocturnal, and severe hypoglycaemia overall and by concomitant OAD during the entire treatment period (Supplementary Fig. 3), the titration phase (Supplementary Fig. 4), and the maintenance phase (Supplementary Fig. 5) of the study are presented.

Both the incident and event rates of overall and nocturnal hypoglycaemia were consistently lower with Gla-100 than with NPH insulin, regardless of the background OAD regimen. The difference between the two basal insulins reached statistical significance for many comparisons, particularly for nocturnal hypoglycaemia. In general, during the whole treatment period, treatment with either Gla-100 or NPH insulin added to background metformin plus a sulfonylurea was associated with numerically higher incidence and event rates of overall and nocturnal hypoglycaemia compared with either basal insulin added to a sulfonylurea alone. A similar pattern was observed in both the titration and maintenance phases of the study. Severe hypoglycaemia was rare across both treatment groups, with no difference observed in incidence or event rates of severe hypoglycaemia between subjects treated with Gla-100 or NPH insulin.

3.4 Composite endpoints

There was no significant difference in the proportion of subjects receiving Gla-100 or NPH insulin achieving HbA1c <7.0% without hypoglycaemia (with plasma glucose <70 mg/dL and <56 mg/dL) overall, and regardless of concomitant OAD taken (Supplementary Table 4). However, those subjects initiating Gla-100 were more likely to achieve HbA1c <7.0% without

nocturnal hyperglycaemia (with plasma glucose <70 mg/dL and <56 mg/dL), predominantly because of the significant difference in the proportion of subjects with Gla-100 added to background metformin plus a sulfonylurea achieving HbA1c <7.0% without nocturnal hyperglycaemia (Supplementary Table 5). Subjects given Gla-100 also were significantly more likely to achieve FPG targets ≤100 mg/dL without overall hypoglycaemia (plasma glucose <56 mg/dL) or nocturnal hyperglycaemia (plasma glucose <70 mg/dL and <56 mg/dL). This difference was again determined by the significant differences observed in those adding Gla-100 to background metformin plus a sulfonylurea (Supplementary Tables 4 and 5).

Differences between subjects treated with Gla-100 and NPH insulin were also apparent when the relationship of hypoglycaemia (plasma glucose <70 mg/dL) with endpoint HbA1c was assessed using meta-regression techniques (Fig. 2). At the lower range of HbA1c levels, the modelled rates of overall and nocturnal hypoglycaemia increased, and were consistently higher in those subjects treated with NPH insulin, although the differences for both overall and nocturnal hypoglycaemia were less apparent when the plasma glucose cut-off was <56 mg/dL.

3.5 Body Weight

Body weight increased in both overall treatment groups. The weight gain in the Gla-100 group from baseline to Week 24 was significantly higher than that observed in the NPH insulin group (+2.7 kg vs +2.3 kg, respectively; P=0.009). This was largely due to greater weight gain in the groups that added Gla-100 or NPH insulin to a background sulfonylurea only. Most of this weight gain occurred in the titration phase of the study (+1.6 kg for Gla-100 vs +1.4 kg for NPH insulin; P=0.032). Mean body weight increase from baseline to Week 24 was lower in subjects adding Gla-100 or NPH insulin to background metformin plus a sulfonylurea compared with adding to a background sulfonylurea only (+1.9 kg and +1.8 kg vs +3.7 kg and +3.0 kg, respectively). However, subjects adding Gla-100 or NPH insulin to a background sulfonylurea had a lower

weight at baseline than those adding to background metformin plus a sulfonylurea (76.6 kg and 76.0 kg vs 87.1 kg and 87.4 kg, respectively).

3.6 Insulin Dose

Insulin dose profiles by weight over time demonstrated a higher dose requirement in subjects treated with Gla-100 compared with NPH insulin from approximately Week 3 onwards (Fig. 3). At the end of the titration phase, insulin dose was significantly higher with Gla-100 compared with NPH insulin (0.38 IU/kg vs 0.35 IU/kg, P=0.001; Fig. 3). Subjects adding Gla-100 and NPH insulin to a background sulfonylurea had a higher insulin dose requirement at baseline and at Week 12 and Week 24 compared with those adding Gla-100 and NPH insulin to background metformin plus a sulfonylurea (Fig. 3).

3.7 Number needed to harm analysis

For NPH insulin versus Gla-100 in the overall treatment period, the NNH for overall hypoglycaemia with plasma glucose <70 mg/dL was 25, and for plasma glucose <56 mg/dL was 20 (Fig. 1). For overall hypoglycaemia with plasma glucose <70 mg/dL and <56 mg/dL by concomitant OAD, the NNH with NPH insulin versus Gla-100 was higher in those subjects treated with metformin plus a sulfonylurea (30 and 26, respectively) compared with a sulfonylurea alone (19 and 15, respectively). For nocturnal hypoglycaemia, the NNH with plasma glucose <70 mg/dL was 12 and with plasma glucose <56 mg/dL was 18. Similar to the observations for overall hypoglycaemia, the NNH for nocturnal hypoglycaemia with plasma glucose <70 mg/dL was higher in those treated with metformin plus a sulfonylurea compared with a sulfonylurea alone (14 vs 8) but was similar for the plasma glucose <56 mg/dL cut-off (20 vs 21). NNH overall and according to concomitant OAD in the titration and maintenance phases of the study are presented in Supplementary Fig. 1 and Supplementary Fig. 2, respectively. The NNH with NPH insulin versus Gla-100 for overall and nocturnal hypoglycaemia was generally

lower during the titration phase compared with the maintenance phase, and where insulin was added to a sulfonylurea alone.

4. Discussion

In this analysis of standardised, subject-level data from four randomised, controlled, treat-to-target trials of people with T2DM inadequately controlled on a sulfonylurea or metformin plus a sulfonylurea, the addition of Gla-100 or NPH insulin at bedtime to existing OADs resulted in similar reductions in HbA1c and FPG, regardless of the concomitant OAD. The majority (>90%) of treatment effect in terms of HbA1c reduction was achieved by Week 12 and sustained or slightly improved by Week 24. At Week 12 and Week 24, the median insulin doses were 29.0 U and 32.0 U, respectively, for Gla-100, and 26.0 U and 30.0 U, respectively, for NPH insulin. Initiation of Gla-100 allowed a similar proportion of participants to achieve HbA1c and FPG targets during the whole treatment period compared with those initiated on NPH insulin with consistently lower rates of overall and nocturnal hypoglycaemia compared with NPH insulin, regardless of background OAD therapy. In terms of the effect of background therapy, the combination of Gla-100 or NPH insulin with metformin plus a sulfonylurea resulted in a higher proportion of subjects achieving HbA1c and FPG targets during the whole treatment period, the titration phase, and the maintenance phase than those adding Gla-100 or NPH insulin to a sulfonylurea alone. However, this was associated with a higher incidence and rate of overall and nocturnal hypoglycaemia in those treated with concomitant metformin plus a sulfonylurea versus a sulfonylurea alone. Although body weight increased in both groups, mostly in the titration phase, weight increases were greater with Gla-100, possibly reflecting the greater insulin dose requirement in the Gla-100 treatment group. Greater increases in weight from baseline were observed in participants who added Gla-100 or NPH insulin to a sulfonylurea alone compared with those adding to metformin plus a sulfonylurea, again reflecting higher insulin dose requirements in those treated with a sulfonylurea-only regimen and a lower initial body weight in this group.

The homogeneity of the 4 studies eligible for inclusion in this subject-level meta-analysis was tested by including the interaction terms between study and treatment in the models utilised for the analysis; these were not significant for the sulfonylurea only and metformin plus a sulfonylurea groups. Furthermore, hypoglycaemia incidence and event rates by treatment group were reviewed by study; these were lower with Gla-100 compared with NPH for most types of hypoglycaemia in the 4 studies. For nocturnal hypoglycaemia in particular, the incidence and event rates were all lower with Gla-100 compared with NPH in all 4 studies (data not shown).

The overall data presented here are supportive of previous meta-analyses and subject-level analyses comparing glycaemic control and hypoglycaemia outcomes between Gla-100 and NPH insulin [7, 15, 16]. Similar to our findings, the most recent Cochrane review meta-analysis comparing Gla-100 and NPH insulin treatment in T2DM reported that HbA1c did not differ in a clinically relevant way between treatment groups (weighted mean difference from baseline to endpoint 0.1% [95% CI –0.1 to 0.2], P=0.49 in favour of NPH insulin for four studies with relevant data) [16]. However, in the three studies with available data included in this analysis, symptomatic overall hypoglycaemia and symptomatic nocturnal hypoglycaemia were significantly lower for Gla-100 compared with NPH insulin (relative risk 0.84 [95% CI 0.75 to 0.95]; P=0.005 and 0.66 (0.55 to 0.80); P<0.000, respectively) [16]. Two previous subject-level analyses have also reported significantly lower rates of hypoglycaemia with Gla-100 compared with NPH insulin [7, 15]. In an analysis of all randomised phase III and IV clinical trials comparing Gla-100 and NPH insulin sponsored by the manufacturer of Gla-100 as of 2004 (six studies in T2DM), unadjusted rates of symptomatic, confirmed, and severe hypoglycaemic events (events per 100 patient-days) were 13.67%, 39.34%, and 53.73% lower, respectively, with Gla-100 compared with NPH insulin (P<0.05) [15]. The risk of nocturnal hypoglycaemia was reduced by approximately 50% with Gla-100 versus NPH insulin (OR 0.44–0.52; P<0.001–0.0047) in a pooled analysis of subject-level data from subjects treated with once-daily evening Gla-100 or

NPH insulin [7]. In this study, it was estimated that eight people with T2DM needed to use Gla-100 rather than NPH insulin to avoid one additional person from experiencing a symptomatic nocturnal hypoglycaemic event during a median of 24 weeks of treatment [7].

Hypoglycaemia has substantial clinical impact on morbidity and quality of life, and has been associated with increased mortality [2, 17]. Fear of hypoglycaemia, and particularly nocturnal hypoglycaemia, by both clinicians and people with diabetes can contribute to a delay in starting insulin therapy, timely insulin intensification, and treatment adherence [6, 17, 18], all of which present major barriers to achieving good glycaemic control. Therefore the achievement of appropriate glycaemic control whilst at the same time minimising hypoglycaemia, particularly nocturnal hypoglycaemia, is a key priority in the management of T2DM.

It should be noted that three of the seven studies that were originally identified for this subject-level meta-analysis were excluded [8, 9, 13]. Studies 3002 and 3006 [8, 9] did not utilise the treat-to-target concept (the titration target was 80-140 mg/dL) and study 4012 [13] had an FPG target of <120 mg/dL. As predefined FPG targets in a study potentially affect efficacy and safety outcomes, our objective was to analyse only treat-to-target studies with the same FPG target of <100 mg/dL to avoid potential bias from different targets which may "dilute" the impact of a pre-specified FPG target as titration procedures and dose adjustments are mainly driven by the FPG target set in the study. Previous subject-level analyses [7, 15] have included treat-to-target and non-treat-to-target studies and did not consider such titration effects varying between the studies. Furthermore, two of the studies did not have HbA1c available data at Week 24 and did not target an insulin naïve population [8, 9]. The excluded studies showed broadly similar results to those shown in this subject-level meta-analysis and if study 4012 [13] were to be included in the analysis, both efficacy and safety results would be expected to be consistent with those already obtained. Briefly, in these studies HbA1c reductions in subjects treated with Gla-100 and NPH

were comparable, with one study demonstrating superiority with Gla-100 [13]. All three studies showed significantly reduced rates of nocturnal hypoglycaemia in Gla-100 treated subjects, while one also showed lower overall and severe hypoglycaemia [13]. Weight gain was either comparable between Gla-100 and NPH [8], lower in subjects treated with Gla-100 [9] or not reported [13].

Compared with the earlier subject-level analyses conducted by Mullins et al. [15] and Home et al. [7], our analysis has several additional strengths. We included only those studies which utilised standardised protocol-driven titration regimens and treatment targets, and in which Gla-100 and NPH insulin were given only at bedtime. Furthermore, all of the derived subject-level data were standardised, permitting consistent endpoint definitions to be applied across the studies. Finally, the subject-level analysis permitted inclusion of baseline characteristics as covariates in the analyses. The analysis is, however, limited by the lack of a metformin-only comparator group and subjects using other OADs, including TZDs, DPP-4 inhibitors, or SGLT2 inhibitors. Had a metformin-only arm been available for analysis, in line with previous data, one might expect improved outcomes, including lower rates of hypoglycaemia and less weight gain, compared with the results of this analysis [6, 19].

In summary, this subject-level analysis supports existing data in finding that Gla-100 is associated with achievement of similar levels of glycaemic control as NPH insulin when both are given once-daily at bedtime. There is a lower risk of overall and particularly nocturnal hypoglycaemia, with Gla-100 despite higher insulin requirements and greater weight gain. Subjects adding Gla-100 to a background regimen of metformin plus a sulfonylurea are more likely to have better outcomes in terms of glycaemic control and weight gain, but a slightly higher risk of hypoglycaemia.

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Conflicts of Interest

D.R.O.: Honoraria for lectures and involvement in advisory boards for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Roche Diagnostics, Roche, and Sanofi; L.T: employee of Sanofi US, Inc.; stockholder of Sanofi; P.M.: statistical consultant who has received payment from Sanofi for statistical work on a variety of insulin glargine-related projects; W.L.: employee and stockholder of Sanofi.

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Table 1 - Glycaemic control as illustrated by change in HbA1c and FPG between baseline, Week 12, and Week 24 o

concomitant OAD.

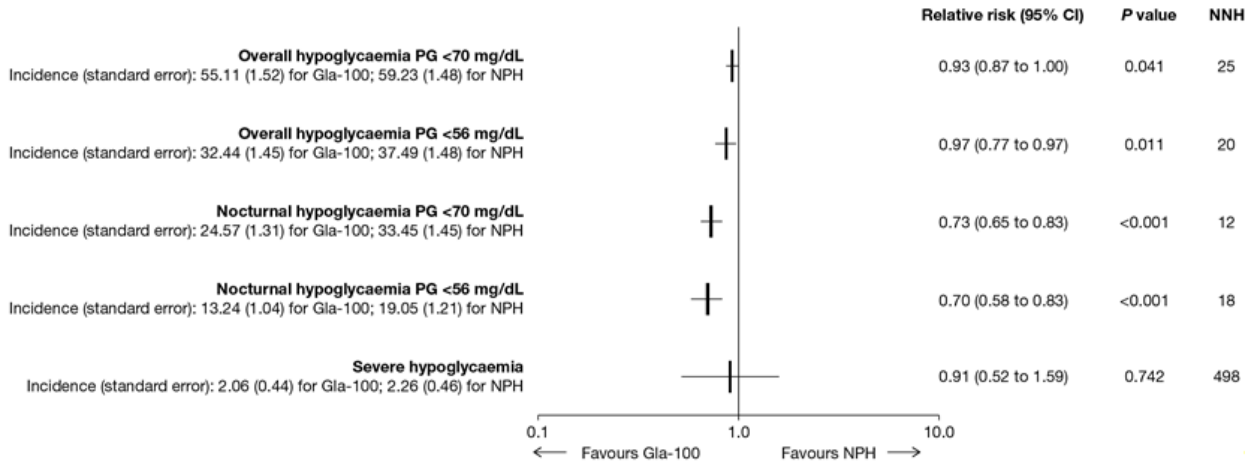
Data represent mean ± standard deviation. *P* values were obtained from an Analysis of Covariance (ANCOVA) mo

as covariate and treatment arm and OAD group as factors. MET, metformin; SU, sulfonylurea.

	Gla-100	NPH insulin	*P* value	Gla-100 + SU	NPH insulin + SU	*P* value	Gla-MET
HbA1c, %							
Baseline	n = 1006	n = 1045		n = 434	n = 462		n =
	8.7 (1.0)	8.7 (1.0)		9.0 (1.0)	9.1 (1.0)		8.3
Change from baseline to Week 12	n = 987/1006	n = 1028/1045		n = 430/434	n = 456/462		n = 5
	–1.2 (1.0)	–1.1 (1.0)	0.190	–1.2 (1.2)	–1.1 (1.2)	0.076	–1.2
Change from baseline to Week 24	n = 1006	n = 1045		n = 434	n = 462		n =
	–1.3 (1.1)	–1.2 (1.1)	0.184	–1.2 (1.3)	–1.1 (1.3)	0.161	–1.3
FPG, mg/dL							
Baseline	n = 1002	n = 1038		n = 438	n = 470		n =
	192.6 (55.9)	190.1 (55.2)		209.8 (60.1)	207.2 (59.4)		178.9
Change from baseline to Week 12	n = 984/1002	n = 1020/1038		n = 437/438	n = 468/470		n = 5
	–75.5 (62.2)	–72.1 (59.3)	0.426	–92.2 (68.6)	–87.9 (64.5)	0.449	–62.2
Change from baseline to Week 24	n = 1002	n = 1038		n = 438	n = 470		n =
	–75.7 (61.6)	–72.5 (59.5)	0.553	–90.4 (67.3)	–87.4 (66.0)	0.832	–64.3

Fig. 1 – Adjusted incidence of hypoglycaemia between baseline and Week 24 in the overall treatment groups (a), the sulfonylurea group (b), and the concomitant metformin plus a sulfonylurea group (c). NPH, neutral protamine Hag plasma glucose.

A



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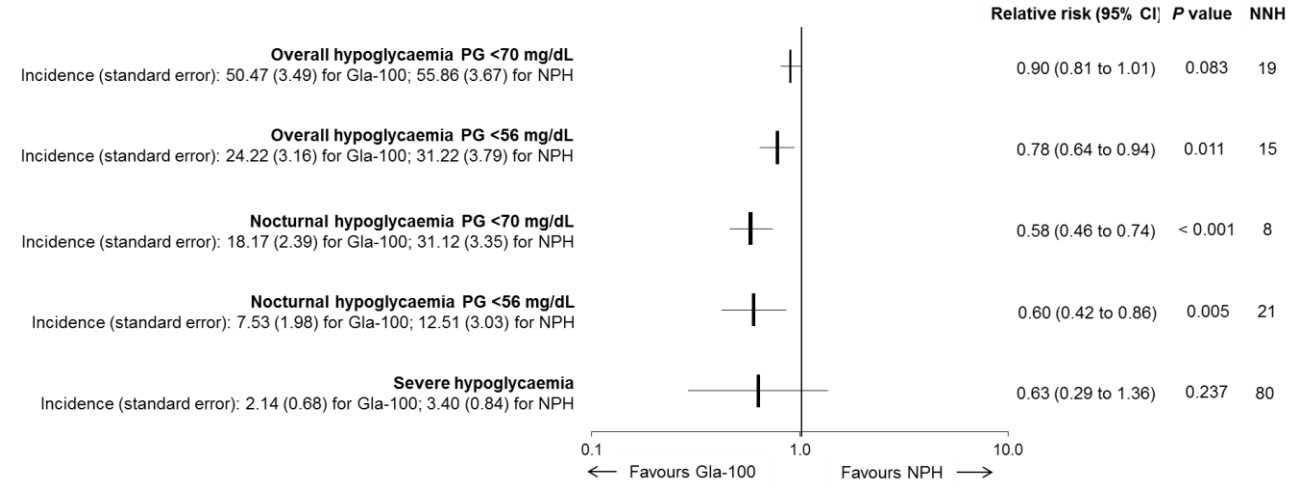

Relative risk (95% CI)
P value
NNH
Overall hypoglycaemia PG <70 mg/dL
Incidence (standard error): 50.47 (3.49) for Gla-100; 55.86 (3.67) for NPH
0.90 (0.81 to 1.01)
0.083
19
Overall hypoglycaemia PG <56 mg/dL
Incidence (standard error): 24.22 (3.16) for Gla-100; 31.22 (3.79) for NPH
0.78 (0.64 to 0.94)
0.011
15
Nocturnal hypoglycaemia PG <70 mg/dL
Incidence (standard error): 18.17 (2.39) for Gla-100; 31.12 (3.35) for NPH
0.58 (0.46 to 0.74)
< 0.001
8
Nocturnal hypoglycaemia PG <56 mg/dL
Incidence (standard error): 7.53 (1.98) for Gla-100; 12.51 (3.03) for NPH
0.60 (0.42 to 0.86)
0.005
21
Severe hypoglycaemia
Incidence (standard error): 2.14 (0.68) for Gla-100; 3.40 (0.84) for NPH
0.63 (0.29 to 1.36)
0.237
80
0.1
1.0
10.0
Favours Gla-100
Favours NPH

C

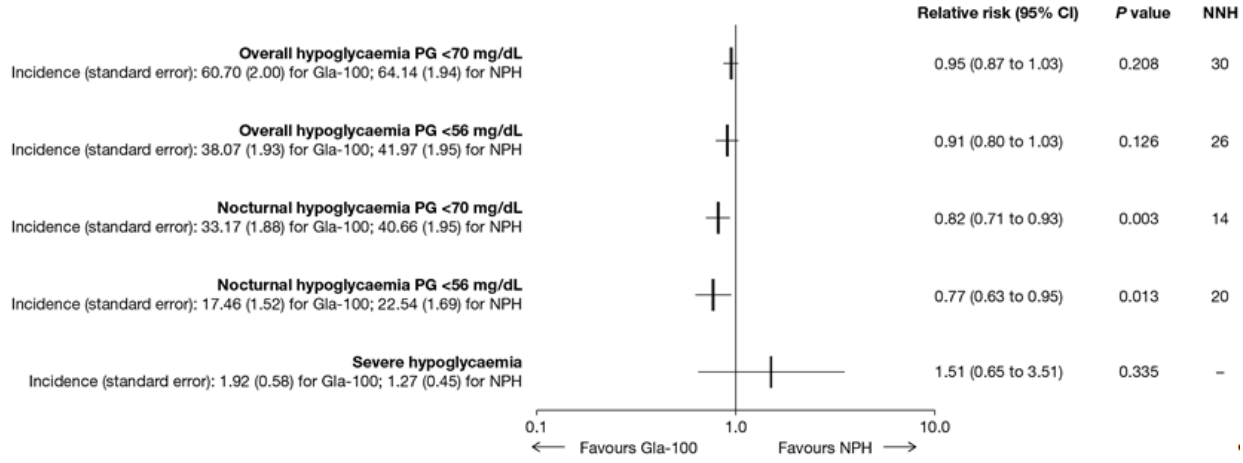

Relative risk (95% CI)
P value
NNH
Overall hypoglycaemia PG <70 mg/dL
Incidence (standard error): 60.70 (2.00) for Gla-100; 64.14 (1.94) for NPH
0.95 (0.87 to 1.03)
0.208
30
Overall hypoglycaemia PG <56 mg/dL
Incidence (standard error): 38.07 (1.93) for Gla-100; 41.97 (1.95) for NPH
0.91 (0.80 to 1.03)
0.126
26
Nocturnal hypoglycaemia PG <70 mg/dL
Incidence (standard error): 33.17 (1.88) for Gla-100; 40.66 (1.95) for NPH
0.82 (0.71 to 0.93)
0.003
14
Nocturnal hypoglycaemia PG <56 mg/dL
Incidence (standard error): 17.46 (1.52) for Gla-100; 22.54 (1.69) for NPH
0.77 (0.63 to 0.95)
0.013
20
Severe hypoglycaemia
Incidence (standard error): 1.92 (0.58) for Gla-100; 1.27 (0.45) for NPH
1.51 (0.65 to 3.51)
0.335
–
0.1
1.0
10.0
Favours Gla-100
Favours NPH

Fig. 2 – Modelled adjusted overall (plasma glucose <70 mg/dL [a] and plasma glucose <56 mg/dL [b]) and nocturna

mg/dL [c] and plasma glucose <56 mg/dL [d]) hypoglycaemia event rates for HbA1c values reported at endpoint.

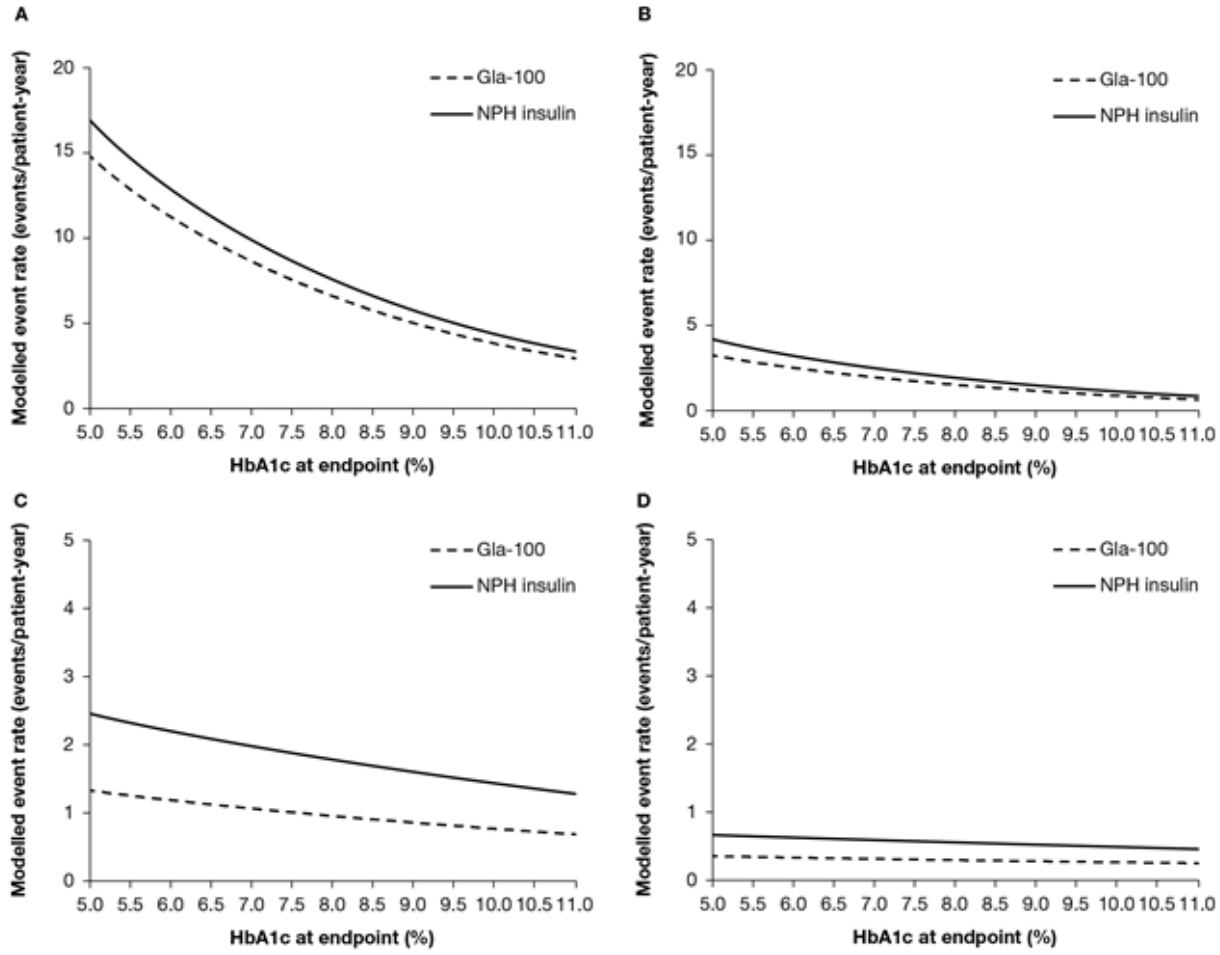
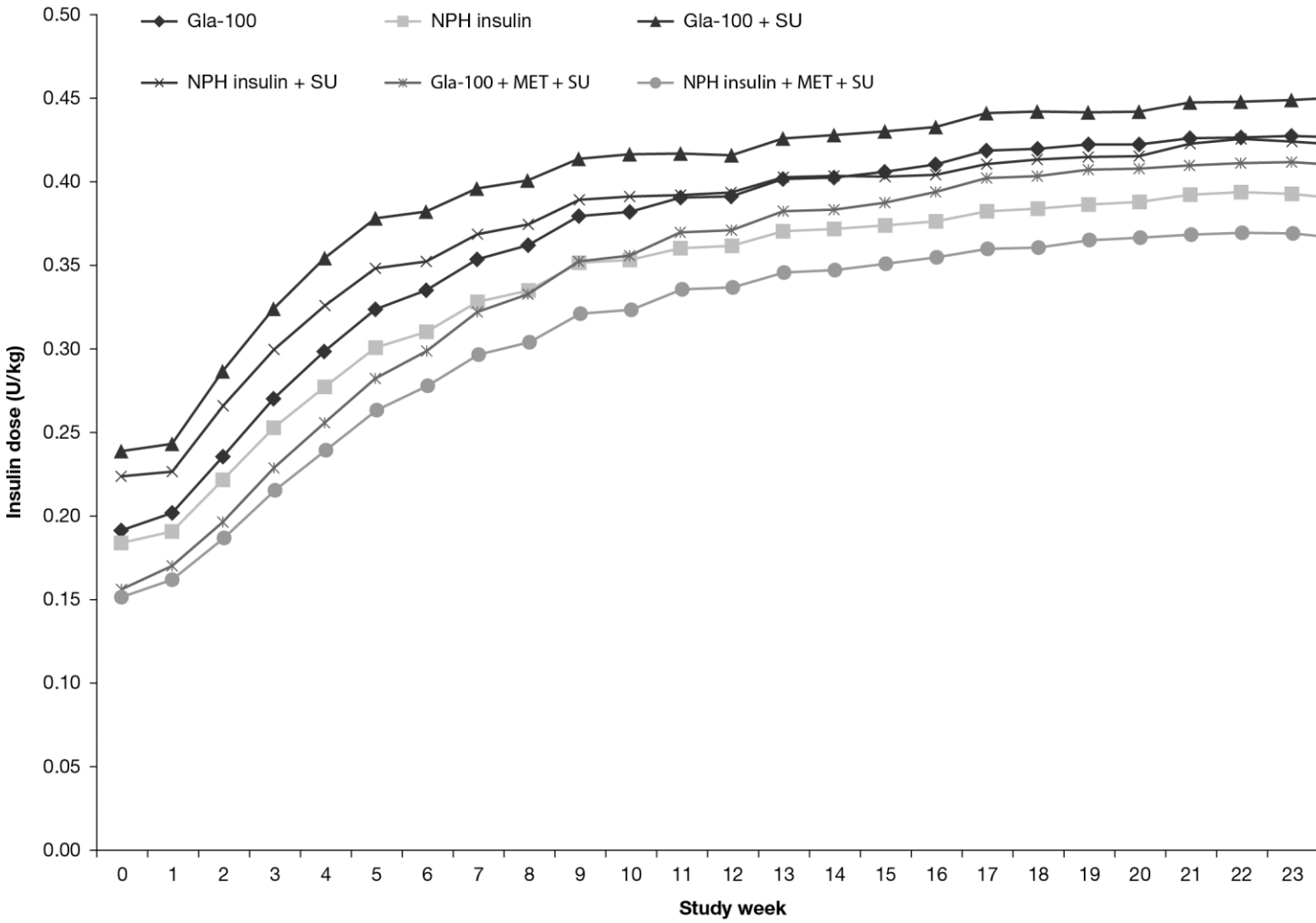


Fig. 3 – Insulin dose profiles by weight (U/kg) over time in subjects treated with Gla-100 or NPH insulin overall and

background oral therapy. Gla-100, insulin glargine 100 U/mL; MET, metformin; NPH, neutral protamine Hagedor



Supplementary materials

Supplementary Table 1 – Key characteristics of included and excluded studies of Gla-100 vs NPH insulin.

Study	Phase	Acronym [Ref]	Treatment	Subjects (N)	Treatment period (weeks)
Included studies: Treat-to-target (FPG ≤100 mg/dL)					
4001	IIIb	FLEXIBLE [10]	Morning vs bedtime Gla-100 + morning glimepiride vs bedtime NPH insulin + morning glimepiride	697	24
4002	IIIb	TTT [11]	Gla-100 bedtime + OADs vs NPH insulin bedtime + OADs	756	24
4013	IIIb	Latin America [12]	Gla-100 bedtime + morning glimepiride vs NPH insulin bedtime + morning glimepiride	481	24
2762	IIIb/IV	LANCELOT [14]	Gla-100 bedtime + metformin ± sulfonylurea vs NPH insulin bedtime + metformin ± sulfonylurea	704	36
Excluded studies: Not treat-to-target (FPG >100 mg/dL)					
3002	III	3002 [8]	Bedtime Gla-100 + OADs vs bedtime NPH insulin + OADs	422	52

3006	III	3006 [9]	Once-daily Gla-100 at bedtime vs once-daily or twice-daily NPH insulin	518	28
4012	IIIb/IV	LEAD [13]	Gla-100 bedtime + morning glimepiride vs NPH insulin bedtime + morning glimepiride	443	24

FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; NPH, neutral protamine Hagedorn; OAD, oral antidiabe

Supplementary Table 2 – Baseline demographic characteristics overall and by concomitant OAD.

Characteristic	Gla-100 (n=1024)	NPH insulin (n=1067)	Gla-100 + SU (n=440)	NPH insulin + SU (n=472)	Gla-100 + MET + SU (n=584)
Age, years	57.5 (9.2)	58.1 (8.8)	58.3 (9.7)	59.3 (9.5)	56.9 (8.7)
Male, n (%)	502 (49.0)	517 (48.5)	223 (50.7)	210 (44.5)	279 (47.8)
Diabetes duration, years	9.3 (6.1)	9.9 (5.9)	9.6 (6.7)	10.2 (6.2)	9.1 (5.7)
Body weight, kg	82.6 (17.3)	82.4 (17.1)	76.6 (14.2)	76.0 (15.2)	87.0 (18.1)
BMI, kg/m^2	29.6 (4.6)	29.6 (4.6)	27.9 (3.9)	28.0 (4.1)	30.9 (4.8)
HbA1c, %	8.6 (1.0)	8.7 (1.0)	9.0 (1.0)	9.1 (1.1)	8.3 (0.9)
FPG, mg/dL[a]	192.1 (55.6)	189.3 (55.1)	209.8 (60.0)	206.8 (59.5)	178.5 (47.8)

Data represent mean (standard deviation) unless otherwise stated.

[a]Denominator for FPG at baseline: n=1013 for Gla-100 overall; n=1047 for NPH insulin overall; n=440 for Gla-100 plus sulfonylurea; plus sulfonylurea; n=573 for Gla-100 plus metformin plus sulfonylurea; n=576 for NPH insulin plus metformin plus sulfonylurea. BMI fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; MET, metformin; NPH, neutral protein H antidiabetes drug; SU, sulfonylurea.

Supplementary Table 3 – Proportion of subjects achieving target HbA1c <7.0% or <6.5% or FPG ≤100 mg/dL duri

treatment period, the titration phase, and the maintenance phase, overall and by concomitant OAD.

	Gla-100	NPH insulin	Relative risk (95% CI) *P* value	Gla-100 + SU	NPH insulin + SU	Relative risk (95% CI) *P* value	Gla-10 MET +
Whole treatment period (Week 0–24)							
HbA1c <7.0%, n (%)	377 (38.0)	377 (36.6)	1.03 (0.93 to 1.13) 0.603	91 (21.3)	100 (21.7)	1.03 (0.82 to 1.30) 0.801	286 (5
HbA1c <6.5%, n (%)	191 (19.0)	170 (16.3)	1.16 (0.97 to 1.38) 0.109	51 (11.8)	43 (9.3)	1.27 (0.88 to 1.84) 0.199	140 (2
FPG ≤100 mg/dL, n (%)	363 (36.9)	344 (33.8)	1.09 (0.97 to 1.23) 0.135	153 (35.3)	174 (37.5)	0.95 (0.80 to 1.13) 0.580	210 (3
Titration phase (Week 0–12)							
HbA1c <7.0%, n (%)	308 (31.6)	324 (32.0)	1.03 (0.93 to 1.15) 0.545	77 (18.1)	95 (20.9)	0.87 (0.66 to 1.13) 0.295	231 (4
HbA1c <6.5%, n (%)	137 (13.9)	116 (11.3)	1.23 (0.99 to 1.53) 0.068	41 (9.6)	38 (8.3)	1.15 (0.75 to 1.75) 0.524	96 (1
FPG ≤100 mg/dL, n (%)	350 (36.2)	337 (33.7)	1.07 (0.95 to 1.21) 0.242	165 (38.2)	178 (38.5)	1.00 (0.84 to 1.18) 0.969	185 (3
Maintenance phase (Week 12–24)							
HbA1c <7.0%, n (%)	110 (16.9)	115 (17.0)	0.97 (0.78 to 1.20) 0.775	32 (9.5)	32 (9.2)	1.04 (0.65 to 1.66) 0.873	78 (24
HbA1c <6.5%, n (%)	87 (10.5)	76 (8.5)	1.28 (0.98 to 1.68) 0.070	20 (5.3)	16 (3.9)	1.36 (0.71 to 2.58) 0.352	67 (14

FPG ≤100 mg/dL, n (%)	170 (27.9)	178 (26.9)	1.06 (0.89 to 1.27) 0.507	59 (23.1)	76 (28.1)	0.80 (0.60 to 1.06) 0.126	111 (3

Category of subjects achieving HbA1c/FPG target was limited to subjects with baseline (or Week 12 baseline) level above target. CI, c
fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; MET, metformin; NPH, neutral protein H
antidiabetes drug; SU, sulfonylurea.

Supplementary Table 4 – Proportion of subjects achieving target HbA1c <7.0% or FPG ≤100 mg/dL without overal

during the whole treatment period, the titration phase, and the maintenance phase, overall and by concomitant OA

	Gla-100	NPH insulin	Relative risk (95% CI) *P* value	Gla-100 + SU	NPH insulin + SU	Relative risk (95% CI) *P* value	Gla-10 MET +
Whole treatment period (Week 0–24)							
HbA1c <7.0% without overall hypoglycaemia PG <70 mg/dL, n (%)	118 (11.9)	114 (11.1)	1.06 (0.83 to 1.34) 0.653	40 (9.3)	41 (8.9)	1.07 (0.72 to 1.59) 0.735	78 (13
HbA1c <7.0% without overall hypoglycaemia PG <56 mg/dL, n (%)	208 (21.0)	198 (19.2)	1.08 (0.91 to 1.27) 0.396	69 (16.1)	60 (13.0)	1.30 (0.97 to 1.74) 0.080	139 (2
FPG ≤100 mg/dL without overall hypoglycaemia PG <70 mg/dL, n (%)	129 (13.1)	116 (11.4)	1.16 (0.92 to 1.47) 0.209	64 (14.8)	65 (14.0)	1.08 (0.79 to 1.47) 0.639	65 (11
FPG ≤100 mg/dL without overall hypoglycaemia PG <56 mg/dL, n (%)	221 (22.4)	191 (18.8)	1.20 (1.01 to 1.42) 0.036	105 (24.2)	103 (22.2)	1.10 (0.87 to 1.39) 0.411	116 (2
Titration phase (Week 0–12)							
HbA1c <7.0% without overall hypoglycaemia PG <70 mg/dL, n (%)	127 (13.0)	133 (13.1)	1.01 (1.01 to 1.26) 0.955	42 (9.9)	52 (11.5)	0.86 (0.59 to 1.27) 0.452	85 (15
HbA1c <7.0% without overall hypoglycaemia PG <56 mg/dL, n (%)	215 (22.1)	214 (21.1)	1.07 (0.92 to 1.25) 0.385	64 (15.1)	72 (15.9)	0.95 (0.70 to 1.29) 0.743	151 (2
FPG ≤100 mg/dL without overall hypoglycaemia PG <70 mg/dL, n (%)	158 (16.3)	132 (13.2)	1.24 (1.00 to 1.53) 0.046	80 (18.5)	79 (17.1)	1.10 (0.83 to 1.45) 0.496	78 (14

FPG ≤100 mg/dL without overall hypoglycaemia PG <56 mg/dL, n (%)	256 (26.4)	230 (23.0)	1.15 (0.99 to 1.34) 0.072	123 (28.5)	131 (28.4)	1.01 (0.82 to 1.24) 0.917	133 (2
Maintenance phase (Week 12–24)							
HbA1c <7.0% without overall hypoglycaemia PG <70 mg/dL, n (%)	64 (9.8)	52 (7.7)	1.24 (0.89 to 1.75) 0.208	21 (6.3)	18 (5.2)	1.21 (0.66 to 2.23) 0.538	43 (1
HbA1c <7.0% without overall hypoglycaemia PG <56 mg/dL, n (%)	83 (12.7)	81 (11.9)	1.03 (0.79 to 1.35) 0.833	27 (8.0)	24 (6.9)	1.17 (0.69 to 1.98) 0.564	56 (1
FPG ≤100 mg/dL without overall hypoglycaemia PG <70 mg/dL, n (%)	86 (14.1)	80 (12.1)	1.17 (0.88 to 1.55) 0.283	35 (13.7)	40 (14.8)	0.92 (0.61 to 1.39) 0.693	51 (1
FPG ≤100 mg/dL without overall hypoglycaemia PG <56 mg/dL, n (%)	129 (21.2)	118 (17.9)	1.20 (0.98 to 1.49) 0.108	50 (19.6)	54 (20.0)	0.97 (0.69 to 1.36) 0.854	79 (2

CI, confidence interval; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; MET, metfo

protein Hagedorn; OAD, oral antidiabetes drug; PG, plasma glucose; SU, sulfonylurea.

Supplementary Table 5 – Proportion of subjects achieving target HbA1c <7.0% or FPG ≤100 mg/dL without noctur

during the whole treatment period, the titration phase, and the maintenance phase, overall and by concomitant OA

	Gla-100	NPH insulin	Relative risk (95% CI) *P* value	Gla-100 + SU	NPH insulin + SU	Relative risk (95% CI) *P* value	Gla-10 MET +
Whole treatment period (Week 0–24)							
HbA1c <7.0% without nocturnal hypoglycaemia PG <70 mg/dL, n (%)	245 (24.7)	209 (20.3)	1.19 (1.02 to 1.39) 0.032	75 (17.5)	70 (15.2)	1.19 (0.90 to 1.58) 0.218	170 (3
HbA1c <7.0% without nocturnal hypoglycaemia PG <56 mg/dL, n (%)	301 (30.3)	278 (27.0)	1.12 (0.98 to 1.27) 0.087	86 (20.1)	82 (17.8)	1.21 (0.94 to 1.55) 0.140	215 (3
FPG ≤100 mg/dL without nocturnal hypoglycaemia PG <70 mg/dL, n (%)	241 (24.5)	201 (19.8)	1.24 (1.05 to 1.46) 0.010	115 (26.6)	116 (25.0)	1.07 (0.86 to 1.33) 0.528	126 (2
FPG ≤100 mg/dL without nocturnal hypoglycaemia PG <56 mg/dL, n (%)	302 (30.7)	264 (26.0)	1.18 (1.03 to 1.36) 0.017	133 (30.7)	141 (30.4)	1.02 (0.84 to 1.24) 0.859	169 (3
Titration phase (Week 0–12)							
HbA1c <7.0% without nocturnal hypoglycaemia PG <70 mg/dL, n (%)	220 (22.6)	219 (21.6)	1.06 (0.91 to 1.24) 0.453	66 (15.5)	72 (15.9)	0.98 (0.72 to 1.33) 0.893	154 (2
HbA1c <7.0% without nocturnal hypoglycaemia PG <56 mg/dL, n (%)	276 (28.3)	267 (26.3)	1.13 (0.99 to 1.28) 0.062	72 (16.9)	85 (18.7)	0.90 (0.68 to 1.20) 0.491	204 (3
FPG ≤100 mg/dL without nocturnal	267 (27.6)	216 (21.6)	1.28 (1.10 to 1.49)	137 (31.7)	125 (27.1)	1.18 (0.96 to 1.44)	130 (2

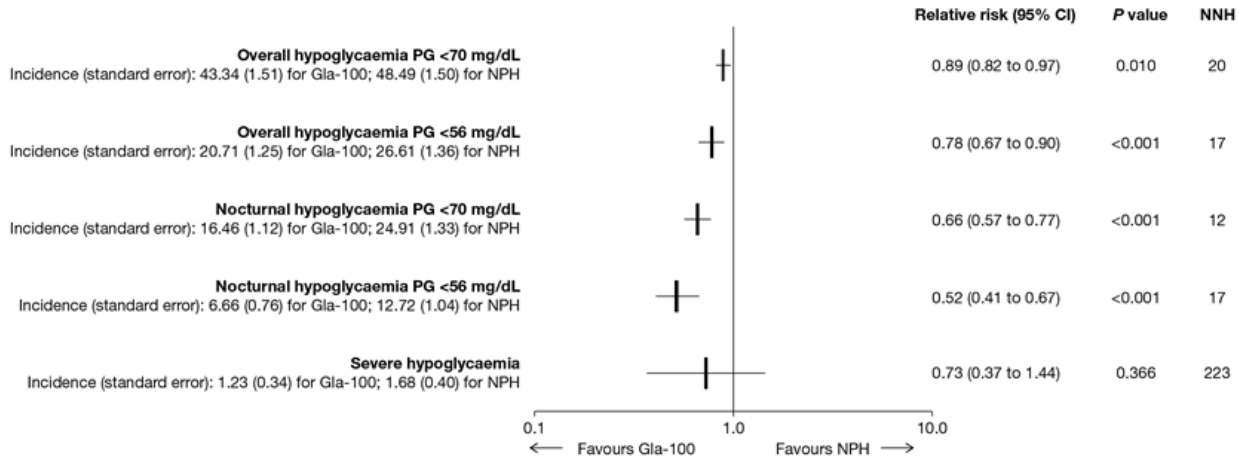
hypoglycaemia PG <mg/dL, n (%)			0.002			0.115	
FPG ≤100 mg/dL without nocturnal hypoglycaemia PG <56 mg/dL, n (%)	318 (32.9)	276 (27.6)	1.19 (1.04 to 1.36) 0.010	153 (35.4)	151 (32.7)	1.09 (0.91 to 1.31) 0.355	165 (3
Maintenance phase (Week 12–24)							
HbA1c <7.0% without nocturnal hypoglycaemia PG <70 mg/dL, n (%)	92 (14.1)	74 (10.9)	1.26 (0.96 to 1.65) 0.095	29 (8.6)	26 (7.4)	1.16 (0.70 to 1.92) 0.570	63 (20
HbA1c <7.0% without nocturnal hypoglycaemia PG <56 mg/dL, n (%)	97 (14.9)	90 (13.3)	1.09 (0.85 to 1.40) 0.495	31 (9.2)	28 (8.0)	1.15 (0.71 to 1.87) 0.575	66 (21
FPG ≤100 mg/dL without nocturnal hypoglycaemia PG <70 mg/dL, n (%)	132 (21.7)	132 (20.0)	1.09 (0.88 to 1.34) 0.449	52 (20.4)	64 (23.7)	0.84 (0.61 to 1.16) 0.289	80 (22
FPG ≤100 mg/dL without nocturnal hypoglycaemia PG < 56 mg/dL, n (%)	152 (25.0)	146 (22.1)	1.14 (0.94 to 1.39) 0.178	56 (22.0)	66 (24.4)	0.88 (0.65 to 1.20) 0.414	96 (27

CI, confidence interval; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; HbA1c, glycated haemoglobin; MET, metfo

protein Hagedorn; OAD, oral antidiabetes drug; PG, plasma glucose; SU, sulfonylurea.

Supplementary Fig. 1 – Adjusted incidence of hypoglycaemia between baseline and Week 12 in the overall treatmen concomitant sulfonylurea group (b), and the concomitant metformin plus a sulfonylurea group (c). CI, confidence in insulin glargine 100 U/mL; NNH, number needed to harm; NPH, neutral protamine Hagedorn insulin.

A



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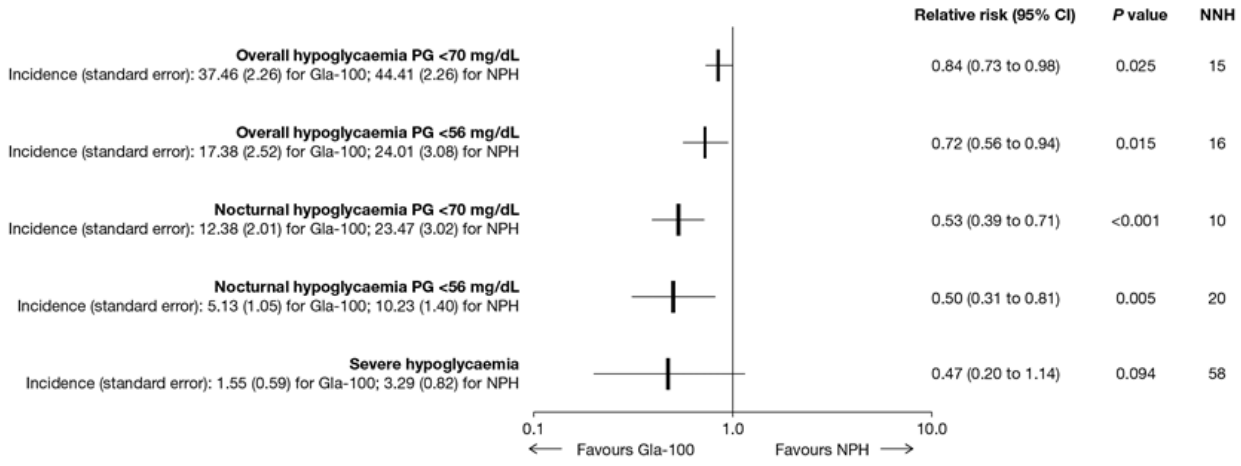
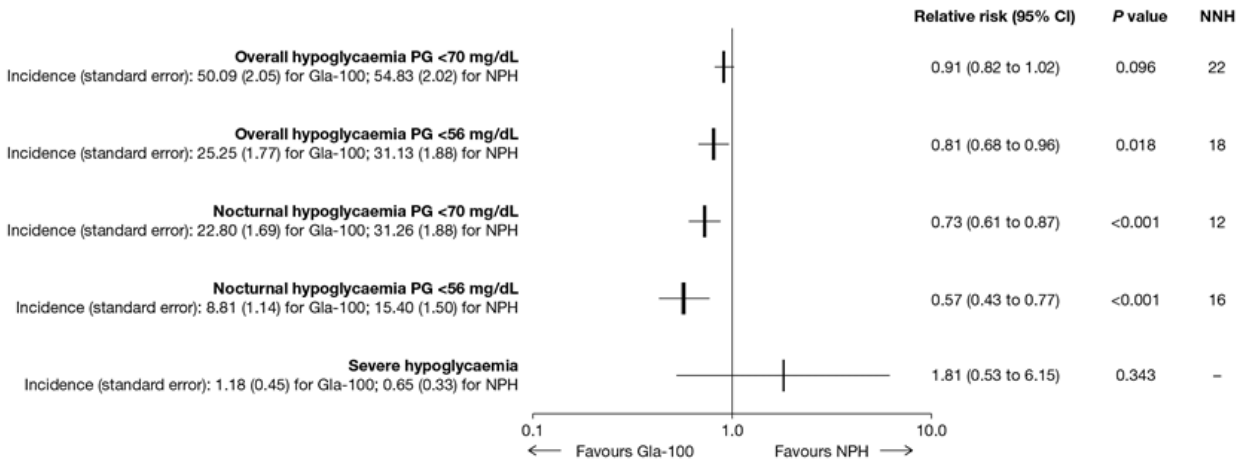
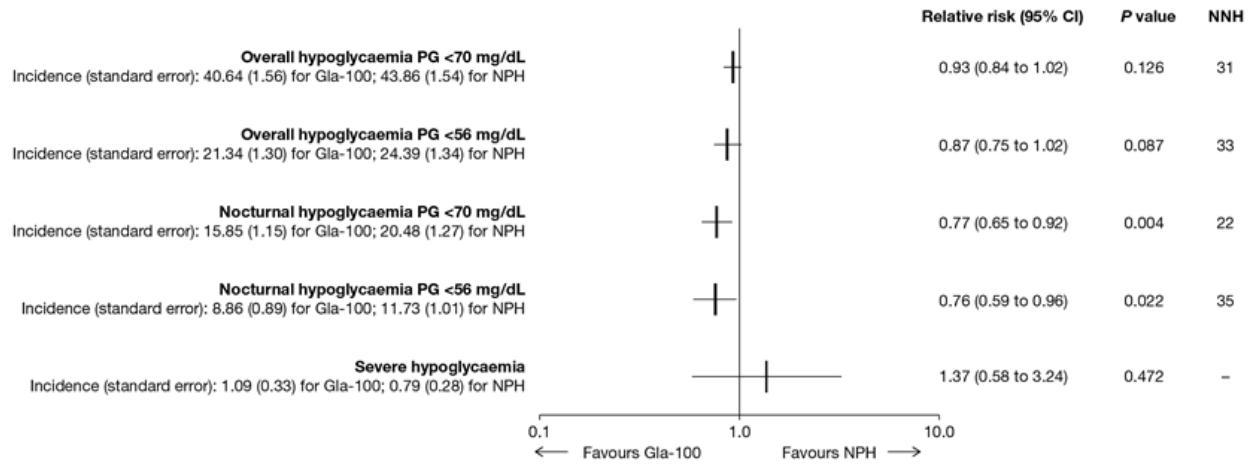

Relative risk (95% CI)
P value
NNH
Overall hypoglycaemia PG <70 mg/dL
Incidence (standard error): 37.46 (2.26) for Gla-100; 44.41 (2.26) for NPH
0.84 (0.73 to 0.98)
0.025
15
Overall hypoglycaemia PG <56 mg/dL
Incidence (standard error): 17.38 (2.52) for Gla-100; 24.01 (3.08) for NPH
0.72 (0.56 to 0.94)
0.015
16
Nocturnal hypoglycaemia PG <70 mg/dL
Incidence (standard error): 12.38 (2.01) for Gla-100; 23.47 (3.02) for NPH
0.53 (0.39 to 0.71)
<0.001
10
Nocturnal hypoglycaemia PG <56 mg/dL
Incidence (standard error): 5.13 (1.05) for Gla-100; 10.23 (1.40) for NPH
0.50 (0.31 to 0.81)
0.005
20
Severe hypoglycaemia
Incidence (standard error): 1.55 (0.59) for Gla-100; 3.29 (0.82) for NPH
0.47 (0.20 to 1.14)
0.094
58
0.1
1.0
10.0
Favours Gla-100
Favours NPH

C

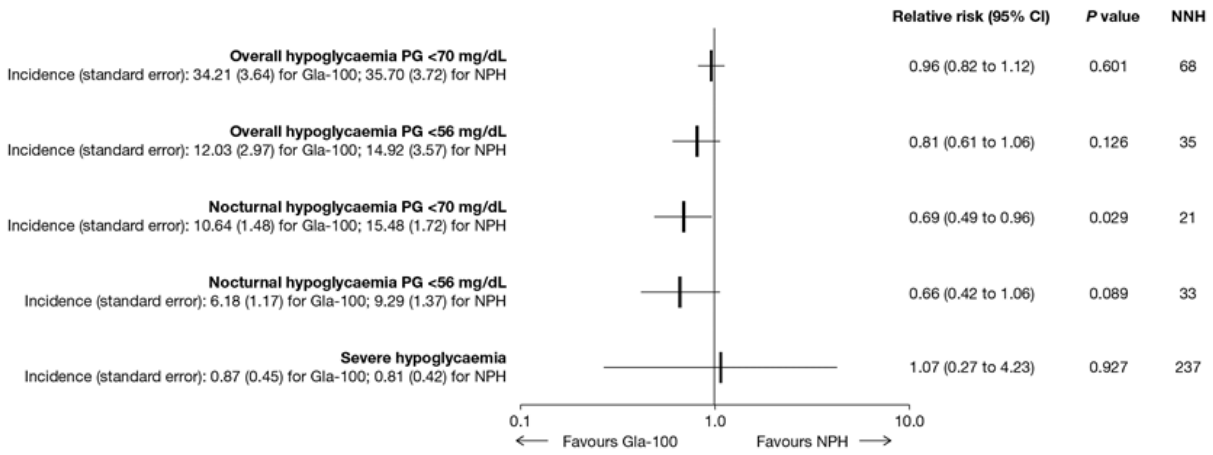

Relative risk (95% CI)
P value
NNH
Overall hypoglycaemia PG <70 mg/dL
Incidence (standard error): 50.09 (2.05) for Gla-100; 54.83 (2.02) for NPH
0.91 (0.82 to 1.02)
0.096
22
Overall hypoglycaemia PG <56 mg/dL
Incidence (standard error): 25.25 (1.77) for Gla-100; 31.13 (1.88) for NPH
0.81 (0.68 to 0.96)
0.018
18
Nocturnal hypoglycaemia PG <70 mg/dL
Incidence (standard error): 22.80 (1.69) for Gla-100; 31.26 (1.88) for NPH
0.73 (0.61 to 0.87)
<0.001
12
Nocturnal hypoglycaemia PG <56 mg/dL
Incidence (standard error): 8.81 (1.14) for Gla-100; 15.40 (1.50) for NPH
0.57 (0.43 to 0.77)
<0.001
16
Severe hypoglycaemia
Incidence (standard error): 1.18 (0.45) for Gla-100; 0.65 (0.33) for NPH
1.81 (0.53 to 6.15)
0.343
–
0.1
1.0
10.0
Favours Gla-100
Favours NPH

Supplementary Fig. 2 – Adjusted incidence of hypoglycaemia between Week 12 and Week 24 in the overall treatme
concomitant sulfonylurea group (b), and the concomitant metformin plus sulfonylurea group (c). CI, confidence int
glargine 100 U/mL; NNH, number needed to harm; NPH, neutral protamine Hagedorn insulin.

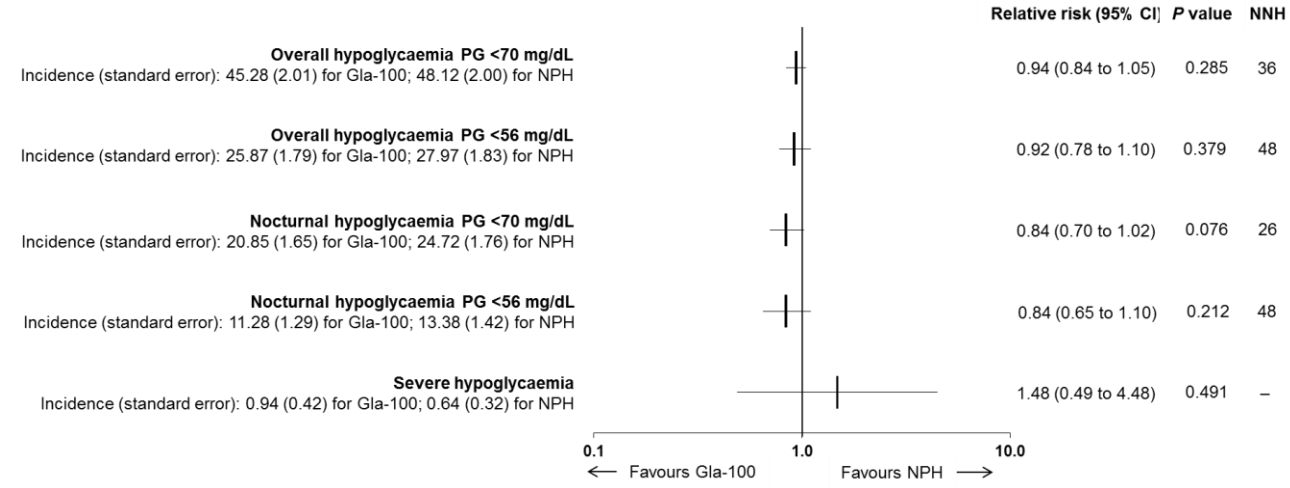
A



B

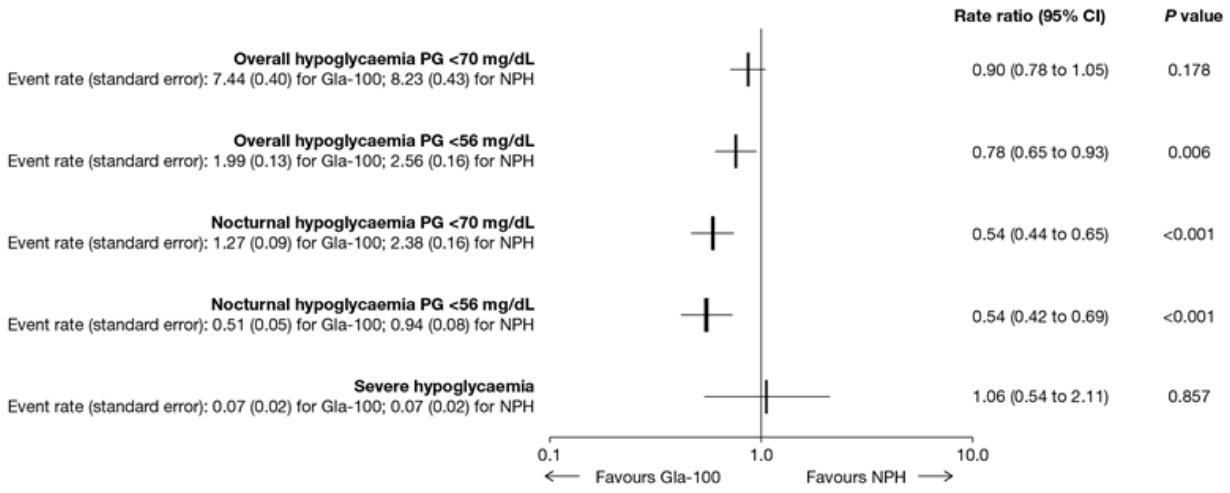

Relative risk (95% CI)
P value
NNH
Overall hypoglycaemia PG <70 mg/dL
Incidence (standard error): 34.21 (3.64) for Gla-100; 35.70 (3.72) for NPH
0.96 (0.82 to 1.12)
0.601
68
Overall hypoglycaemia PG <56 mg/dL
Incidence (standard error): 12.03 (2.97) for Gla-100; 14.92 (3.57) for NPH
0.81 (0.61 to 1.06)
0.126
35
Nocturnal hypoglycaemia PG <70 mg/dL
Incidence (standard error): 10.64 (1.48) for Gla-100; 15.48 (1.72) for NPH
0.69 (0.49 to 0.96)
0.029
21
Nocturnal hypoglycaemia PG <56 mg/dL
Incidence (standard error): 6.18 (1.17) for Gla-100; 9.29 (1.37) for NPH
0.66 (0.42 to 1.06)
0.089
33
Severe hypoglycaemia
Incidence (standard error): 0.87 (0.45) for Gla-100; 0.81 (0.42) for NPH
1.07 (0.27 to 4.23)
0.927
237
0.1
1.0
10.0
Favours Gla-100
Favours NPH

C


Relative risk (95% CI)
P value
NNH
Overall hypoglycaemia PG <70 mg/dL
Incidence (standard error): 45.28 (2.01) for Gla-100; 48.12 (2.00) for NPH
0.94 (0.84 to 1.05)
0.285
36
Overall hypoglycaemia PG <56 mg/dL
Incidence (standard error): 25.87 (1.79) for Gla-100; 27.97 (1.83) for NPH
0.92 (0.78 to 1.10)
0.379
48
Nocturnal hypoglycaemia PG <70 mg/dL
Incidence (standard error): 20.85 (1.65) for Gla-100; 24.72 (1.76) for NPH
0.84 (0.70 to 1.02)
0.076
26
Nocturnal hypoglycaemia PG <56 mg/dL
Incidence (standard error): 11.28 (1.29) for Gla-100; 13.38 (1.42) for NPH
0.84 (0.65 to 1.10)
0.212
48
Severe hypoglycaemia
Incidence (standard error): 0.94 (0.42) for Gla-100; 0.64 (0.32) for NPH
1.48 (0.49 to 4.48)
0.491
–
0.1
1.0
10.0
Favours Gla-100
Favours NPH

Supplementary Fig. 3 – Adjusted hypoglycaemia event rate between baseline and Week 24 in the overall treatment concomitant sulfonylurea group (b), and the concomitant metformin plus a sulfonylurea group (c).

A



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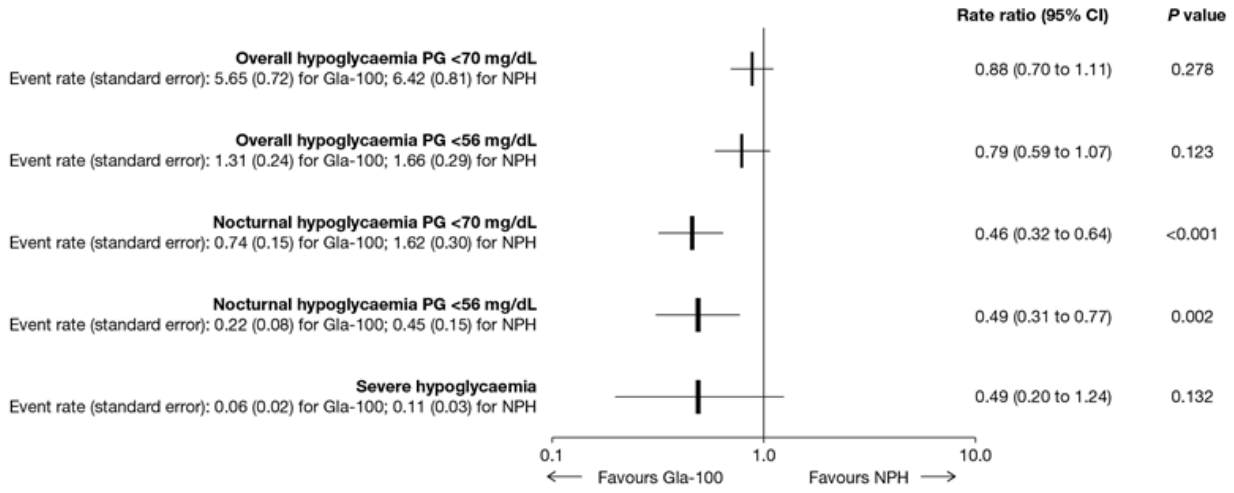
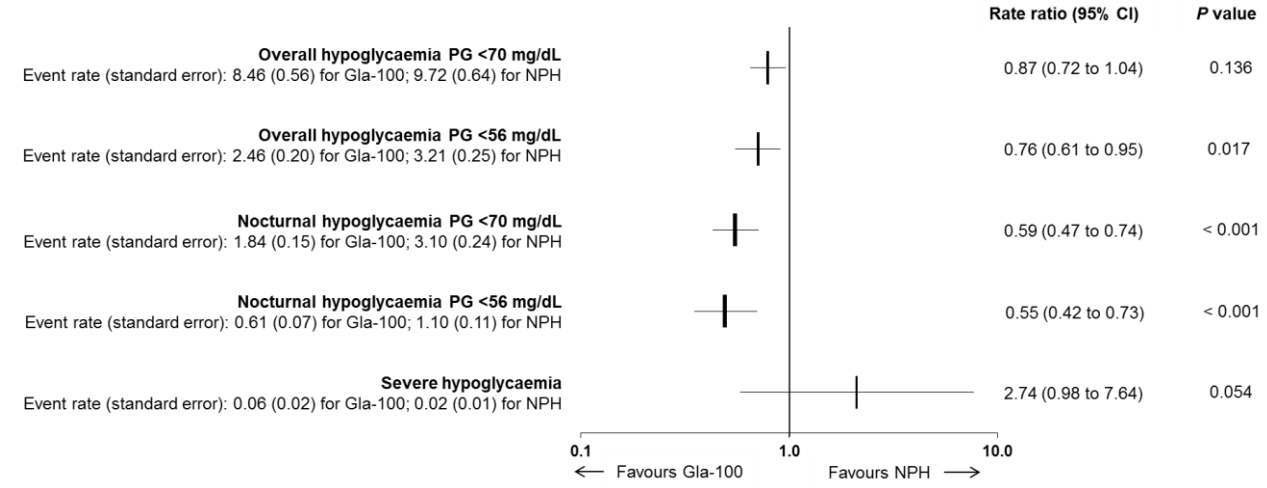

Rate ratio (95% CI)
P value
Overall hypoglycaemia PG <70 mg/dL
Event rate (standard error): 5.65 (0.72) for Gla-100; 6.42 (0.81) for NPH
0.88 (0.70 to 1.11)
0.278
Overall hypoglycaemia PG <56 mg/dL
Event rate (standard error): 1.31 (0.24) for Gla-100; 1.66 (0.29) for NPH
0.79 (0.59 to 1.07)
0.123
Nocturnal hypoglycaemia PG <70 mg/dL
Event rate (standard error): 0.74 (0.15) for Gla-100; 1.62 (0.30) for NPH
0.46 (0.32 to 0.64)
<0.001
Nocturnal hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.22 (0.08) for Gla-100; 0.45 (0.15) for NPH
0.49 (0.31 to 0.77)
0.002
Severe hypoglycaemia
Event rate (standard error): 0.06 (0.02) for Gla-100; 0.11 (0.03) for NPH
0.49 (0.20 to 1.24)
0.132
0.1
1.0
10.0
Favours Gla-100
Favours NPH

C

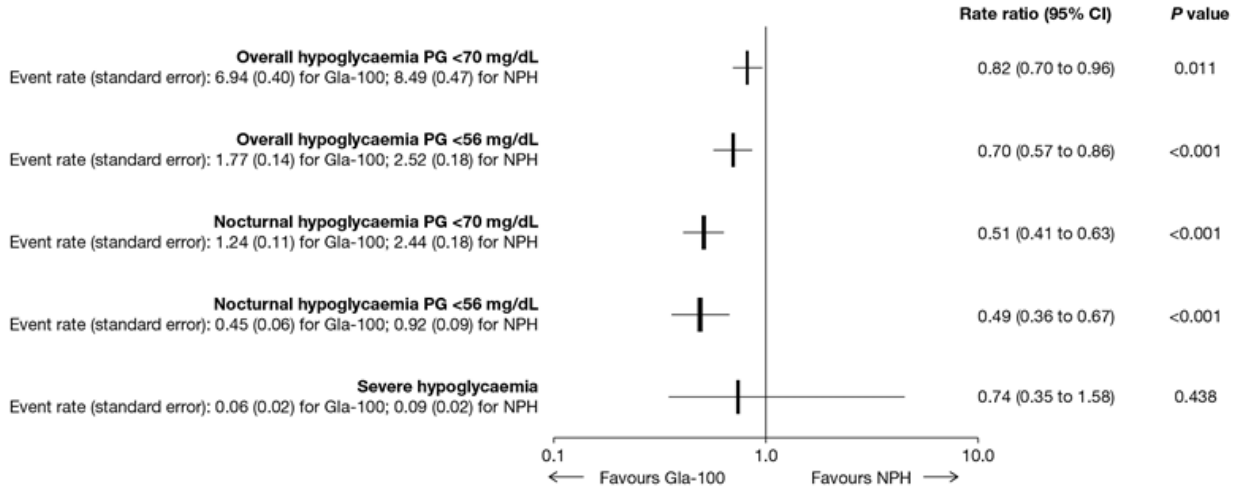

Rate ratio (95% CI)
P value
Overall hypoglycaemia PG <70 mg/dL
Event rate (standard error): 8.46 (0.56) for Gla-100; 9.72 (0.64) for NPH
0.87 (0.72 to 1.04)
0.136
Overall hypoglycaemia PG <56 mg/dL
Event rate (standard error): 2.46 (0.20) for Gla-100; 3.21 (0.25) for NPH
0.76 (0.61 to 0.95)
0.017
Nocturnal hypoglycaemia PG <70 mg/dL
Event rate (standard error): 1.84 (0.15) for Gla-100; 3.10 (0.24) for NPH
0.59 (0.47 to 0.74)
< 0.001
Nocturnal hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.61 (0.07) for Gla-100; 1.10 (0.11) for NPH
0.55 (0.42 to 0.73)
< 0.001
Severe hypoglycaemia
Event rate (standard error): 0.06 (0.02) for Gla-100; 0.02 (0.01) for NPH
2.74 (0.98 to 7.64)
0.054
0.1
1.0
10.0
Favours Gla-100
Favours NPH

Supplementary Fig. 4 – Adjusted hypoglycaemia event rate between baseline and Week 12 in the overall treatment g

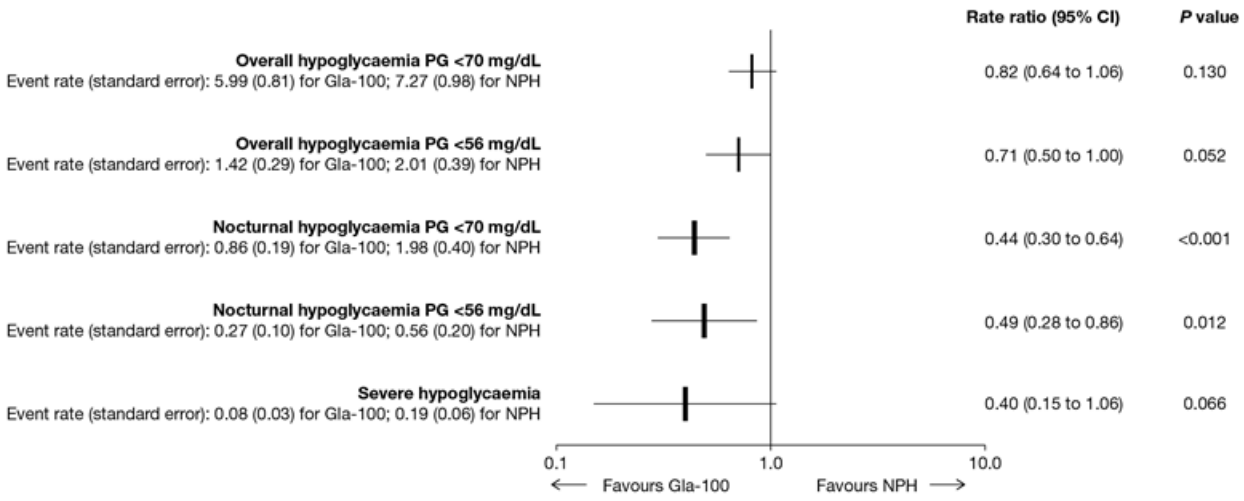
concomitant sulfonylurea group (b), and the concomitant metformin plus a sulfonylurea group (c). CI, confidence in

insulin glargine 100 U/mL; NNH, number needed to harm; NPH, neutral protamine Hagedorn insulin.

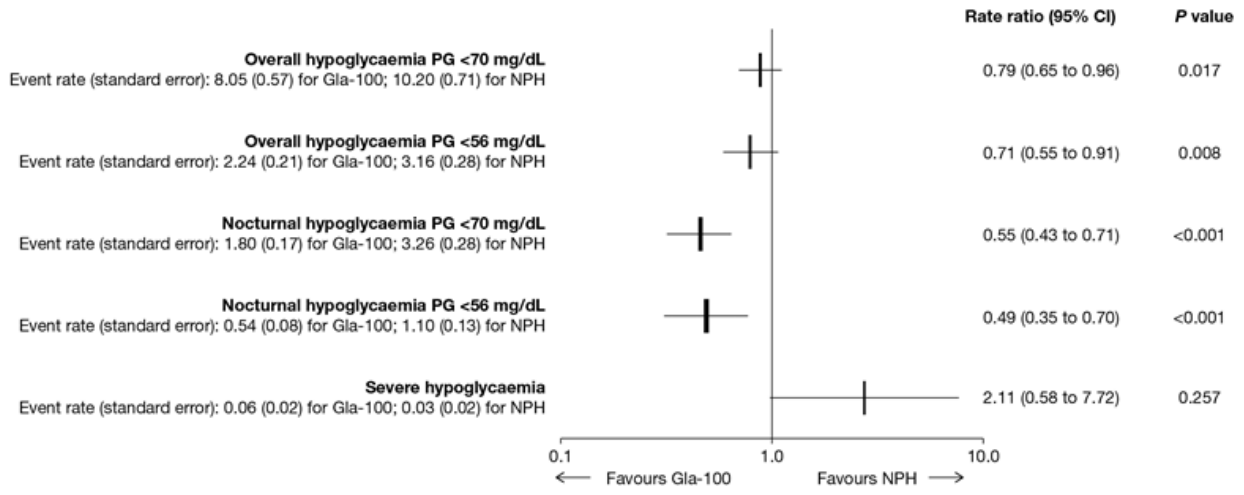
A



B

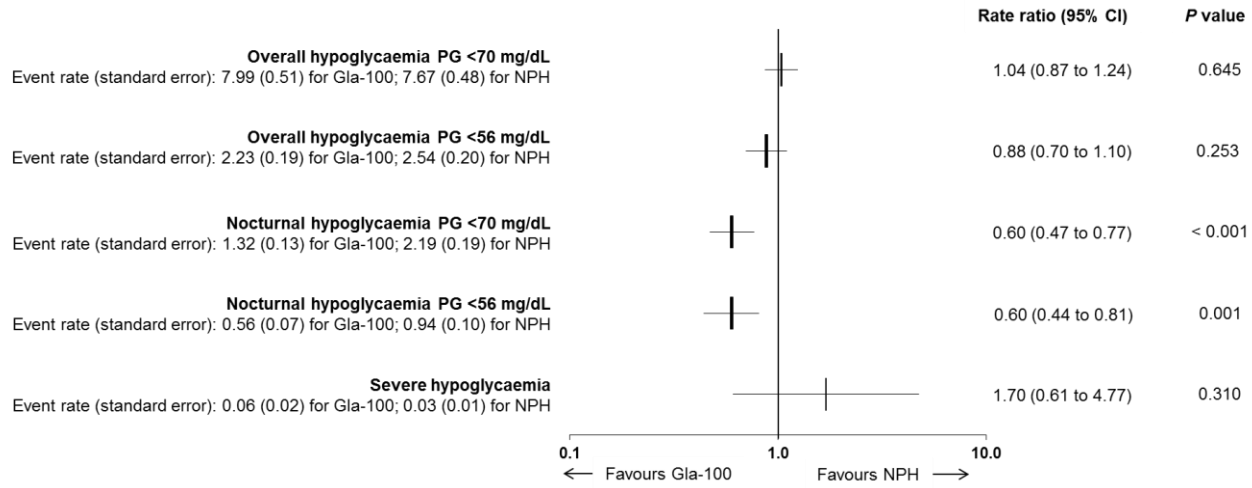

Rate ratio (95% CI)
P value
Overall hypoglycaemia PG <70 mg/dL
Event rate (standard error): 5.99 (0.81) for Gla-100; 7.27 (0.98) for NPH
0.82 (0.64 to 1.06)
0.130
Overall hypoglycaemia PG <56 mg/dL
Event rate (standard error): 1.42 (0.29) for Gla-100; 2.01 (0.39) for NPH
0.71 (0.50 to 1.00)
0.052
Nocturnal hypoglycaemia PG <70 mg/dL
Event rate (standard error): 0.86 (0.19) for Gla-100; 1.98 (0.40) for NPH
0.44 (0.30 to 0.64)
<0.001
Nocturnal hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.27 (0.10) for Gla-100; 0.56 (0.20) for NPH
0.49 (0.28 to 0.86)
0.012
Severe hypoglycaemia
Event rate (standard error): 0.08 (0.03) for Gla-100; 0.19 (0.06) for NPH
0.40 (0.15 to 1.06)
0.066
0.1
1.0
10.0
Favours Gla-100
Favours NPH

C

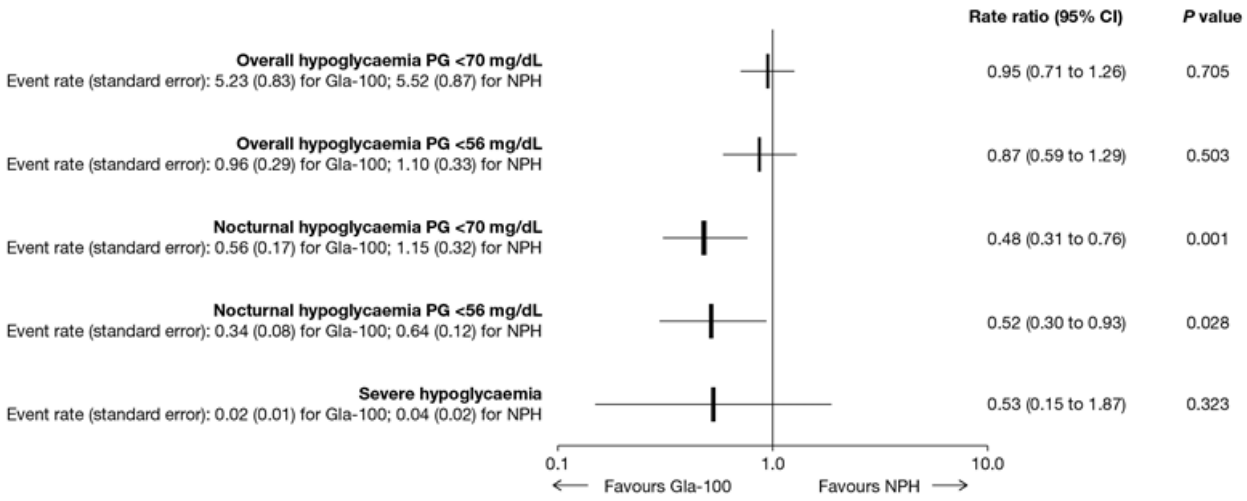

Rate ratio (95% CI)
P value
Overall hypoglycaemia PG <70 mg/dL
Event rate (standard error): 8.05 (0.57) for Gla-100; 10.20 (0.71) for NPH
0.79 (0.65 to 0.96)
0.017
Overall hypoglycaemia PG <56 mg/dL
Event rate (standard error): 2.24 (0.21) for Gla-100; 3.16 (0.28) for NPH
0.71 (0.55 to 0.91)
0.008
Nocturnal hypoglycaemia PG <70 mg/dL
Event rate (standard error): 1.80 (0.17) for Gla-100; 3.26 (0.28) for NPH
0.55 (0.43 to 0.71)
<0.001
Nocturnal hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.54 (0.08) for Gla-100; 1.10 (0.13) for NPH
0.49 (0.35 to 0.70)
<0.001
Severe hypoglycaemia
Event rate (standard error): 0.06 (0.02) for Gla-100; 0.03 (0.02) for NPH
2.11 (0.58 to 7.72)
0.257
0.1
1.0
10.0
Favours Gla-100
Favours NPH

Supplementary Fig. 5 – Adjusted hypoglycaemia event rate between Week 12 and Week 24 in the overall treatment concomitant sulfonylurea group (b), and in the concomitant metformin plus a sulfonylurea group (c). CI, confidenc insulin glargine 100 U/mL; NNH, number needed to harm; NPH, neutral protamine Hagedorn insulin.

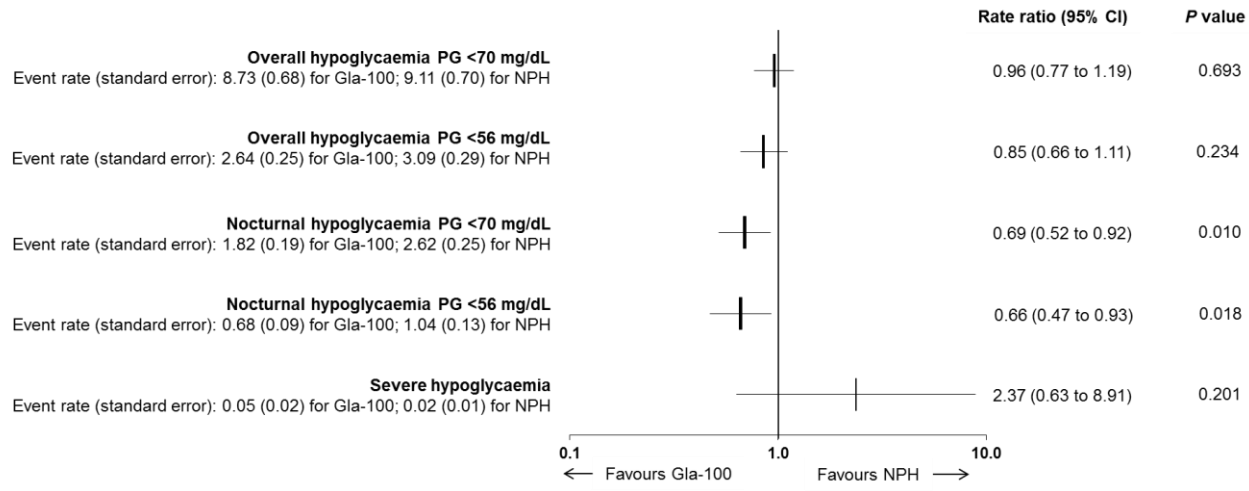
A



B


Rate ratio (95% CI)
P value
Overall hypoglycaemia PG <70 mg/dL
Event rate (standard error): 5.23 (0.83) for Gla-100; 5.52 (0.87) for NPH
0.95 (0.71 to 1.26)
0.705
Overall hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.96 (0.29) for Gla-100; 1.10 (0.33) for NPH
0.87 (0.59 to 1.29)
0.503
Nocturnal hypoglycaemia PG <70 mg/dL
Event rate (standard error): 0.56 (0.17) for Gla-100; 1.15 (0.32) for NPH
0.48 (0.31 to 0.76)
0.001
Nocturnal hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.34 (0.08) for Gla-100; 0.64 (0.12) for NPH
0.52 (0.30 to 0.93)
0.028
Severe hypoglycaemia
Event rate (standard error): 0.02 (0.01) for Gla-100; 0.04 (0.02) for NPH
0.53 (0.15 to 1.87)
0.323
0.1
1.0
10.0
Favours Gla-100
Favours NPH

C


Rate ratio (95% CI)
P value
Overall hypoglycaemia PG <70 mg/dL
Event rate (standard error): 8.73 (0.68) for Gla-100; 9.11 (0.70) for NPH
0.96 (0.77 to 1.19)
0.693
Overall hypoglycaemia PG <56 mg/dL
Event rate (standard error): 2.64 (0.25) for Gla-100; 3.09 (0.29) for NPH
0.85 (0.66 to 1.11)
0.234
Nocturnal hypoglycaemia PG <70 mg/dL
Event rate (standard error): 1.82 (0.19) for Gla-100; 2.62 (0.25) for NPH
0.69 (0.52 to 0.92)
0.010
Nocturnal hypoglycaemia PG <56 mg/dL
Event rate (standard error): 0.68 (0.09) for Gla-100; 1.04 (0.13) for NPH
0.66 (0.47 to 0.93)
0.018
Severe hypoglycaemia
Event rate (standard error): 0.05 (0.02) for Gla-100; 0.02 (0.01) for NPH
2.37 (0.63 to 8.91)
0.201
0.1
1.0
10.0
Favours Gla-100
Favours NPH