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Insulin glargine compared with premixed insulin for management of insulin-naïve type 2 diabetes patients uncontrolled on oral antidiabetic drugs: the open-label, randomized GALAPAGOS study

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ABSTRACT

Aims: Demonstrate superiority of insulin glargine (±glulisine) strategy versus premixed insulin strategy for percentage of patients reaching HbA1c <7% (<53 mmol/mol) at study end without any documented symptomatic hypoglycemia (bloof glucose [BG] ≤3.1 mmol/L) in type 2 diabetes (T2DM) patients failing oral agents.
Methods: This 24-week, open-label, multinational trial randomized patients to glargine OD or premix OD or BID, continuing metformin ± insulin secretagogue (IS). Second premix injection could be added any time; glulisine could be added with main meal in glargine OD patients with HbA1c ≥7% and fasting blood glucose (FBG) <7 mmol/L at week 12. IS was stopped with any second injection. Insulin titration targeted FBG ≤5.6 mmol/L.
Results: Modified intent-to-treat population comprised 923 patients (glargine, 462; premix, 461). Baseline characteristics were similar (mean T2DM duration: 9 years; HbA1c: 8.7% (72 mmol/mol); FBG: 10.4 mmol/L). Primary endpoint was achieved by 33.2% of glargine (±glulisine) and 31.4% of premix patients. Superiority was not demonstrated, but non-inferiority was (pre-specified margin: 25% of premix rate). More patients using premix achieved target (52.6% vs. 43.2%, $p = 0.005$); symptomatic hypoglycemia was less with glargine (1.17 vs. 2.93 events/patient–year).
Conclusions: Glargine (±glulisine) and premix strategies resulted in similar percentages of well-controlled patients without hypoglycemia, with more patients achieving target HbA1c with premix whereas overall symptomatic hypoglycemia was less with glargine.

1. Introduction

The objective of therapy for patients with type 2 diabetes (T2DM) is to achieve and maintain good glycemic control in order to minimize the risk of micro- and macrovascular long-term complications (Holman, Paul, Bethel, Matthews, & Neil, 2008; Ray et al., 2009; Turnbull et al., 2009). While lifestyle changes and oral antidiabetic drugs (OADs) may be sufficient initially, many patients eventually require insulin therapy (Handelsman et al., 2011; International Diabetes Federation: IDF Clinical Guidelines Task Force, 2012; Inzucchi et al., 2012). Basal insulin, such as the long-acting insulin analogues insulin glargine or insulin detemir, or the intermediate-acting neutral protamine Hagedorn (NPH) insulin, is most often recommended as initial insulin therapy (Handelsman et al., 2011; International Diabetes Federation: IDF Clinical Guidelines Task Force,

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2012; Inzucchi et al., 2012). However, a premixed insulin regimen is also frequently used in clinical practice. Systematic reviews and meta-analyses of glargine versus premix trials concluded that HbA1c reduction was greater with premix, but with a higher risk of hypoglycemia (Giugliano, Maiorino, Bellastella, Chiodini, & Esposito, 2011; Lasserson, Glasziou, Perera, Holman, & Farmer, 2009; Pontiroli, Miele, & Morabito, 2012).

Many patients who initiate insulin therapy with basal insulin or premix eventually need to intensify their insulin treatment (Handelsman et al., 2011; International Diabetes Federation: IDF Clinical Guidelines Task Force, 2012; Inzucchi et al., 2012). The strategy for intensification with premix entails adding another injection, but it is not uncommon in clinical practice to start insulin therapy with two injections of premix despite the lack of an evidence-based algorithm for it. For basal insulin, the regimen involves adding one injection of short-acting insulin at the main meal of the day. The latter strategy, often described as the 'basal plus' strategy, is a valid choice initiating intensification of a basal insulin-based regimen (Davidson, Raskin, Tanenberg, Vlajnic, & Hollander, 2011; Lankisch, Ferlinz, Leahy, & Scherbaum, 2008; Owens, Luzio, Sert-Langeron, & Riddle, 2011). Here, we report the results of the Insulins Glargine And gluLisine strAtegy versus Premixed insulin strAteGy: a cOmparative Study (GALAPAGOS), a 24-week clinical trial designed to demonstrate the superiority of an insulin glargine (±glulisine) strategy compared with a premix strategy.

2. Methods

2.1. Patients

Eligible individuals were insulin-naïve men and women with T2DM diagnosed more than 1 year ago, age 35 years or more, with a body mass index (BMI) <40 kg/m^2 and an HbA1c level of 7.0–10.5% (53–91 mmol/mol). They had to have been treated with lifestyle interventions and oral antidiabetic agents (OADs) for at least 3 months, with at least metformin at the maximum tolerated dose (≥1 g/day). Exclusion criteria included type 1 diabetes, current or anticipated pregnancy, or treatment with glucagon-like peptide-1 (GLP-1) agonists in the 3 months prior to study entry. Individuals with proliferative retinopathy or clinically relevant cardiovascular, hepatic, renal, neurological, other endocrine or major disease were also excluded. Written informed consent was obtained from all participants, and institutional review board/independent ethics committee approval was obtained for each participating study center.

2.2. Study design

This was a 24-week, randomized, open-label, parallel-arm, multinational, phase IV study conducted at 91 sites in Europe (44), Asia (32), and Latin America (15) between June 2010 and March 2012. The study included a 2-week screening period, followed by 24 weeks of treatment and 1 week of follow-up (Supplementary Fig. 1). There were five clinic visits at weeks–2 (selection), 0 (randomization), 12, 24 (end of treatment), and 25 (follow-up), plus telephone contact at weeks 1, 3, 4, 5, 8, 10, and 20. During the 2-week screening period, patients continued on their existing therapy, including diet, exercise, and stable dose of OADs. They were also trained to measure self-monitored blood glucose (SMBG) values using a blood glucose meter (Accu-CHEK Active, Roche Diagnostic, Indianapolis, IN, USA), and test strips were provided by the sponsor to record these in a log book.

At the end of the screening period, eligible patients were randomized (1:1) to receive either glargine (once a day) or premix (once or twice a day, based on the investigator's judgment). Randomization was conducted using an interactive voice response/interactive Web response system. The blocked randomization schedule was generated with alternating blocks of size 4 and 2, and randomization was stratified on center. Patients who started with one injection of glargine or premix continued to take their metformin, sulfonylureas, glinides, or dipeptidylpeptidase (DPP)-4 inhibitor therapy; any other diabetes treatments (e.g., thiazolidinediones, alpha-glucosidase inhibitors) were discontinued at this time. Patients who started with or later switched to two injections discontinued their use of sulfonylureas, glinides, or DPP-4 inhibitors at that time; metformin therapy was continued unchanged. No add-on or increase in OADs was permitted. Premixed insulin consisted of insulin aspart (30%) and protamine-crystallized insulin aspart (70%) in all countries except Mexico, where it consisted of insulin lispro (25%) and insulin lispro protamine (75%).

The dosing regimen followed the manufacturer's recommendations for insulin glargine or premix insulin. The starting dose of glargine was 0.2 U/kg or 12 U, given in the evening. For premix, the starting dose was 12 U at dinner if given once daily or 6 U each at breakfast and dinner if given twice daily. Patients on insulin glargine were to perform daily measurements of fasting blood glucose (FBG) before breakfast, while those on premix were to measure pre-meal BG before breakfast (and before dinner if two injections per day) daily. A forced insulin titration was implemented every 3 days where the goal was to achieve self-monitored fasting blood glucose (SMFBG) or pre-meal BG levels of 4.4–5.5 mmol/L (80–100 mg/dl) (Supplementary Fig. 1). Patients used the median of the last three SMBG values, with the exception that the lowest value was used if it was <4.4 mmol/L. An international titration committee reviewed SMBG values and insulin doses on an ongoing basis via a Web site, and the study investigators were contacted by e-mail if titration was inadequate.

Patients on premix could add another injection at any time during the 24 weeks. As recommended in basal plus protocols, patients on glargine for whom HbA1c remained ≥7% (≥53 mmol/mol) with FBG <7.0 mmol/L at the end of the first 12 weeks of treatment received in addition one injection per day of insulin glulisine prior (0–15 minutes) to the main meal of the day. They continued with glulisine injections until the end of the treatment period. The main meal was the one with the highest postprandial BG (PBG) on the three 7-point BG profiles performed before week 12. The starting glulisine dose was 4 U per day. Subsequent doses were titrated to achieve PBG <7.8 mmol/L, based on the previous three PBG values measured 2 hours after the start of the main meal (Supplementary Fig. 1).

Blood samples for HbA1c were collected at screening (week –2) or at least 4 days before the baseline visit (week 0), at least 72 hours before week 12, and at week 24. SMBG values were recorded on three consecutive days prior to the visit on weeks 2, 6, and 16. BG values were also recorded whenever the patient experienced any symptoms of hypoglycemia. Seven-point BG profiles were recorded on 3 consecutive days in the week prior to weeks 0, 12, and 24. Patients self-monitored their BG values immediately before and 2 hours after the start of breakfast, lunch, and dinner, and at bedtime, which was to be at least 2.5 hours after dinner. The dose of insulin, plus the time and number of injections, were recorded at each visit, including telephone visits. Hypoglycemic episodes were recorded throughout the study.

The primary endpoint was the proportion of patients achieving HbA1c <7.0% (<53 mmol/mol) at study end with no documented symptomatic hypoglycemia (confirmed by a BG ≤3.1 mmol/L) over the 24-week treatment period. Secondary endpoints included changes in HbA1c, percentage of patients who achieved HbA1c <7% (<53 mmol/mol) and <6.5% (<48 mmol/mol), seven-point PG profiles, body weight, insulin dose, hypoglycemia, and treatment-emergent adverse events (TEAEs). Documented symptomatic hypoglycemia was any event with clinical symptoms that was considered to have resulted from hypoglycemia and confirmed by a

BG ≤3.9 mmol/L or by a BG ≤3.1 mmol/L. Severe hypoglycemia was any event requiring the assistance of another person to administer carbohydrate, glucagon, or other resuscitative measures. A descriptive subgroup analysis of the number of insulin injections per treatment arm was also performed on the primary endpoint. The study is registered at ClinicalTrials.gov: NCT 01121835.

2.3. Statistical analysis

At least 784 assessable patients were needed (392 in each arm) in order to demonstrate that a two-sided Pearson chi-square test had 90% power to detect a treatment difference in rate at the 5% significance level, assuming 30% of patients reached the primary criterion in the glargine (±glulisine) group versus 20% in the premix group. Assuming an estimated 10% rate of non-assessable patients, 870 patients were to have been randomized (435 in each group).

All primary and secondary efficacy endpoints were assessed in a modified intent-to-treat (mITT) population, comprised of all randomized subjects who received study medication and who had at least one post-baseline assessment on-treatment of any primary or secondary efficacy variables. Additional analyses for the primary endpoint and change in HbA1c were also performed for the per protocol (PP) population, a subset of the mITT population that excluded patients with a major protocol violation.

The primary objective of the study was to show superiority of the glargine (±glulisine) strategy over a premix strategy in the percentage of patients who achieved the primary endpoint. The comparison between groups was performed with a Pearson chi-square test at the 5% level; the two-sided 95% confidence interval (CI) of the difference in success rate (glargine [± glulisine] – premix) was also calculated. The main analysis population was the mITT population, with analysis on the PP population considered as a supportive approach. If superiority was not demonstrated, switching to non-inferiority was predefined in the protocol objectives, with a prospectively defined non-inferiority margin of 25% of the premix rate. This stepwise closed testing approach ensured control of the type 1 error at the level of 5% for the primary endpoint. Two-sided 95% CIs of the difference were used. Non-inferiority was reached if the lower limit of the CI was higher than or equal to the prespecified margin. The non-inferiority analysis on the mITT population had to be confirmed on the PP population. *P*-values provided for secondary endpoints were not controlled for multiplicity.

The incidence and rates of hypoglycemia, body weight gain, insulin dose, and occurrence of adverse events were analyzed in the safety population, composed of all randomized and treated patients. A Pearson chi-square or Fisher's exact test was used for categorical variables, while an analysis of covariance was used for continuous variables, with treatment used as the fixed effect and baseline value as a covariate. Missing data were imputed by the last observation carried forward. The cumulative mean number of hypoglycemia events per patient throughout the study was drawn using the Nelson–Aalen method. The relationship between HbA1c at study end and event rate of hypoglycemia throughout the study was analyzed using a negative binomial regression model.

Univariate and multivariate analyses were performed to identify potential factors that predict a successful primary outcome. Univariate analyses were performed on a predefined number of candidate explanatory variables, with comparisons between subgroups made by chi-square tests. The candidate explanatory variables were gender, geographical region, age, BMI, number of antidiabetic medications, diabetes duration, and HbA1c at baseline. Risk ratios were calculated along with 95% CI and *p*-values. A stepwise logistic regression model was used for the multivariate analysis, adjusted for region. Odds ratios were calculated with their 95% CI and *p*-values from Wald chi-square tests.

3. Results

3.1. Patient disposition and characteristics

A total of 1243 patients were screened, and 934 were randomized (1:1) to treatment with glargine or premix (Supplementary Fig. 2). Three hundred nine patients (24.9%) failed screening, mainly due to failure to meet the inclusion/exclusion criteria (255 [20.5%]); most were due to out-of-range HbA1c (191 [15.4%]) or the patient not wishing to continue (43 [3.5%]). Of the 934 randomized patients, 11 (1.2%) were randomized but not treated: 4 (0.9%) in the glargine group and 7 (1.5%) in the premix group. A total of 923 (98.8%) patients were randomized and treated (glargine, 462; premix, 461). There were 860 patients who completed the 24-week study treatment: 438 (94.8%) in the glargine (±glulisine) group and 422 (91.5%) in the premix group. More patients in the premix group (8.5%) than in the glargine (±glulisine) group (5.2%) prematurely discontinued the 24-week study treatment ($p < 0.05$). For both treatment groups, the main reason for discontinuation was the patient not wishing to continue (1.9% for glargine [±glulisine] and 2.6% for premix). One patient (0.1%) was randomized to the premix group but received glargine instead. Therefore, the safety population comprised 463 patients treated with glargine (±glulisine) and 460 treated with premix. Baseline characteristics of the randomized patients were comparable with the total population and were balanced between the two treatment groups (Table 1).

3.2. Insulin dose and number of insulin injections

Among the 463 patients in the safety population treated with glargine, 197 (42.5%) also received insulin glulisine with the main meal beginning at week 12 (Supplementary Fig. 3). Glulisine was taken at breakfast (25.4% of patients), lunch (38.6%), or dinner (36.0%). In the premix group, 297 (64.6%) of the 460 patients started with one injection, while 163 (35.4%) started with two injections. Of those who started with one injection, 129 (43.4%) switched during the treatment period to two injections a day, for a total at the end of the treatment period of 292 (63.5%) patients who were treated with premix two times each day (Supplementary Fig. 3). At study end, 266 (57.5%) glargine and 168 (36.5%) premix patients remained on one injection. As expected, more patients on glargine than on a single premix insulin injection took concomitant sulfonylureas during the study period (57.5% vs. 36.5%).

The mean (standard deviation [SD]) starting dose was the same with glargine (0.17 [0.03] U/kg; 12.4 [2.1] U) and premix (0.17 [0.05] U/kg; 12.2 [2.9] U), while the overall dose at study end was 0.47 (0.33) U/kg (36.1 [24.7] U) with glargine (±glulisine) and 0.61 (0.46) U/kg (47.2 [35.8] U) for those treated with premix (Table 2). For those who received glargine + glulisine, the mean daily dose of glulisine starting at week 12 was 0.06 (0.02) U/kg (4.2 [1.4] U) and increased to 0.18 (0.16) U/kg (13.6 [11.5] U) at study end, for a total dose of 0.60 (0.38) U/kg (44.5 [28.6] U) at study end. The insulin dose at study end for those who remained on one injection of glargine was 0.38 (0.25) U/kg (29.8 [19.2] U). For those who remained on one premix injection, the insulin dose at study end was 0.27 (0.14) U/kg (20.9 [11.0] U), while the dose was 0.81 (0.46) U/kg (62.3 [36.4] U) for those taking two premix injections.

3.3. Efficacy outcomes

A similar percentage of patients treated with glargine (±glulisine) (33.2%) or premix (31.4%) achieved HbA1c <7% (<53 mmol/mol) at study end with no documented symptomatic hypoglycemia (BG ≤3.1 mmol/L) over the 24-week treatment period (Table 2). The glargine (±glulisine) strategy did not show superiority compared with a premix strategy on the primary endpoint (difference in success

rate = 1.8%; $p = 0.56$). Following the stepwise closed testing approach, non-inferiority of glargine (± glulisine) was demonstrated, as the lower limit of the 95% CI of the percentage difference was higher than the non-inferiority margin defined prospectively as 25% of the premix rate measure (95% CI [–4.32% to 7.91%]; non-inferiority margin –7.85%). Non-inferiority was confirmed in the PP population (difference in success rate = 2.7%; $p = 0.41$). The primary endpoint was met by 43.8% of those treated with glargine alone, 19.3% treated with glargine + glulisine, and 37.7% and 27.9% of those treated with once-daily and twice-daily premix, respectively.

Of the two components of the primary outcome, a greater percentage of patients using the premix strategy achieved HbA1c <7% (<53 mmol/mol) at study end (52.6% vs. 43.2%, $p = 0.005$), whereas more patients using the glargine (± glulisine) strategy had no documented symptomatic hypoglycemia during treatment (77.6% vs. 63.7%, $p < 0.001$; Table 2). HbA1c <7% (<53 mmol/mol) was achieved by 57.6% of those treated with glargine alone, 24.4% with glargine + glulisine, 55.7% with once-daily and 50.9% with twice-daily premix (Table 2). A total of 76.7% of patients treated with glargine alone had no documented hypoglycemia during treatment, 78.7% with glargine + glulisine, 69.8% with once-daily, and 60.3% with twice-daily premix (Table 2).

The primary outcome was attained by 24% of patients in the Middle and Central East, 29.0% in Latin America, 32.9% in Asia, and 36.5% in Europe. In addition to geographical region ($p = 0.039$), BMI ($p = 0.047$), number of antidiabetic medications ($p < 0.001$), diabetes duration ($p < 0.001$), and HbA1c at baseline ($p = 0.002$) were identified in univariate analyses as potential factors that predict a successful primary outcome. In the multivariate analysis (adjusting by geographical region), taking ≤1 antidiabetic medication at study entry ($p < 0.001$), diabetes duration of <5 years ($p < 0.001$), HbA1c <8.2% at baseline ($p < 0.001$), and living in Europe or Asia ($p = 0.012$) were significant factors that predicted success. There was also a region effect ($p = 0.012$), but the treatment effect was homogeneous between the regions (Supplementary Fig. 4).

Mean HbA1c values were the same at baseline in both groups (8.7%; 72 mmol/mol), decreased throughout the study, and were 7.2 (0.9) % (55 [10] mmol/mol) with glargine (± glulisine) and 7.0 (0.9) % (53 [10] mmol/mol) with premix at study end. The least squares (LS) mean change (standard error [SE]) from baseline to study end was –1.48 (0.04) % and –1.64 (0.04) % with glargine (± glulisine) and premix, respectively. The LS mean difference between groups was 0.16% (95% CI 0.04–0.27) in favor of premix ($p = 0.008$). FBG levels declined quickly in both groups, reaching a plateau between weeks 6–12. At study end, FBG was 6.0 (1.2) mmol/l in the glargine (± glulisine) group and 6.3 (1.4) mmol/l in the premix group. The LS mean change (SE) from baseline was greater with glargine (± glulisine) (–3.0 [0.06] mmol/l) than with premix (–2.6 [0.06] mmol/l), with an LS mean difference of –0.3 mmol/l (95% CI –0.5 to –0.2; $p < 0.001$).

The seven-point BG profile improved in both groups at study end, with the decline in BG more pronounced for glargine (± glulisine) before breakfast and for premix before lunch, after dinner, and at bedtime (Fig. 1). As a consequence, the mean daily BG declined from 10.3 (2.3) mmol/L at baseline to 7.9 (1.6) mmol/L at the end of the study with glargine (± glulisine) and from 10.5 (2.4) to 7.7 (1.4) mmol/L with premix. The LS mean difference between the groups was 0.2 mmol/L (95% CI 0.03–0.4]; $p = 0.024$), in favor of premix.

3.4. Hypoglycemia and safety

Hypoglycemia by overall group as well as by the number of injections is shown in Table 2. The incidence rate for overall symptomatic hypoglycemia confirmed by BG ≤ 3.1 mmol/L was less with glargine (± glulisine) than premix (22.0% vs. 35.2%), as was confirmed nocturnal symptomatic hypoglycemia (7.3% vs. 18.7%). The

Table 1
Baseline characteristics: modified intent-to-treat population.

	Glargine (n = 462)	Premixed insulin (n = 461)	All (n = 923)
Age, years	56.7 (9.0)	55.8 (9.5)	56.3 (9.2)
Female, *n* (%)	231 (50.0)	221 (47.9)	452 (49.0)
Weight, kg	75.7 (13.5)	76.0 (13.9)	75.8 (13.7)
Body mass index, kg/m^2	28.4 (4.7)	28.3 (4.4)	28.4 (4.5)
Duration of diabetes, years	9.1 (6.0)	8.8 (5.8)	8.9 (5.9)
Duration of OAD treatment, years	7.9 (5.8)	7.6 (5.5)	7.7 (5.7)
Patients with ≥1 late diabetes complication, *n* (%)	125 (27.1)	122 (26.5)	247 (26.8)
Number of meals and snacks	4.1 (1.0)	4.0 (1.0)	4.1 (1.0)
Any prior medication (except antidiabetics), *n* (%)	339 (73.2)	339 (73.7)	678 (73.5)
Prior antidiabetic drugs, *n* (%)			
Any prior OAD	461 (99.8)	461 (100)	922 (99.9)
Biguanides	460 (99.6)	461 (100)	921 (99.8)
Sulfonylureas	333 (72.1)	324 (70.3)	657 (71.2)
Glinides	35 (7.6)	33 (7.2)	68 (7.4)
GLP-1 agonist	1 (0.2)	0 (0.0)	1 (0.1)
Dipeptidylpeptidase-4 inhibitors	66 (14.3)	57 (12.4)	123 (13.3)
Alpha-glucosidase inhibitors	38 (8.2)	39 (8.5)	77 (8.3)
Thiazolidinediones	37(8.0)	43(9.3)	80 (8.7)
Blood pressure, mmHg			
Systolic	129 (14)	131 (14)	130 (14)
Diastolic	78 (8)	79 (8)	78 (8)
Cholesterol, mmol/L			
Total	4.7 (1.0)	4.7 (1.1)	4.7 (1.1)
LDL	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)
HDL	1.3 (0.3)	1.2 (0.3)	1.2 (0.3)
Triglycerides, mmol/L	1.9 (1.2)	2.0 (1.4)	2.0 (1.3)
HbA1c, % units	8.7 (0.9)	8.7 (0.9)	8.7 (0.9)
mmol/mol	72 (10)	72 (10)	72 (10)
Fasting blood glucose, mmol/L	8.9 (2.1)	9.0 (2.3)	8.9 (2.2)
Mean daily blood glucose, mmol/L	10.3 (2.3)	10.5 (2.4)	10.4 (2.3)

Mean (SD) or *n* (%).
Abbreviation: GLP, glucagon-like peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OAD, oral antidiabetic drug.

Table 2
Primary endpoint, insulin dose, and hypoglycemia — by number of injections.

	Glargine ± Glulisine			Premix		
mITT population	Overall (N = 455)	GLA (n = 258)	GLA + GLU (n = 197)	Overall (N = 446)	OD PRE (n = 159)	BID PRE (n = 287)
HbA1c <7% and no documented symptomatic hypoglycemia (BG ≤3.1 mmol/L), n (%)	151 (33.2)	113 (43.8)	38 (19.3)	140 (31.4)	60 (37.7)	80 (27.9)
HbA1c <7%, n (%)	196 (43.2)	148 (57.6)	48 (24.4)	234 (52.6)	88 (55.7)	146 (50.9)
No documented symptomatic hypoglycemia (BG ≤3.1 mmol/L), n (%)	353 (77.6)	198 (76.7)	155 (78.7)	284 (63.7)	111 (69.8)	173 (60.3)
Safety population	Overall (N = 463)	GLA (n = 266)	GLA + GLU (n = 197)	Overall (n = 460)	OD PRE (n = 168)	BID PRE (n = 292)
Insulin dose (U/kg), mean (SD)						
Starting	0.17 (0.03)	0.16 (0.03)	0.17 (0.03)	0.17 (0.05)	0.16 (0.03)	0.17 (0.05)
At study end	0.47 (0.33)	0.38 (0.25)	0.60 (0.38)	0.61 (0.46)	0.27 (0.14)	0.81 (0.46)
Symptomatic hypoglycemia (BG ≤3.1 mmol/L)						
Overall symptomatic, n (%)	102 (22.0)	60 (22.6)	42 (21.3)	162 (35.2)	48 (28.6)	114 (39.0)
Events/Patient–Year	1.17	1.14	1.20	2.93	2.11	3.40
Nocturnal symptomatic, n (%)	34 (7.3)	21 (7.9)	13 (6.6)	86 (18.7)	23 (13.7)	63 (21.6)
Events/Patient–Year	0.36	0.37	0.35	1.03	1.10	1.01
Symptomatic hypoglycemia (BG ≤3.9 mmol/L)						
Overall symptomatic, n (%)	211 (45.6)	118 (44.4)	93 (47.2)	251 (54.6)	74 (44.0)	177 (60.6)
Events/Patient–Year	4.51	4.17	4.85	8.37	5.52	10.03
Nocturnal symptomatic, n (%)	82 (17.7)	46 (17.3)	36 (18.3)	127 (27.6)	36 (21.4)	91 (31.2)
Events/Patient–Year	1.07	1.03	1.14	2.28	2.22	2.36

GLA, insulin glargine; GLU, insulin glulisine; PRE, premix; OD, once daily; BID, twice daily; BG, blood glucose.

estimated event rate (episodes/patient–year) of overall hypoglycemia confirmed by BG ≤3.1 mmol/L was less with glargine (±glulisine) than premix (1.17 vs. 2.93), as was nocturnal hypoglycemia (0.36 vs. 1.03). The incidence and event rates were similar in those who received only glargine or glargine + glulisine, whereas both the incidence and event rates were greater in those receiving premix twice daily vs. once daily. When hypoglycemia was confirmed by BG ≤3.9 mmol/L, the comparative results were similar (Table 2). There were 9 events of severe hypoglycemia (6 patients, 1.3%) in the glargine (±glulisine) group and 15 events (8 patients, 1.7%) in the premixed insulin group.

The relative risk for overall and nocturnal symptomatic hypoglycemia was significantly less with glargine (±glulisine) than with premix whether hypoglycemia was confirmed by BG ≤3.1 mmol/L or by BG ≤3.9 mmol/L (Fig. 2A–D). When the estimated event rate of overall hypoglycemia or nocturnal hypoglycemia confirmed by BG ≤3.1 mmol/L was plotted against HbA1c at study end, there was a greater risk with premix than glargine (±glulisine) treatment at all HbA1c levels, with the difference becoming greater as good glycemic control was approached (Fig. 3). At an HbA1c of 7.0% and hypoglycemia confirmed by BG ≤3.1 mmol/L, the estimated event rate of overall hypoglycemia was approximately 1.3 events/patient–year with glargine (±glulisine) and 2.9 with premix and was approximately 0.4 and 1.2 events/patient–year, respectively, for nocturnal hypoglycemia. With hypoglycemia confirmed by BG ≤3.9 mmol/L, the estimated event rate of overall hypoglycemia at an HbA1c of 7.0% was approximately 4.8 events/patient–year with glargine (±glulisine) and 8.7 with premix and was approximately 1.1 and 2.3 events/patient–year, respectively, for nocturnal hypoglycemia.

A similar percentage of patients treated with glargine (±glulisine) or premix experienced at least one TEAE (34.6% vs. 35.7%). TEAEs related to glargine or to premix were reported by 2.6% and 6.7% of patients, respectively. Eight patients reported TEAEs related to glulisine; TEAEs related to metformin occurred in three patients in each group. Serious TEAEs were reported in 5.0% of the premix group and in 2.6% of the glargine (±glulisine) group. One fatal TEAE (pulmonary embolism) occurred in the glargine (±glulisine) group. Mean body weight gain was similar for glargine (±glulisine) (1.1 kg) and premix (1.4 kg; the LS mean difference was not significant (−0.3 kg; $p = 0.12$).

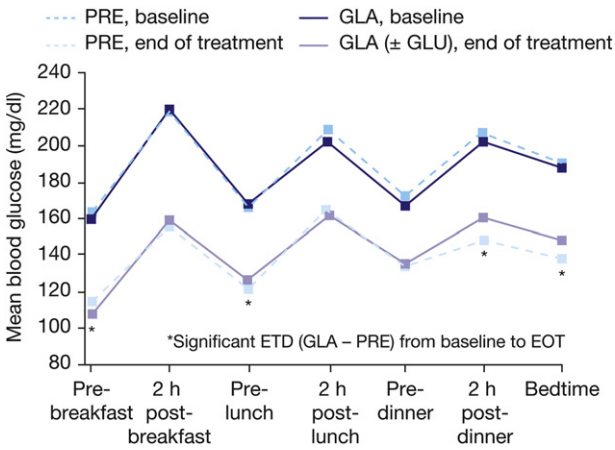

Fig. 1. Seven-point BG profile of overall groups at baseline and study end. Abbreviation: ETD, end of treatment difference; EOT, end of treatment; GLA, glargine; GLU, glulisine; PRE, premixed insulin.

4. Discussion

This trial was designed to compare the effects of two insulin-based strategies in subjects with T2DM who were not achieving adequate glycemic control with oral therapy. One strategy initiated insulin therapy with one injection a day of the basal insulin, insulin glargine, and added one injection of insulin glulisine, a rapid-acting insulin before the main meal if glycemic control was insufficient. This strategy (basal-plus) is a recommended second step when basal insulin is insufficient to achieve the therapeutic goal (Handelsman et al., 2011; International Diabetes Federation: IDF Clinical Guidelines Task Force, 2012; Inzucchi et al., 2012). The other strategy initiated insulin therapy with one or two injections of premixed insulin as needed. This strategy is in line with product information for premixed insulin use and with the way significant numbers of patients begin insulin therapy in routine clinical practice. The approach of the study aimed to more accurately represent the nature of therapy adjustment in routine clinical practice where further

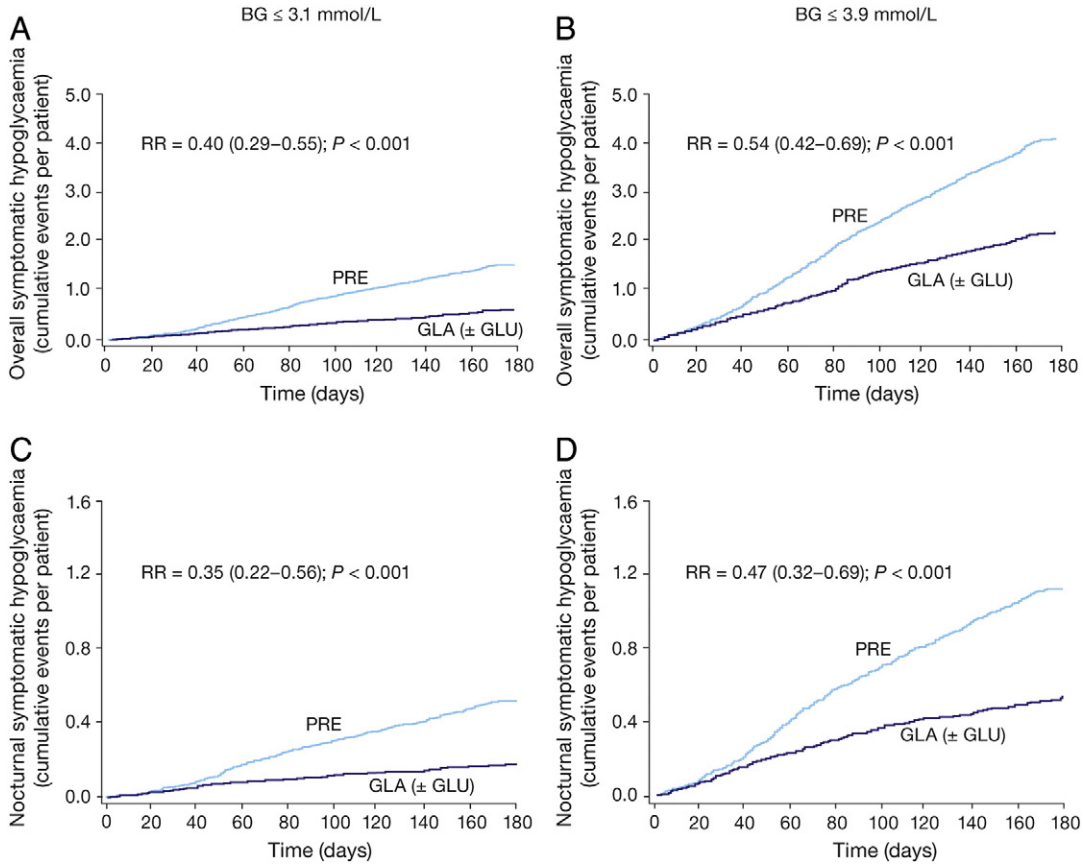

Fig. 2. Cumulative rates of overall (A, B) and nocturnal (C, D) symptomatic hypoglycemia confirmed with BG ≤3.1 (A, C) or BG ≤3.9 mmol/L (B, D): safety population. Abbreviations: BG, blood glucose; GLA, glargine; GLU, glulisine; PRE, premixed insulin; RR, relative risk.

titration/intensification was decided by the investigator rather than by a protocol-driven decision tree.

The primary objective of the study was to show superiority of the glargine (±glulisine) strategy on the composite endpoint of patients who achieved HbA1c <7% (<53 mmol/mol) at study end and who had no symptomatic hypoglycemia confirmed by BG ≤3.1 mmol/L throughout the treatment period. The composite endpoint was chosen as being more clinically relevant than either hypoglycemia or glycemic control alone, because the two are correlated. The use of the composite endpoint was based on previous findings that glargine, while less effective than premixed insulin in reducing HbA1c levels, had significantly less risk of hypoglycemia (Giugliano et al., 2011; Lasserson et al., 2009; Pontiroli et al., 2012). Thus, it could be expected that glargine (±glulisine) would be superior to premix using a composite efficacy/lack of hypoglycemia outcome as the primary endpoint. However, glargine (±glulisine) did not demonstrate superiority, though non-inferiority was demonstrated as a similar percentage of patients from both groups achieved the endpoint. However, titrating insulin glargine to an FBG target caused less overall and nocturnal hypoglycemia than a similar titration scheme for premix insulin, confirming earlier findings (Giugliano et al., 2011; Lasserson et al., 2009; Pontiroli et al., 2012).

Reasons for the failure to show superiority of glargine (±glulisine) may be related to limitations of the study. The availability of prandial insulin was different in the two groups. Patients in the premixed insulin group were given prandial insulin from the beginning and could add another injection at any time during the study, whereas those on glargine could only add one prandial insulin injection starting at week 12 as recommended in basal plus protocols. Thus, prandial insulin could be given twice daily with premixed insulin, compared with only once daily with glargine (±glulisine), and it could be given for the entire study duration in those who were initiated on a twice-daily dose, or at least for longer than in the glargine + glulisine group when the second premix injection was initiated prior to week 12. This disparity in dosing regimen led to a disparity in insulin dose, with patients on glargine (±glulisine) receiving less insulin over the course of the study, particularly when both groups received two injections. While limiting the use of rapid insulin in the glargine group to the second three months of the study was a limitation, this strategy assured an efficient titration of the basal insulin. Another possible limitation was the greater use of insulin secretagogues in patients on glargine than in patients on premix who received two injections. This may have contributed to the good response in the glargine-only group, even though the insulin dose was less. The withdrawal of insulin secretagogues when glulisine was added may have contributed to the relative ineffectiveness of the basal insulin strategy due to the absence of a prandial treatment at the other meals. Also, it is clear that postprandial and pre-meal glucose levels during the day contributed to overall glycemia with both regimens.

In a study with a similar composite endpoint, patients with poor glycemic control on metformin and sulfonylurea were randomized to add glargine or to stop OADs and to start premixed insulin twice daily (Malone, Kerr, Campaigne, Sachson, & Holcombe, 2004). Both regimens were strictly titrated to a fasting or preprandial blood glucose ≤5.6 mmol/L, and glargine was found to be superior to premix in achieving HbA1c <7% (<53 mmol/mol) without confirmed nocturnal hypoglycemia. Other studies have compared basal insulin and premixed insulin, albeit without a similar composite endpoint. In a 24-week study with a patient population similar to GALAPAGOS, treatment with glargine + glimepiride and metformin resulted in greater HbA1c reduction and less confirmed hypoglycemia than

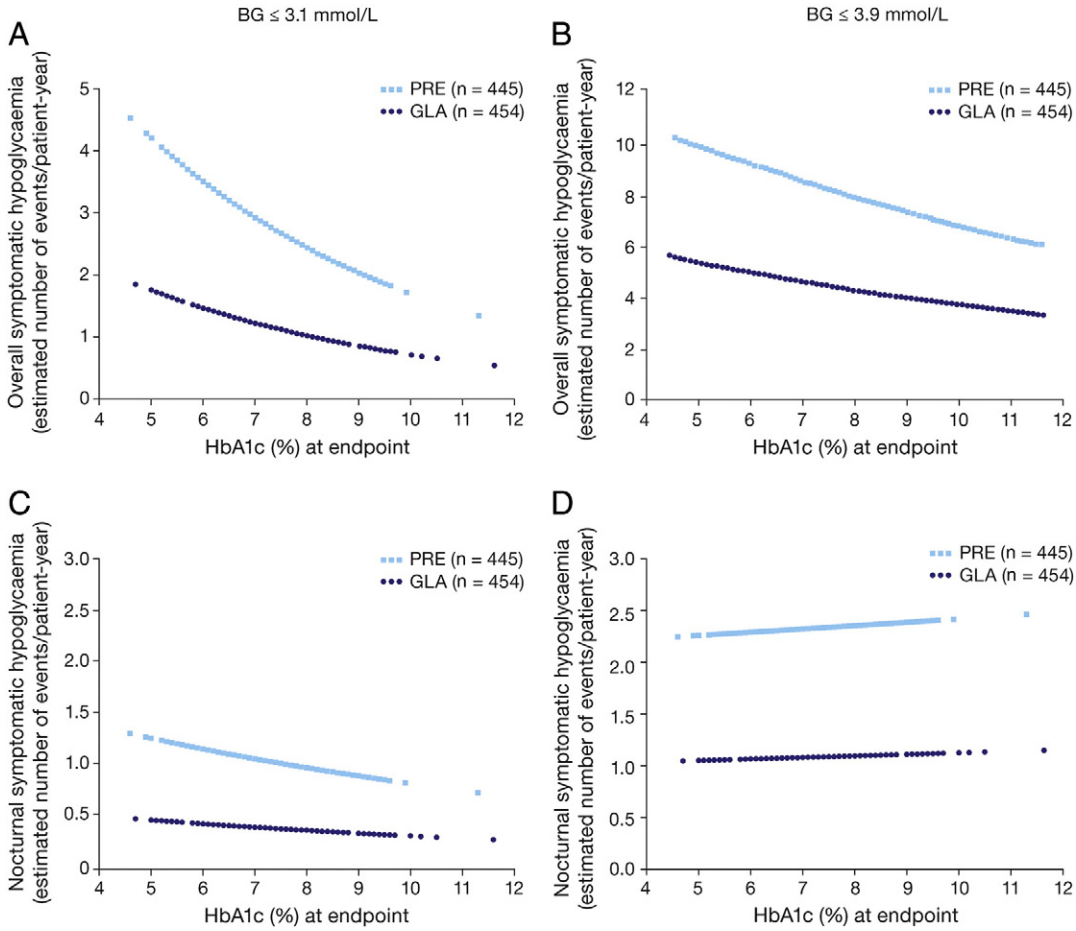

Fig. 3. Estimated rates of symptomatic hypoglycemia versus HbA1c at study end: overall (A, B) and nocturnal (C, D) symptomatic hypoglycemia confirmed by BG ≤3.1 mmol/L (A, C) or BG ≤3.9 mmol/L (B, D). Abbreviations: BG, blood glucose; GLA, glargine; PRE, premixed insulin.

treatment with a twice-daily premix without any concomitant OADs (Janka et al., 2005). More patients on glargine achieved targeted goals for HbA1c and FPG, while body weight gain was not significantly different between treatments. In the 4-T study (Holman et al., 2007), patients who were uncontrolled on maximum doses of metformin and sulfonylurea added either short-acting (three times a day), premix (twice a day), or basal insulin (insulin detemir, once or twice a day). By 24 weeks, premixed insulin and prandial insulin were slightly more efficacious than basal insulin but with greater risks of hypoglycemia, as in the current study, and weight gain.

The strategy of adding a rapid-acting insulin dose to basal insulin ("basal plus") was examined in a 6-month proof-of-concept study where patients who were on glargine for 3 months and who had HbA1c >7% (>53 mmol/mol) were randomized to either continue their prior OAD and glargine therapy or to add a single dose of glulisine immediately prior to the main meal for a further 3 months. More participants on glargine (+glulisine) reached HbA1c <7.0% (<53 mmol/mol) than on glargine only, with significantly greater reduction of HbA1c, while rates of hypoglycemia and mean weight change were comparable between the treatment groups (Owens et al., 2011). A more recent study randomized subjects with T2DM and HbA1c >7% to twice-daily premixed insulin, once-daily insulin glargine plus zero to one prandial insulin glulisine injection, or insulin glargine plus zero to three prandial injections (Riddle, Rosenstock, Vlajnic, & Gao, 2014). During the first 24 weeks of the trial, their results were quite similar to ours — mean HbA1c reduction was the same with premix and basal plus one prandial bolus, but the hypoglycemia rate was higher with premix. HbA1c did not improve during the following six months. In our study, adding an injection of prandial insulin to the basal insulin did not improve the glycemic control, even after reaching a sizeable dose.

In conclusion, our results show that a glargine- or premixed insulin-based regimen resulted in similar percentages of well-controlled patients without hypoglycemia, demonstrating non-inferiority, but not superiority, of glargine (±glulisine). More patients achieved HbA1c <7% (<53 mmol/mol) with premixed insulin, whereas overall symptomatic hypoglycemia was less with glargine. Hypoglycemia should be considered in evaluating the treatment benefit/risk.

Author contributions

P.A., B.S., F.G.-P., and A.C. contributed to the study design, data analysis, writing the manuscript, and critically re-reading the manuscript. W.L. contributed to the study design, study conduct/data collection, data analysis, writing the manuscript, and critically re-reading the manuscript. V.L. contributed to the study conduct/data collection, data analysis, and critically re-reading the manuscript. M.-P.D. contributed to the study design, data analysis, and critically re-reading the manuscript. V.P. contributed to the study conduct/data collection, data analysis, writing the manuscript, and critically re-reading the manuscript. All authors had free access to the data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2015.04.003.

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