original article

Randomized double–blind clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 2 diabetes: IMAGINE 4

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Aims: To evaluate the efficacy and safety of basal insulin peglispro (BIL) with those of insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (T2D).
Methods: In this phase III, multicentre, double-blind, 26-week study, we randomized patients with T2D [glycated haemoglobin (HbA1c) ≥ 7 and $<12\%$, on ≥ 1 insulin injections daily] to BIL (n = 691) or glargine (n = 678), in combination with lispro.
Results: At week 26, the primary objective of non-inferiority of BIL versus glargine for HbA1c reduction was achieved (least squares mean difference -0.21%; 95% confidence interval -0.31 to -0.11%), with statistical superiority of BIL with multiplicity adjustment ($p < 0.001$). HbA1c at baseline was 8.4% versus 8.5% for BIL versus glargine and at 26 weeks it was 6.8% versus 7.0%. At 26 weeks, more patients reached HbA1c $<7\%$ with BIL than with glargine (63.3% vs 53.3%; $p < 0.001$), the nocturnal hypoglycaemia rate (≤ 3.9 mmol/l) was lower with BIL (0.51 vs 0.92 events/30 days; $p < 0.001$), but the daytime hypoglycaemia rate was higher with BIL (5.47 vs 4.53 events/30 days; $p < 0.001$). The total hypoglycaemia relative rate was 1.10 ($p = 0.053$). At 26 weeks, patients in the BIL group had lower fasting serum glucose levels, higher basal insulin dosing, with no statistically significant difference in prandial or total insulin dosing, reduced glucose variability and less weight gain (1.3 kg vs 2.2 kg) compared with the glargine group. The BIL group had higher mean triglyceride and aminotransferase levels.
Conclusions: In patients with T2D, BIL with insulin lispro provided greater improvement in glycaemic control with less nocturnal hypoglycaemia, lower glucose variability and less weight gain compared with glargine. The daytime hypoglycaemia rate and mean triglyceride and aminotransferase levels were higher with BIL.
Keywords: basal insulin, glycaemic control, hypoglycaemia, randomized trial, type 2 diabetes

Introduction

The development and progression of type 2 diabetes (T2D) is characterized by insulin resistance and defects in pancreatic β-cell function [1,2]. Although T2D treatment is individualized, treatment intensification to basal insulin and eventually to basal-bolus therapy is required for a significant number of patients [2–4]. Intensive insulin therapy and glycaemic control increase the risk of hypoglycaemia [2,4,5]. The development of an ideal basal insulin with 24-h basal coverage, reduced hypoglycaemia risk, decreased glucose variability and effective suppression of hepatic glucose production, with minimal weight gain and/or weight loss, has not yet been fully achieved [6],

although newer basal insulins such as degludec and glargine U-300 have some of the aforementioned attributes [7,8].

Basal insulin peglispro (BIL) is a novel basal insulin analogue comprised of insulin lispro covalently bound to a 20 kDa polyethylene glycol moiety, and has a larger hydrodynamic size than lispro [9]. BIL has delayed absorption and reduced clearance, with a half-life of 2–3 days in patients with T2D [10,11]. In healthy subjects and in patients with type 1 diabetes (T1D), BIL resulted in similar inhibition of hepatic glucose output, but reduced stimulation of glucose disposal compared with glargine [12–14]. Patients with T1D treated with equivalent therapeutic concentrations of BIL versus glargine had significantly higher free fatty acid and glycerol levels during euglycaemic clamp [12]. These human data are consistent with a conscious dog study showing that BIL had a peripheral-to-hepatic activity distribution more like endogenous insulin [15].

The present 26-week, double-blind, phase III study is the first trial to evaluate the efficacy and safety of BIL compared with insulin glargine U-100, both in combination with prandial

insulin lispro, in patients with T2D previously treated with insulin.

Materials and Methods

This phase III, double-blind, randomized, controlled, multinational, parallel-arm trial was approved by local ethics committees and conducted according to International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all patients. An unblinded independent data monitoring committee monitored patient safety. The study was conducted from January 2012 to August 2013 at 156 sites in 24 countries by endocrinologists or physicians with insulin clinical trial expertise (Appendix S1, Supporting Information). The clinical trial registry number was: NCT01468987.

Participants

Adults (aged ≥ 18 years) with T2D [16] [glycated haemoglobin (HbA1c) ≥7.0 and <12.0%] treated with one or more insulin injections daily were eligible. Participants were allowed to continue metformin; other oral antihyperglycaemic medications were discontinued at randomization. Appendix S2, Supporting Information shows the additional inclusion/exclusion criteria.

Study Design and Treatment

The study included a 2-week pre-randomization period, including electronic diary (e-diary) collection of baseline hypoglycaemia data, 26 weeks of double-blind treatment, and a 4-week safety follow-up period after discontinuation of study basal insulin (Figure S1, Supporting Information). Randomization (1 : 1 BIL:glargine) was stratified by HbA1c (≤8.5, >8.5%), LDL cholesterol (<2.6, ≥2.6 mmol/l), country and baseline number (1, 2, ≥3) of daily insulin injections (Appendix S3, Supporting Information). Lipid and hepatic criteria for study insulin discontinuation are listed in Appendix S4, Supporting Information.

Study basal insulins were injected once daily at approximately the same time at bedtime using a syringe and covered vial for blinding purposes. Based on phase II studies, BIL was formulated at 900 nmol/ml to achieve a U-100 concentration, as 9 nmol BIL has approximately the same effect on glycaemic measures as 1 unit of glargine [17]. Insulin lispro was injected by disposable pen with meals, starting at randomization. A customized wireless e-diary system was used to collect self-monitored blood glucose (SMBG) values, hypoglycaemic events/outcomes, and insulin dosing data [18]. A treat-to-target algorithm was used with a fasting/pre-meal SMBG goal of 5.6 mmol/l and a bedtime goal of 7.2 mmol/l (Appendix S5, Supporting Information). The e-diary included the three protocol bolus dosing plans (Appendix S5, Supporting Information) and provided basal and bolus protocol algorithm dosing recommendations, which could be adjusted by investigators for individual patient considerations. Insulin dosing was assessed weekly for 12 weeks and thereafter at each visit, or more often as needed.

Hypoglycaemia was defined as SMBG ≤3.9 mmol/l or hypoglycaemia signs/symptoms. Nocturnal hypoglycaemia was defined both as an event between bedtime and waking, as recorded by the patient in the e-diary, and between 22:00 and 10:00 hours, as e-diaries collected SMBG values with the time/date of measurement. Hypoglycaemia at other times was defined as daytime hypoglycaemia. Documented symptomatic hypoglycaemia was defined as both signs/symptoms and SMBG ≤3.9 mmol/l. Severe hypoglycaemia was investigator-determined as accompanied by neurological impairment requiring medical assistance to administer carbohydrates, glucagon, other resuscitative actions. Patients performed SMBG with daily 4-point SMBG profiles (fasting, pre-meal, bedtime), two 9-point SMBG profiles (fasting, post-morning meal, pre-/post-midday/evening meal, bedtime, 03:00 hours, next day fasting) the week before pre-specified visits, and whenever hypoglycaemia was suspected.

Deaths and non-fatal cardiovascular events including myocardial infarction, stroke and hospitalization for unstable angina were adjudicated by an independent Clinical Endpoint Committee. Lipid-lowering therapy adjustments were prohibited from week 0 to week 12.

Sample Size and Statistical Analysis

A total of 1369 randomized patients provided ≥99% statistical power to demonstrate non-inferiority of BIL to glargine [margin = 0.4%] for HbA1c change from 0 to 26 weeks, with assumptions of no treatment difference, standard deviation 1.1%, a two-sided α value of 0.05, and a 20% dropout rate. This sample size also provided ≥80% power to demonstrate the superiority of BIL over glargine for HbA1c change, nocturnal hypoglycaemia rate, and fasting serum glucose (FSG) level.

Data were analysed according to the pre-defined statistical analysis plan. The primary objective was non-inferiority of BIL to glargine for HbA1c change from week 0 (baseline) to week 26. To control for overall type 1 error at $\alpha = 0.05$, a sequential gatekeeping strategy was used to adjust for multiplicity for the primary and six key secondary objectives [19]. The gated objective was achieved if all preceding objectives were met, and the objective reached statistical significance at $\alpha = 0.05$. The gated secondary objectives (in order) were: superiority of BIL to glargine at 26 weeks for: nocturnal hypoglycaemia rate, proportion of patients with HbA1c <7% and no nocturnal hypoglycaemia, HbA1c change from baseline, proportion of patients with HbA1c <7%, FSG level and total hypoglycaemia rate. Other analyses were not adjusted for multiplicity.

Analyses (sas 9.1 or higher, Cary, NC, USA) were conducted in all randomized patients who received at least one study insulin dose. Mixed-model repeated measures analysis was used for continuous outcomes with repeated post-baseline measurements. Between-treatment differences are presented as least squares (LS) mean (BIL-glargine). Analysis of variance or analysis of covariance was used for continuous variables collected at baseline and/or endpoint. Logistic regression was used for categorical efficacy outcomes and Fisher's exact test for other categorical outcomes. Negative binomial regression was used to analyse the hypoglycaemia rate [20]. The baseline value of the analysis variable was included as a covariate in the analysis

Table 1. Patient demographic and baseline characteristics.

	Glargine (n = 678)	BIL (n = 691)
Age, years	57.8 ± 9.2	57.4 ± 9.2
Men, n (%)	404 (59.6)	376 (54.4)
Race, n (%)		
American-Indian or Alaskan Native	2 (0.3)	2 (0.3)
Asian	30 (4.4)	25 (3.6)
Black or African-American	50 (7.4)	42 (6.1)
Multiple	9 (1.3)	5 (0.7)
Native Hawaiian or Other Pacific Islander	2 (0.3)	2 (0.3)
White	585 (86.3)	615 (89.0)
Hispanic or Latino ethnicity, n (%)	78 (11.5)	74 (10.7)
Weight, kg	95.8 ± 19.5	96.1 ± 19.8
Body mass index, kg/m^2	33.0 ± 5.6	33.3 ± 5.7
Duration of diabetes, years	14.2 ± 7.8	14.1 ± 7.0
HbA1c ≤8.5%, n (%)	396 (58.4)	426 (61.6)
Basal insulin at baseline, n (%)		
Glargine	329 (49)	345 (50)
NPH (Isophane)	90 (13)	87 (13)
Detemir	97 (14)	90 (13)
Insulin premix	121 (18)	136 (20)
Other	2 (<1)	<1 (<1)
Baseline number of insulin injections, n (%)		
1	160 (23.6)	171 (24.7)
2	134 (19.8)	136 (19.7)
≥3	384 (56.6)	384 (55.6)
Bolus insulin dosing plan, n (%)		
Carbohydrate counting	93 (14)	104 (15)
Preprandial action plan with fixed diet	172 (25)	167 (24)
Pattern adjustment plan	413 (61)	420 (61)
Lipid-lowering medications, n (%)		
Statins	421 (62.1)	429 (62.1)
Non-statin lipid lowering medications	124 (18.3)	122 (17.7)
Hypertension, n (%)	577 (85.1)	590 (85.4)

BIL, basal insulin peglispro; HbA1c, glycated haemoglobin.
Data are mean ± standard deviation, unless otherwise noted.

model when applicable. All tests were conducted at two-sided $\alpha = 0.05$, and 95% confidence intervals (CIs) calculated.

Results

A total of 1369 patients were randomly assigned to treatment with BIL (n = 691) or glargine (n = 678), with similar demographic/baseline characteristics between groups (Table 1). Metformin use during the study was similar between groups: 69.5% BIL, 68.5% glargine. Baseline data were similar between groups except for laboratory FSG values (Table 2). Patient disposition was similar in the two groups (Figure S2, Supporting Information).

The primary objective of non-inferiority of BIL compared with glargine for change in HbA1c at week 26 was achieved with an LS mean difference of −0.21% (95% CI −0.31 to −0.11%), with p < 0.001 indicating statistical superiority of BIL versus glargine with multiplicity adjustment (Table 2 and Figure 1A). The results of multiple sensitivity analyses, including per-protocol analysis for HbA1c, were consistent with the primary analysis results.

Treatment with BIL resulted in more patients achieving the HbA1c goal of <7.0% than with glargine [63.3% vs 53.3%; p < 0.001 (Figure 1B)] and more patients achieving the HbA1c goal of ≤6.5% (44.4% vs 32.6%; p < 0.001) at week 26. More BIL- than glargine-treated patients reached the HbA1c goal of <7.0% at week 26 without any episodes of nocturnal hypoglycaemia between weeks 0 and 26 (24.4% vs 12.2%; p < 0.001). BIL-treated patients also had lower laboratory FSG values than glargine-treated patients at week 26 (LS mean difference −0.37 mmol/l (95% CI −0.67 to −0.07; Table 2 and Figure 1C).

Fasting blood glucose, assessed using SMBG values, was not significantly different between the BIL and glargine groups at week 26 [7.8 ± 0.1 mmol/l vs 7.5 ± 0.1 mmol/l; p = 0.056 (Figure 1D)]. Nine-point SMBG profiles at week 26 showed lower SMBG values at midday post-meal and evening pre-/post-meal with BIL than with glargine (Figure 1D). At week 26, the BIL group also had a smaller magnitude of overnight glucose excursion compared with glargine from bedtime to pre-morning meal (LS mean difference 0.6 mmol/l; p = 0.005).

Between-day glucose variability, as measured by fasting blood glucose standard deviation 7 days before the visit, was lower with BIL than with glargine at week 26 (1.6 ± 0.04 mmol/l vs 1.9 ± 0.04 mmol/l; p < 0.001). Within-day glucose variability, as measured by nine-point SMBG profile standard deviation, was also lower with BIL than with glargine at week 26 (2.5 ± 0.1 mmol/l vs 2.7 ± 0.1 mmol/l; p = 0.023).

Nocturnal hypoglycaemia and documented symptomatic nocturnal hypoglycaemia rates and incidences were significantly lower with BIL than with glargine throughout the treatment period (Table 2 and Figure 1E). From weeks 0 to 26, the relative rate of nocturnal hypoglycaemia for BIL:glargine was 0.55 (95% CI 0.47, 0.65; p < 0.001).

The total hypoglycaemia relative rate from weeks 0 to 26 for BIL:glargine was 1.10 (95% CI 1.00, 1.21; p = 0.053), driven by a higher total hypoglycaemia rate with BIL from weeks 12 to 26, as there was no significant difference between groups from weeks 0 to 12 (Table 2 and Figure 1F). Total hypoglycaemia incidence and documented symptomatic hypoglycaemia rate/incidence from 0 to 26 weeks were similar (Table 2). The daytime hypoglycaemia relative rate was higher with BIL than with glargine [1.21 (95% CI 1.09, 1.34); p < 0.001 (Table 2)]. The percentage of symptomatic hypoglycaemia episodes (BIL 46%; glargine 46%) and mean SMBG associated with symptomatic hypoglycaemia (BIL 3.3 mmol/l; glargine 3.3 mmol/l) were not different (p = 0.90). Cumulative total hypoglycaemia events/100 patients over 26 weeks were not different (Figure S3A, Supporting Information). Cumulative nocturnal hypoglycaemia events/100 patients over 26 weeks were lower with BIL than with glargine (Figure S3B, Supporting Information). There were no significant differences between the BIL and glargine groups in the rate or incidence of severe hypoglycaemia (Table 2).

The basal insulin dose (units/day and units/kg/day) was significantly higher with BIL from weeks 3 to 26 (p < 0.05; Figure 2A). At week 26, the mean basal insulin dose for BIL was 67.6 ± 1.2 units/day (0.68 ± 0.01 units/kg/day) and for glargine was 60.3 ± 1.2 units/day (0.60 ± 0.01 units/kg/day;

Table 2. Baseline values and treatment outcomes at 26 weeks.

| Outcome | Baseline* | | 26 weeks | | |
	Glargine (N = 678)	BIL (N = 691)	Glargine (N = 678)	BIL (N = 691)	p
HbA1c, %†	8.47 ± 0.04	8.38 ± 0.04	6.97 ± 0.04	6.76 ± 0.04	<0.001
Change from baseline	—	—	−1.45 ± 0.04	−1.66 ± 0.04	
LS mean difference (95% CI)		—	−0.21 (−0.31, −0.11)		
FSG, mmol/l†	9.1 ± 0.1	8.7 ± 0.1	7.3 ± 0.1	7.0 ± 0.1	0.015
Nocturnal hypoglycaemia rate‡	0.90 ± 0.08	0.84 ± 0.08	0.92 ± 0.05	0.51 ± 0.03	<0.001
Nocturnal hypoglycaemia incidence, n (%)	163 (24.1)	158 (22.9)	500 (74.0)	410 (59.5)	<0.001
Documented symptomatic nocturnal hypoglycaemia rate‡	0.30 ± 0.04	0.38 ± 0.05	0.48 ± 0.04	0.24 ± 0.02	<0.001
Documented symptomatic nocturnal hypoglycaemia incidence, n (%)	65 (9.6)	81 (11.8)	327 (48.4)	252 (36.6)	<0.001
Total hypoglycaemia rate‡	3.58 ± 0.20	3.10 ± 0.18	5.42 ± 0.19	5.97 ± 0.20	0.053
Total hypoglycaemia Incidence, n (%)	390 (57.7)	374 (54.3)	653 (96.6)	656 (95.2)	0.26
Documented symptomatic hypoglycaemia rate‡	1.02 ± 0.09	1.14 ± 0.10	2.60 ± 0.15	2.80 ± 0.16	0.34
Documented symptomatic hypoglycaemia incidence, n (%)	169 (25.0)	190 (27.6)	562 (83.1)	575 (83.5)	0.95
Daytime hypoglycaemia rate‡	2.68 ± 0.17	2.26 ± 0.14	4.53 ± 0.17	5.47 ± 0.20	<0.001
Daytime hypoglycaemia incidence, n (%)	340 (50.3)	327 (47.5)	643 (95.1)	651 (94.5)	0.72
Severe hypoglycaemia rate¶	3.59 ± 3.59	0 ± 0.0	4.72 ± 1.91	5.28 ± 1.34	0.81
Severe hypoglycaemia incidence, n (%)	1 (0.1)	0 (0.0)	10 (1.5)	16 (2.3)	0.15
Anti-BIL treatment-emergent antibody response§ n (%)	—	—	161 (24.0)	152 (22.3)	0.33
Systolic blood pressure‡ mm Hg	133 ± 0.6	134 ± 0.6	135 ± 0.5	136 ± 0.5	0.51
Diastolic blood pressure‡ mm Hg	77 ± 0.4	78 ± 0.4	78 ± 0.4	78 ± 0.4	0.93
Triglycerides‡ mmol/l	1.66 ± 0.04	1.69 ± 0.04	1.60 ± 0.03	1.91 ± 0.03	<0.001
HDL cholesterol‡ mmol/l	1.24 ± 0.01	1.25 ± 0.01	1.23 ± 0.01	1.20 ± 0.01	<0.001
LDL cholesterol‡ mmol/l	2.47 ± 0.03	2.46 ± 0.03	2.56 ± 0.03	2.53 ± 0.03	0.47
Total cholesterol‡ mmol/l	4.45 ± 0.04	4.47 ± 0.04	4.52 ± 0.03	4.58 ± 0.03	0.14
ALT‡ IU/l	27.8 ± 0.6	27.8 ± 0.5	27.2 ± 0.5	35.4 ± 0.5	<0.001
AST‡ IU/l	24.1 ± 0.4	24.7 ± 0.4	24.3 ± 0.4	28.7 ± 0.4	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, basal insulin peglispro; FSG, fasting serum glucose; HbA1c, glycated haemoglobin; s.e., standard error.

*Baseline values were not significantly different between groups (p > 0.05), except for FSG (p = 0.026).

†Least squares mean ± s.e.

¶Events/patient/100 years; aggregated rate ± standard deviation.

‡Events/patient/30 days; group mean ± s.e.

§Treatment-emergent antibody response defined as change from baseline to post-baseline in the anti-BIL antibody level either from undetectable to detectable, or from detectable to the value with at least 130% relative increase from baseline.

p < 0.001). At week 26, the mean bolus (BIL 61.1 ± 1.7 units/day vs glargine 62.8 ± 1.7 units/day) and total insulin (BIL 126 ± 2.6 units/day vs glargine 121 ± 2.6 units/day) doses were not statistically significantly different between the groups. There was no statistically significant difference between groups in investigator adherence to the basal insulin algorithm over 26 weeks. Weight increased with both treatments, and at week 26, patients in the BIL group had significantly less weight gain compared with baseline than those in the glargine group [LS mean change 1.3 kg vs 2.2 kg; p < 0.001 (Figure 2B)].

With the pre-specified gate-keeping strategy for the primary and six key secondary objectives, the superiority of BIL versus glargine at 26 weeks with regard to nocturnal hypoglycaemia rate, proportion of patients achieving HbA1c <7% without nocturnal hypoglycaemia, HbA1c change, proportion of patients with HbA1c <7%, and FSG was statistically significant with multiplicity adjustment. The sixth objective of superiority of BIL versus glargine for total hypoglycaemia rate from 0 to 26 weeks did not meet the gate-keeping test for multiplicity.

Subgroup analyses for the stratification factor of baseline number of insulin injections/day (1, 2, ≥3; Table 1) were also performed. There were no significant treatment by subgroup interactions (p > 0.1) for HbA1c change or nocturnal or total hypoglycaemia rate from 0 to 26 weeks. BIL-treated patients had higher rates of total hypoglycaemia in all three subgroups than glargine-treated patients; however, patients with one baseline insulin injection had the highest relative risk (BIL:glargine) of 1.23, and patients with ≥3 baseline injections had the lowest relative risk of 1.05 from 0 to 26 weeks.

Overall, treatment-emergent adverse events and severe adverse events were similar in the two treatment groups (Table S1, Supporting Information). Eleven (1.6%) BIL- versus no glargine-treated patients experienced prospectively defined injection site reaction treatment-emergent adverse events, primarily lipohypertrophy (n = 8, 1.2%). There was no difference in treatment-emergent anti-BIL antibody response between treatments (Table 2).

Adjudicated major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, were similar for BIL and glargine [1.01
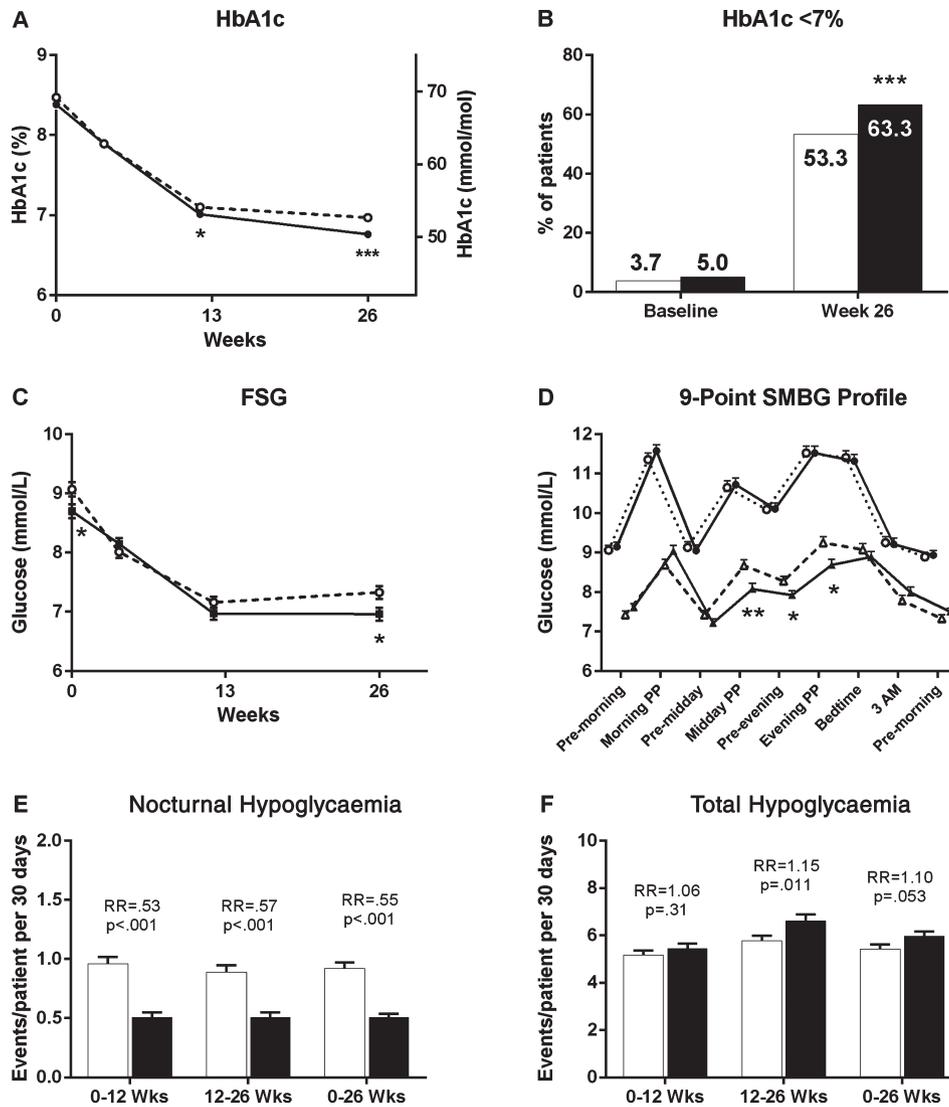
Figure 1. Glycaemic and hypoglycaemia outcome measures over 26 weeks of treatment for basal insulin peglispro (BIL)- and glargine-treated patients. (A) Glycated haemoglobin (HbA1c) over time [least squares (LS) mean ± standard error (s.e.)]. (B) Proportion of patients with HbA1c <7% at baseline and 26 weeks. (C) Fasting serum glucose (FSG) over time (LS mean ± s.e.). (D) Nine-point SMBG profiles by treatment at baseline and 26 weeks (LS mean ± s.e.). (E) Nocturnal hypoglycaemia rate (group mean ± s.e.). (F) Total hypoglycaemia rate (group mean ± s.e.). White markers or bars/dashed line = glargine; black markers or bars/solid line = BIL. PP, 2-h postprandial; RR, relative rate; SMBG, self-monitored blood glucose. *p < 0.05; **p < 0.01; ***p < 0.001 for differences between treatments.

and 0.89%, hazard ratio 1.14 (95% CI 0.38, 3.40) p = 0.81]. MACE+, which included unstable angina hospitalization, were similar for BIL and glargine (1.45 and 1.18%, hazard ratio 1.23 (95% CI: 0.48, 3.10) p = 0.67). Six deaths occurred; four (0.58%) in the BIL- and two (0.30%) in the glargine-treated group. There were no treatment differences in blood pressure from week 0 to week 26 (Table 2).

Mean triglyceride levels increased from week 0 (baseline) to week 4 and remained stable overall up to week 26 in the BIL group, with 13% higher triglyceride levels with BIL than with glargine at week 26 and a LS mean difference (BIL-glargine) 0.30 mmol/l (p < 0.001) at week 26 (Table 2 and Figure 2C). At study endpoint (including 4 weeks after discontinuation of BIL), triglyceride levels returned to baseline

with BIL and were similar in the two groups. Nine patients (1.3%) in the BIL group and six (0.9%) in the glargine group met the discontinuation criteria of triglycerides >6.8 mmol/l. HDL cholesterol decreased from weeks 0 to 4 with BIL and remained stable overall up to week 26, resulting in a statistically significant treatment difference of −0.03 mmol/l at week 26 (Table 2 and Figure S4B, Supporting Information). At study endpoint, HDL cholesterol levels returned to baseline with BIL and were higher with BIL than with glargine. There were no statistically significant treatment differences in LDL cholesterol or total cholesterol at week 26 (Table 2 and Figure S4C and D, Supporting Information). There were no significant group differences in use (Table 1) or changes to lipid-lowering medications.
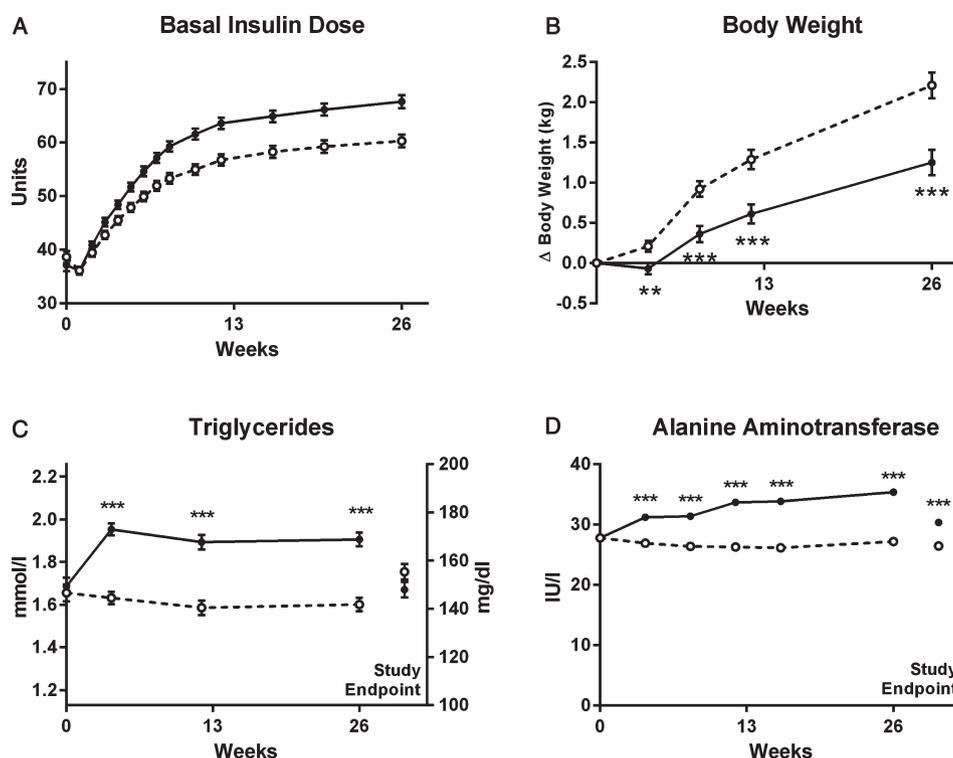
Figure 2. Insulin dose, body weight, serum triglyceride, and alanine aminotransferase (ALT) change over 26 weeks of treatment. (A) Basal insulin dose. Treatment difference was statistically significant (p < 0.05) from weeks 3–26. (B) Change in body weight. (C) Serum triglyceride. (D) ALT. All data are least squares mean ± standard error. White markers or bars/dashed line = glargine; black markers or bars/solid line = basal insulin peglispro (BIL). Study endpoint indicates last visit completed including 4-week follow-up visit. *p < 0.05; **p < 0.01; ***p < 0.001 for differences between treatments.

With BIL treatment, mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased from baseline to week 26 by 27% and 16%, respectively, and there were LS mean treatment differences of 8.2 IU/l and 4.4 IU/l, respectively, at week 26. Mean ALT and AST levels decreased at study endpoint, including after discontinuation of BIL, but remained statistically significantly different from baseline and between groups (Table 2 and Figure 2D). Mean ALT and AST levels remained within or slightly above the central laboratory reference ranges. Twelve patients (1.8%) in the BIL group and five (0.7%) in the glargine group experienced ALT elevation ≥3 × upper limit of normal (ULN) during treatment (p = 0.14), with one additional patient in each group experiencing ALT >3 × ULN during the post-treatment follow-up period. Among the 12 BIL-treated patients, 11 patients had a reduction in ALT to <3 × ULN during the study with nine patients continuing treatment and two patients discontinuing BIL and completing study visits. No patients in the BIL group and two in the glargine group experienced elevations in total bilirubin ≥2 × ULN.

Discussion

In this double-blind, basal-bolus study of patients with T2D previously treated with insulin, treatment with BIL compared with insulin glargine resulted in a statistically significantly greater reduction in HbA1c at 26 weeks. Both treatment groups had significant improvement in HbA1c during the study, with

26-week mean HbA1c values of 6.8% with BIL versus 7.0% with glargine, indicating that the glargine group overall had effective insulin titration to reach glycaemic goals. More BIL-treated patients were able to reach target HbA1c of <7.0% and had greater reduction in FSG versus glargine-treated patients. Although the HbA1c treatment difference was modest and not clinically significant in the present study, the BIL phase III programme included six studies in patients with T1D or T2D and resulted in 0.2–0.5% greater HbA1c reductions versus glargine or NPH over 26, 52 and 78 weeks [21–25]. These results may be related to reduced glucose variability and the time–action profile of BIL, which allowed optimization of basal insulin uptitration.

The reduction in HbA1c with BIL was accompanied by a 45% relative rate reduction in nocturnal hypoglycaemia, a key barrier in the ability to titrate basal insulin to reach glycaemic goals. In addition, more BIL-treated patients reached target HbA1c <7% without any episodes of nocturnal hypoglycaemia over 26 weeks. Basal insulin dose was ~11% higher with BIL than with glargine at week 26, suggesting that BIL dosing may be optimized to reach glycaemic targets due to a reduced risk of nocturnal hypoglycaemia and less glucose variability. Greater reduction in afternoon/evening SMBG levels when the effects of bedtime dosing of glargine may be waning, as well as longer duration of action, may have also contributed to the greater improvement in glycaemic control with BIL. The total hypoglycaemia rate was 10% higher with a 21% increase in daytime

hypoglycaemia rate with BIL versus glargine. Approximately 25% of patients were treated with one insulin injection/day at baseline, and these patients had an increased relative risk of total hypoglycaemia with the transition to basal-bolus therapy compared with patients previously treated with basal-bolus therapy. Although basal insulin dosing was higher and BIL had a greater effect on glycaemic variables, there was statistically significantly less weight gain with BIL compared with glargine.

Bolus dosing was not significantly different between groups in this 26-week study; however, in the 52-week double-blind IMAGINE 3 study in patients with T1D, there was a 30% decrease in bolus insulin dose and a 29% increase in basal insulin dose with BIL versus glargine [25]. In this T1D study, when bolus insulin dosages were adjusted over longer time periods, total and daytime hypoglycaemia rates did not differ between treatments from 26 to 52 weeks. In addition, in T2D basal insulin-only studies, including a double-blind study, nocturnal hypoglycaemia rates were reduced by 26–59% with no significant differences in total or daytime hypoglycaemia rates with BIL versus glargine [21,24]. It is possible that bolus requirements in patients with T2D could also be lower when used in combination with BIL.

With BIL, there was an increase in mean triglycerides accompanied by a decrease in HDL cholesterol and no significant difference in LDL cholesterol versus glargine. Switching from insulin glargine to BIL may have led to reduced suppression of peripheral lipolysis and increased hepatic triglyceride re-esterification and very low density lipoprotein secretion. The triglyceride and HDL levels remained stable up to 26 weeks, and returned towards baseline after discontinuation of BIL. These triglyceride and HDL cholesterol findings are consistent with other BIL studies in patients with T1D or T2D previously treated with insulin [17,21,24–27]. In contrast, in the IMAGINE 2 study of insulin-naïve patients with T2D, triglyceride levels were essentially unchanged with initiation of BIL and decreased with glargine over 26 weeks [21]. A decrease in triglycerides with insulin glargine and other conventional insulins has been described [28–30]. Across the BIL phase II and III programme, there were no significant differences in incidence rates of MACE+, MACE, or all-cause death between BIL and the comparator [31]. In the present study and additional BIL phase III T2D studies, there were no significant differences in blood pressure with BIL versus glargine [21,24].

Increased mean ALT levels were observed in the BIL group, with a 26-week treatment difference of 8 IU/l. Mean ALT levels remained within or slightly above laboratory reference ranges, and decreased toward baseline after discontinuation of BIL. More patients experienced ALT $\geq 3 \times$ the ULN with BIL than with glargine, but no cases were associated with increases in total bilirubin to $\geq 2 \times$ the ULN. The aetiology of the increase in ALT with BIL is unknown, but could reflect reduced peripheral suppression of lipolysis and an increase in free fatty acid delivery to the liver, which may also be associated with the increase in serum triglycerides compared with conventional insulins [32,33].

Liver fat content (LFC) was not assessed in the present study, but was evaluated by MRI [34] in subsets of patients in two other BIL phase III T2D studies, and overall the findings parallel the changes in triglycerides over 26 weeks in these two studies. In insulin-naïve patients (IMAGINE 2), mean LFC decreased from baseline with glargine, but was unchanged with BIL over 52 weeks [21]. Previous studies in insulin-naïve patients with T2D have shown decreases in LFC with initiation of currently available basal and pre-mixed insulins, similar to those reported in IMAGINE 2 [35,36]. By contrast, in the IMAGINE 5 study of patients with T2D previously treated with basal insulin (primarily glargine), mean LFC remained unchanged with glargine and increased from baseline at 26 weeks with stable levels from 26 to 52 weeks after switching to BIL [24]. Changes in LFC may also be a potential aetiology of the mean ALT increase with BIL; however, mean increases in ALT with BIL were also observed in insulin-naïve patients in whom there was no change in LFC.

The strengths of the IMAGINE 4 study include its double-blind design, the large sample size of >1300 patients (with power to evaluate not only glycaemic efficacy with HbA1c but also nocturnal hypoglycaemia), as well as the global nature of the study, involving 25 countries including North/South America, Europe and Asia. The use of the e-diary allowed wireless, direct capture of SMBG levels and hypoglycaemia events [18]. In addition, the treat-to-target SMBG fasting blood glucose levels were not significantly different in the BIL and glargine groups. Potential limitations include the 26-week duration of the study, the inability to translate the findings outside of a clinical trial setting, and that the findings are limited to the population included. It is also unknown from the present study if a reduction in bolus dosing in patients with T2D would decrease the daytime hypoglycaemia rate with BIL. In addition, although this was a multinational study, the majority of the study population was white.

This 26-week, double-blind study in patients with T2D previously treated with insulin demonstrates that treatment with BIL compared with glargine, in combination with prandial insulin lispro, provides superior glycaemic efficacy with a reduced risk of nocturnal hypoglycaemia, lower glucose variability and less weight gain. Increases in daytime hypoglycaemia, ALT, AST and triglycerides in comparison with glargine were observed.

Conflict of Interest

T. B. has served on the advisory panel for Eli Lilly and Company and Sanofi-Aventis, has received research support from Novo Nordisk, Eli Lilly and Company, Merck and Co., Sanofi-Aventis, Janssen Pharmaceuticals and Mylan, and has served on the speaker's bureau for Boehringer Ingelheim, Eli Lilly and Company, Sanofi-Aventis, Astra Zeneca and Merck and Co. T. R. P. has served on the advisory panel for Eli Lilly and Company, Novo Nordisk, Bristol Myers Squibb and Roche Diagnostics,

has served as a consultant for Eli Lilly and Company, and has served on the speaker's bureau for Novo Nordisk and Astra Zeneca. G. C. V. has served on the advisory panel for BMS Diabetes Advisory Board and Eli Lilly and Company and has served on the speaker's bureau for Astra Zeneca and Eli Lilly and Company. S. Z. is an employee and shareholder of Eli Lilly and Company. E. J. B. was an employee of Eli Lilly and Company during the trial and is currently a consultant to Viacyte, Inc., San Diego, CA, USA. A. M. C. is an employee and shareholder of Eli Lilly and Company.

T. B., T. R. P. and G. C. V. participated as trial investigators and in the discussion of the research, and reviewed/edited the manuscript. S. Z. contributed to the study design, designed and conducted the statistical analyses and participated in the interpretation of the research and in writing the manuscript. E. J. B. participated in the study design, the conduct of the study, the data analysis and interpretation of the research, and reviewed/edited the manuscript. A. M. C. was responsible for medical oversight during the trial and contributed to the study design, the data analysis and interpretation of the research and in writing the manuscript. All authors approved the final manuscript to be published.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

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