Randomized Clinical Trial Comparing Basal Insulin Peglispro and Insulin Glargine in Patients With Type 2 Diabetes Previously Treated With Basal Insulin: IMAGINE 5

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OBJECTIVE

To evaluate the efficacy and safety of basal insulin peglispro (BIL) versus insulin glargine in patients with type 2 diabetes (hemoglobin A1c [HbA_{1c}] ≤9% [75 mmol/mol]) treated with basal insulin alone or with three or fewer oral antihyperglycemic medications.

RESEARCH DESIGN AND METHODS

This 52-week, open-label, treat-to-target study randomized patients (mean HbA_{1c} 7.42% [57.6 mmol/mol]) to BIL (n = 307) or glargine (n = 159). The primary end point was change from baseline HbA_{1c} to 26 weeks (0.4% [4.4 mmol/mol] non-inferiority margin).

RESULTS

At 26 weeks, reduction in HbA_{1c} was superior with BIL versus glargine (−0.82% [−8.9 mmol/mol] vs. −0.29% [−3.2 mmol/mol]; least squares mean difference −0.52%, 95% CI −0.67 to −0.38 [−5.7 mmol/mol, 95% CI −7.3 to −4.2; $P < 0.001$); greater reduction in HbA_{1c} with BIL was maintained at 52 weeks. More BIL patients achieved HbA_{1c} <7% (53 mmol/mol) at weeks 26 and 52 ($P < 0.001$). With BIL versus glargine, nocturnal hypoglycemia rate was 60% lower, more patients achieved HbA_{1c} <7% (53 mmol/mol) without nocturnal hypoglycemia at 26 and 52 weeks ($P < 0.001$), and total hypoglycemia rates were lower at 52 weeks (P = 0.03). At weeks 26 and 52, glucose variability was lower ($P < 0.01$), basal insulin dose was higher ($P < 0.001$), and triglycerides and aminotransferases were higher with BIL versus glargine ($P < 0.05$). Liver fat content (LFC), assessed in a subset of patients (n = 162), increased from baseline with BIL versus glargine ($P < 0.001$), with stable levels between 26 and 52 weeks.

CONCLUSIONS

BIL provided superior glycemic control versus glargine, with reduced nocturnal and total hypoglycemia, lower glucose variability, and increased triglycerides, aminotransferases, and LFC.

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Many patients with type 2 diabetes fail to achieve glycemic control with basal insulin plus oral antihyperglycemic medications (OAMs) (1). Barriers to achieving optimal glycemic control include fear of hypoglycemia and weight gain (2). Hypoglycemia is a limiting factor in titration of basal insulin to achieve glycemic targets (3,4).

Basal insulin peglispro (BIL) is PEGylated insulin lispro with a half-life of 2–3 days in patients with type 2 diabetes and duration of action related to delayed insulin absorption and reduced clearance (5). In patients with type 1 diabetes and healthy subjects, BIL has hepatopreferential action compared with insulin glargine, resulting from lesser peripheral action rather than an accentuated or enhanced effect on the liver (6–8). This liver-to-peripheral tissue activity distribution is more consistent with the physiological action of endogenous insulin secretion (9,10).

In a 12-week phase 2 study comparing BIL with glargine in patients with type 2 diabetes previously treated with basal insulin, BIL was associated with similar glycemic control, reductions in nocturnal hypoglycemia and weight, and higher triglycerides and aminotransferases (11). This 52-week phase 3 open-label study compares the efficacy and safety of switching to BIL in patients with type 2 diabetes previously treated with basal insulin alone or in combination with up to three OAMs.

RESEARCH DESIGN AND METHODS

This phase 3, open-label, multicenter, multinational, randomized, controlled, parallel-design trial (Supplementary Fig. 1) was approved by local ethics review boards and conducted in accordance with Good Clinical Practice of the International Conference on Harmonisation guideline. All patients provided written informed consent. An unblinded, independent data monitoring committee monitored patient safety. Enrollment started in May 2012, and the last patient completed in December 2013.

Data were analyzed according to the predefined statistical analysis plan. To minimize potential bias in this open-label study, the sponsor study team, including the physician overseeing global conduct of the study and statistician, remained blinded prior to primary database lock at 26 weeks. Investigators and patients were aware of treatment assignment.

Participants

Adults with type 2 diabetes (12) were eligible if treated with basal insulin (insulin glargine, insulin detemir, or NPH insulin) alone or with three or fewer OAMs for ≥90 days and had hemoglobin A1c (HbA_{1c}) ≤9% (75 mmol/mol) (additional inclusion/exclusion criteria in Supplementary Table 1). Investigators at 65 study centers in eight countries participated (Supplementary Table 2).

Study Design and Treatment

After a 1-week prerandomization period, including collection of baseline hypoglycemia data, randomization to BIL or glargine (Lantus, Sanofi) occurred by country with block size of six (2:1 randomization), stratified on baseline HbA_{1c} (≤ or >8.0% [64 mmol/mol]), LDL cholesterol (LDL-C) (< or ≥100 mg/dL), and sulfonylurea/meglitinide use. OAM doses were to remain stable except in emergency situations or if contraindications developed.

Bedtime dosing of study basal insulin was initiated (Supplementary Table 3) and adjusted according to a treat-to-target algorithm (goal fasting blood glucose [FBG] by self-monitored blood glucose [SMBG] ≤100 mg/dL) (Supplementary Table 3). Algorithm adherence was mandatory up to week 26. After week 26, basal insulin dosing was determined by the investigator, and rescue therapy (prandial rapid-acting insulin) was permitted for HbA_{1c} ≥8.0% (64 mmol/mol) or FBG ≥250 mg/dL for 3 days over 2 weeks. Lipid and hepatic criteria for study insulin discontinuation are listed in Supplementary Table 4.

Patients performed SMBG each morning fasting, with two 6-point SMBG profiles (fasting, prior to midday/evening meals, bedtime, 0300 h, and next day fasting) prior to prespecified visits, and whenever hypoglycemia was suspected. Hypoglycemia was defined as signs/symptoms of hypoglycemia or measured SMBG ≤70 mg/dL. Nocturnal hypoglycemia was an event occurring between bedtime and waking. Documented symptomatic hypoglycemia was an event associated with signs/symptoms of hypoglycemia and measured SMBG ≤70 mg/dL. Severe hypoglycemia was determined by the investigator as an episode with a medical need for assistance of another person to administer carbohydrates, glucagon, or other resuscitative actions.

Deaths and nonfatal cardiovascular events (myocardial infarction, stroke, and hospitalization for unstable angina) were adjudicated by an independent clinical end point committee. Adjustments in lipid-lowering therapy were prohibited from randomization to week 12. In a patient subgroup, MRI was performed to assess liver fat content (LFC) and abdominal visceral-to-subcutaneous fat ratio (13). MRI sites in the U.S., Puerto Rico, Germany, and Greece underwent qualification procedures, including phantom scanning. Study images were centrally read by a vendor with MRI expertise in multicenter trials (VirtualScopics, Inc., Rochester, NY).

Statistical Analyses

Analyses (SAS 9.1 or higher, Cary, NC) were based on all randomized patients who took at least one dose of study insulin. The primary efficacy measure in this 52-week study was noninferiority of BIL to glargine for HbA_{1c} change from 0 to 26 weeks (margin 0.4% [4.4 mmol/mol]). For control of the overall type 1 error at $\alpha = 0.05$, a sequential gatekeeping strategy (14) was used to adjust for multiplicity for the primary and six key secondary objectives. The six key secondary objectives (in order) were to demonstrate superiority of BIL versus glargine at/during 26 weeks of treatment for nocturnal hypoglycemia rate, percent patients with HbA_{1c} <7% (53 mmol/mol) without experiencing nocturnal hypoglycemia, change in HbA_{1c}, percent patients with HbA_{1c} <7% (53 mmol/mol), total hypoglycemia rate, and laboratory fasting serum glucose (FSG). The gated objective was met if all preceding objectives were met, and the gated objective reached statistical significance at $\alpha = 0.05$.

A total of 426 randomized patients provided 90% statistical power to demonstrate noninferiority of BIL to glargine (margin 0.4% [4.4 mmol/mol]) for change in HbA_{1c} from 0 to 26 weeks with assumptions of no difference between treatment, SD of 1.1%, at two-sided α-level 0.05, and 15% dropout rate in 26 weeks.

A mixed-model repeated-measures model was used to analyze HbA_{1c}, continuous glycemic variables, and weight. HbA_{1c} <7.0% (53 mmol/mol) and HbA_{1c} <7% (53 mmol/mol) without nocturnal hypoglycemia (last observation carried forward) were analyzed using logistic regression. Hypoglycemia rates were compared using negative binomial regression with adjustment for treatment, baseline sulfonylurea/meglitinide use, and baseline hypoglycemia rate (15). Between-group differences are presented as least squares mean (LSM) difference (BIL − glargine) and baseline and end point values as LSM ± SE unless otherwise indicated.

RESULTS

Patients (*N* = 466) were randomized to BIL (*n* = 307) or glargine (*n* = 159). Patient disposition was similar between groups (Supplementary Fig. 2). There were no significant differences in incidence of discontinuations at 26 or 52 weeks. Baseline characteristics, including OAM use, were similar between groups (Table 1). OAM treatment overall remained stable throughout the study; 1.5% of patients had protocol violations for OAM changes other than safety reasons as allowed per protocol.

The primary objective, noninferiority of BIL compared with glargine for HbA_{1c} change from 0 to 26 weeks, was achieved with LSM difference of −0.52% (95% CI −0.67 to −0.38) (−5.7 mmol/mol [95% CI −7.3 to −4.2]) indicating statistical superiority of BIL compared with glargine with multiplicity adjustment ($P < 0.001$) (Fig. 1*A*). At 52 weeks, change from baseline HbA_{1c} (LSM) for BIL- and glargine-treated patients was −0.67% (−7.3 mmol/mol) and −0.22% (−2.5 mmol/mol), respectively ($P < 0.001$) (Fig. 1*A*). More BIL-treated patients achieved HbA_{1c} <7% (53 mmol/mol) at week 26 (72.5 vs. 52.2%, $P < 0.001$) and week 52 (63.9 vs. 45.9%, $P < 0.001$) (Fig. 1*B*). At week 26, more BIL-treated patients achieved HbA_{1c} ≤6.5% (48 mmol/mol) (50.3 vs. 28.7%, $P < 0.001$), HbA_{1c} <7% (53 mmol/mol) without experiencing nocturnal hypoglycemia from 0–26 weeks (40.1 vs. 18.5%, $P < 0.001$), and HbA_{1c} ≤6.5% (48 mmol/mol) without experiencing nocturnal hypoglycemia from 0 to 26 weeks (28.1 vs. 8.9%, $P < 0.001$); at week 52, more BIL-treated patients also achieved these HbA_{1c} targets ($P < 0.001$). Laboratory FSG was lower for BIL versus glargine at weeks 26 and 52 (Table 2).

FBG from SMBG was similar between BIL and glargine at weeks 26 (106.3 ± 1.1 vs. 104.5 ± 1.5 mg/dL) and 52 (110.6 ± 1.2 vs. 107.5 ± 1.7 mg/dL). At weeks 26 and 52, six-point SMBG profile daily mean glucose and midday premeal, evening premeal, and bedtime SMBG levels were lower with BIL (Fig. 2*A* and Supplementary Fig. 3).

Between-day FBG variability (SD of FBG in preceding 7 days) was lower with BIL at weeks 26 (−4.19 mg/dL, $P < 0.001$) and 52 (−3.20 mg/dL, $P = 0.004$), as was within-day variability (SD of six-point SMBG) at weeks 26 (−6.30 mg/dL, $P < 0.001$) and 52 (−4.81 mg/dL, $P = 0.001$). Bedtime to premorning meal excursion was reduced with BIL versus glargine at weeks 26 (−18.22 mg/dL; $P < 0.001$) and 52 (−19.16 mg/dL; $P < 0.001$), as was bedtime to 0300 h excursion at weeks 26 (−12.27 mg/dL, $P = 0.003$) and 52 (−15.67 mg/dL, $P < 0.001$).

Total hypoglycemia relative rate for BIL/glargine was 0.79 from 0 to 26 weeks ($P = 0.05$) and 0.77 from 0 to 52 weeks ($P = 0.03$) (Table 2). Total hypoglycemia incidence from 0 to 26 and 0 to 52 weeks was similar between treatments. There were no differences in rate or incidence of documented symptomatic hypoglycemia (Table 2). Nocturnal hypoglycemia rate and incidence and documented symptomatic nocturnal hypoglycemia rate and incidence were lower for BIL than glargine from weeks 0–26 and 0–52 (Table 2). The percentage of symptomatic hypoglycemia episodes (BIL, 52%; glargine, 51%) and the LSM glucose value associated with symptomatic hypoglycemia events

Table 1—Baseline demographics and disease characteristics

	Glargine	BIL
n	159	307
Age (years), mean ± SD	60.4 ± 10.1	61.8 ± 8.5
Men, *n* (%)	93 (58.5)	175 (57.0)
Race/ethnicity, *n* (%)		
American Indian or Alaskan Native	0 (0.0)	2 (0.7)
Asian	2 (1.3)	4 (1.3)
Black or African American	9 (5.7)	17 (5.6)
Multiple	0 (0.0)	1 (0.3)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.3)
White	148 (93.1)	280 (91.8)
Hispanic or Latino	25 (15.7)	57 (18.6)
Weight (kg), mean ± SD	91.8 ± 18.5	92.2 ± 17.1
BMI (kg/m^2), mean ± SD	31.9 ± 5.0	32.1 ± 5.0
Duration of diabetes (years), mean ± SD	12.1 ± 6.8	12.4 ± 6.9
Baseline insulin use, *n* (%)		
Insulin glargine	119 (74.8)	218 (71.0)
Insulin detemir	25 (15.7)	65 (21.2)
NPH insulin	15 (9.4)	24 (7.8)
OAMs at or prior to randomization, *n* (%)		
Metformin	140 (88.1)	270 (88.5)
Sulfonylureas or meglitinides	74 (46.5)	144 (46.9)
Dipeptidyl peptidase-4 inhibitors	34 (21.4)	76 (24.9)
Thiazolidinediones	7 (4.4)	19 (6.2)
OAM use during treatment, *n* (%)		
None	8 (5.0)	16 (5.2)
One	57 (35.8)	108 (35.4)
Two	83 (52.2)	141 (46.2)
Three	11 (6.9)	40 (13.1)
Patients using concomitant medications, *n* (%)		
Lipid-lowering medications	109 (68.9)	213 (69.4)
Statins	103 (64.8)	195 (63.5)
Nonstatin lipid-lowering medications	24 (15.1)	63 (20.5)
HbA_{1c} ≤8.0% (64 mmol/mol), *n* (%)	125 (78.6)	243 (79.2)
Hypertension, *n* (%)	133 (83.6)	264 (86.0)

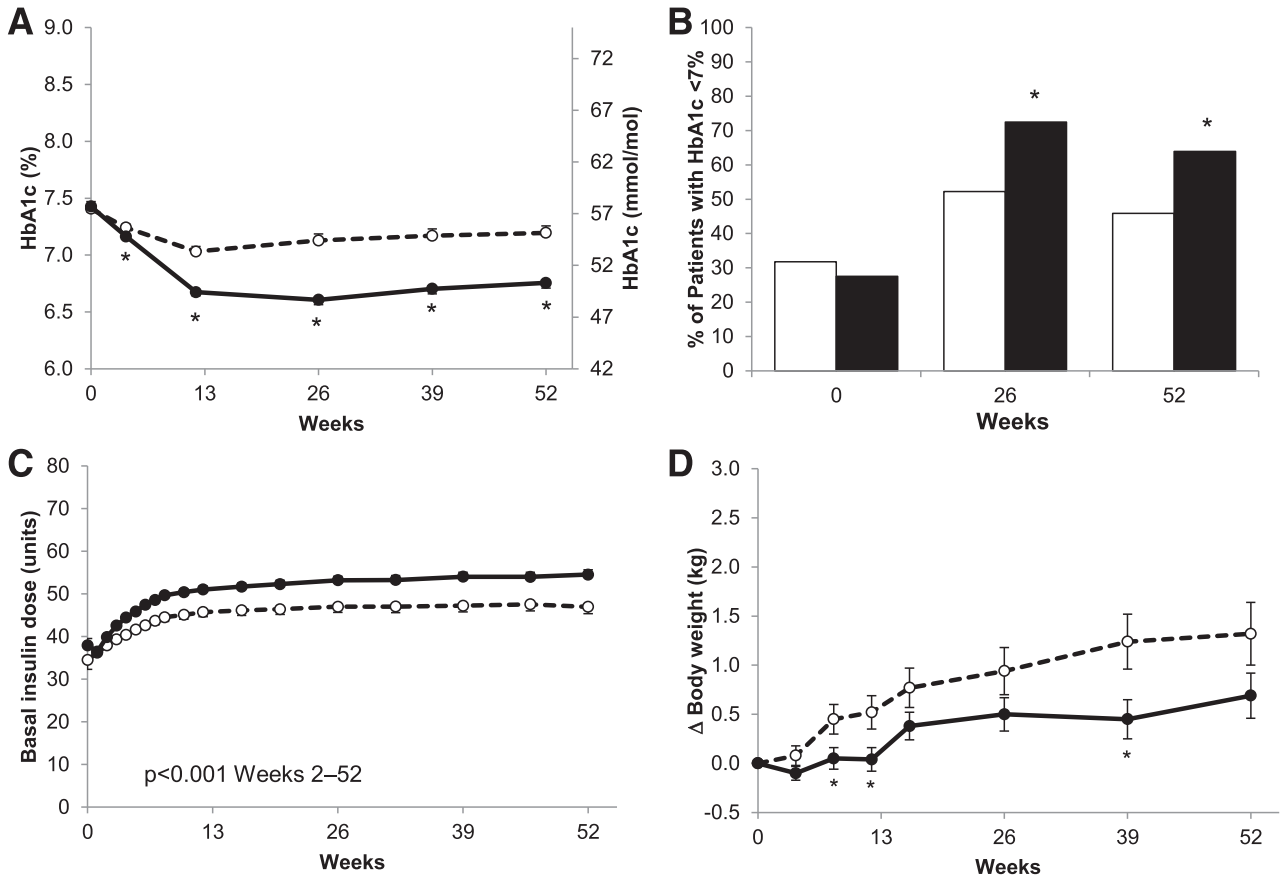

Figure 1—HbA_{1c}, percent of patients with HbA_{1c} <7%, basal insulin dose, and change in body weight over 52 weeks of treatment for BIL- and glargine-treated patients. *A*: HbA_{1c} (LSM ± SE) over time. *B*: Percent of patients with HbA_{1c} <7.0% (53 mmol/mol) at baseline, 26 weeks, and 52 weeks. *C*: Basal insulin dose over time (LSM ± SE). *D*: Change in body weight over time (LSM ± SE). Closed circles with solid line or black bar, BIL; open circles with dashed line or white bar, insulin glargine. *$P < 0.05$ for between-treatment group comparisons.

(BIL, 62.4 mg/dL; glargine, 61.3 mg/dL) were not statistically significant between groups ($P = 0.071$).

Cumulative total and nocturnal hypoglycemia events/100 patients over 52 weeks were lower for BIL than for glargine (Fig. 2). Total hypoglycemia rate by 2-h intervals over 24 h from 0 to 52 weeks is displayed in Fig. 2*D*. BIL patients had overall stable total hypoglycemia rates over 24 h. In contrast, glargine patients had higher rates from 0000 to 1000 h, with lower rates during the day and the largest difference between groups occurring from 0400 to 0600 h. Through week 52, there were two cases of severe hypoglycemia in glargine-treated patients (Table 2).

Basal insulin dose (units/day and units/kg/day) was higher for BIL patients beginning at week 2 through week 52 ($P < 0.001$) (Fig. 1*C*). At week 26, basal insulin dose was higher with BIL (53.2 units/day [0.57 units/kg/day]) vs. glargine (47.0 units/day [0.49 units/kg/day]; $P < 0.001$). At week 52, basal dose was essentially unchanged from week 26 for the BIL and glargine groups (54.5 units/day [0.58 units/kg/day] vs. 47.0 units/day [0.49 units/kg/day], respectively; $P < 0.001$). Investigator adherence to the dosing algorithm postbaseline up to week 26, when algorithm compliance was required, was not statistically significantly different between groups. From week 26 to 52, eight patients (BIL, $n = 3$ [1.1%]; glargine, $n = 5$ [3.5%]; $P = 0.13$) received bolus insulin when rescue therapy was allowed per the protocol based on glycemic parameters. Weight increased with both treatments and was not statistically significantly different in BIL versus glargine-treated patients at 26 or 52 weeks (Fig. 1*D*).

With the prespecified gate-keeping strategy for the primary and six key secondary objectives, superiority of BIL versus glargine at or during 26 weeks in change in HbA_{1c}, nocturnal hypoglycemia rate, proportion of patients with HbA_{1c} <7% (53 mmol/mol), and proportion achieving HbA_{1c} <7% (53 mmol/mol) without nocturnal hypoglycemia was statistically significant with multiplicity adjustment. The fifth gated objective for superiority of BIL versus glargine for total hypoglycemia rate from baseline to 26 weeks did not meet the gate-keeping test for multiplicity. The FSG for BIL was lower versus glargine but did not meet the gate-keeping test for multiplicity.

Treatment-emergent adverse events were comparable between groups except for more skin and subcutaneous tissue disorders with BIL (Supplementary Table 5). Six (2.0%) BIL- and no glargine-treated patients experienced prospectively defined treatment-emergent adverse events of injection site reactions of special interest, including injection site hypertrophy ($n = 2$), lipohypertrophy ($n = 2$), injection site edema ($n = 1$), and lipodystrophy ($n = 1$). Serious adverse events were similar between treatments

Table 2—Treatment outcomes at baseline and after 26 and 52 weeks of treatment

	Baseline*		26 weeks			52 weeks		
Outcome	Glargine (*n* = 159)	BIL (*n* = 307)	Glargine (*n* = 159)	BIL (*n* = 307)	*P***	Glargine (*n* = 159)	BIL (*n* = 307)	*P***
HbA_{1c}, %†	7.41 ± 0.06	7.43 ± 0.05	7.13 ± 0.06	6.60 ± 0.04	<0.001	7.20 ± 0.06	6.75 ± 0.05	<0.001
Change from baseline	—	—	−0.29 ± 0.06	−0.82 ± 0.04		−0.22 ± 0.06	−0.67 ± 0.05	
LSM difference (95% CI)	—	—	−0.52 (−0.67 to −0.38)			−0.44 (−0.60 to −0.29)		
HbA_{1c}, mmol/mol†	57.5 ± 0.7	57.7 ± 0.5	54.4 ± 0.7	48.7 ± 0.5	<0.001	55.1 ± 0.7	50.3 ± 0.5	<0.001
Change from baseline	—	—	−3.2 ± 0.7	−8.9 ± 0.5		−2.5 ± 0.7	−7.3 ± 0.5	
LSM difference (95% CI)	—	—	−5.7 (−7.3 to −4.2)			−4.9 (−6.5 to −3.2)		
FSG, mg/dL†	128 ± 3	135 ± 2	120 ± 3	104 ± 2	<0.001	116 ± 3	108 ± 2	0.02
Total hypoglycemia rate‡‖	1.40 ± 0.30	1.08 ± 0.16	1.98 ± 0.19	1.55 ± 0.13	0.05	1.62 ± 0.15	1.24 ± 0.10	0.03
Total hypoglycemia incidence§	30 (18.9)	51 (16.8)	128 (80.5)	232 (76.3)	0.35	132 (83.0)	244 (80.3)	0.54
Nocturnal hypoglycemia rate‡‖	0.62 ± 0.16	0.53 ± 0.12	1.04 ± 0.15	0.43 ± 0.06	<0.001	0.88 ± 0.14	0.35 ± 0.06	<0.001
Nocturnal hypoglycemia incidence§	18 (11.3)	25 (8.2)	99 (62.3)	140 (46.1)	0.001	107 (67.3)	153 (50.3)	<0.001
Documented symptomatic hypoglycemia rate‡‖	0.51 ± 0.15	0.58 ± 0.12	0.90 ± 0.15	0.78 ± 0.10	0.47	0.77 ± 0.12	0.60 ± 0.07	0.21
Documented symptomatic hypoglycemia incidence§	13 (8.2)	29 (9.5)	88 (55.3)	160 (52.6)	0.549	98 (61.6)	176 (57.9)	0.411
Documented symptomatic nocturnal hypoglycemia rate‡‖	0.25 ± 0.11	0.27 ± 0.09	1.17 ± 0.57	0.38 ± 0.19	<0.001	0.80 ± 0.30	0.23 ± 0.09	<0.001
Documented symptomatic nocturnal hypoglycemia incidence§	7 (4.4)	13 (4.3)	64 (40.3)	86 (28.3)	0.007	71 (44.7)	98 (32.2)	0.007
Severe hypoglycemia incidence§	0	0	1 (0.6)	0 (0.0)	—	2 (1.3)	0 (0.0)	0.12
ALT (IU/L)†	25.8 ± 1.1	26.3 ± 0.8	26.6 ± 1.1	35.9 ± 0.8	<0.001	26.4 ± 1.1	34.3 ± 0.8	<0.001
AST (IU/L)†	22.9 ± 0.7	23.3 ± 0.5	23.3 ± 0.8	28.7 ± 0.5	<0.001	23.5 ± 0.8	27.7 ± 0.6	<0.001
LDL-C (mg/dL)†	95.6 ± 2.9	97.2 ± 2.1	100.8 ± 2.0	96.2 ± 1.4	0.06	99.6 ± 2.0	92.8 ± 1.5	0.007
HDL-C (mg/dL)†	46.4 ± 1.0	48.0 ± 0.7	47.3 ± 0.5	45.7 ± 0.4	0.009	45.4 ± 0.5	43.9 ± 0.4	0.02
Non-HDL-C (mg/dL)†	124.4 ± 3.2	126.5 ± 2.3	129.0 ± 2.2	129.2 ± 1.6	0.927	130.1 ± 2.3	127.1 ± 1.6	0.28
Triglycerides (mg/dL)†	144 ± 6	149 ± 4	143 ± 5	169 ± 4	<0.001	158 ± 6	174 ± 4	0.03
Systolic blood pressure (mmHg)†	132 ± 1	132 ± 1	135 ± 1	134 ± 1	0.309	133 ± 1	133 ± 1	0.930
Diastolic blood pressure (mmHg)†	76 ± 1	77 ± 1	78 ± 1	78 ± 0	0.899	77 ± 1	78 ± 0	0.601
Treatment-emergent antibody response¶	—	—	9 (6.3)	33 (11.7)	0.089	13 (9.7)	27 (10.4)	0.85
LFC (%)†#	10.0 ± 1.1	10.4 ± 0.8	9.1 ± 0.7	15.1 ± 0.5	<0.001	9.6 ± 0.8	14.9 ± 0.5	<0.001
Abdominal visceral-to-subcutaneous fat ratio#††	0.72	0.68	0.69	0.72	0.001	0.68	0.74	<0.001

n reflects maximal sample size. *No between-treatment differences ($P > 0.05$) in any baseline parameter. †LSM ± SE. ‡Group mean ± SE. §Number of patients (%). ‖For hypoglycemia rate data, values shown are events/patients/30 days for baseline to week 26 and baseline to week 52. ¶Treatment-emergent anti-BIL antibody response is defined as change from baseline to postbaseline in the anti-BIL antibody level either *1*) from undetectable to detectable and the postbaseline value ≥1% + cut point or *2*) from detectable to the value with a relative change ([postbaseline − baseline]/baseline) ≥30% and absolute change ≥1%. #*N* = 52 for glargine; *N* = 110 for BIL. **Between-treatment differences. ††LSM.

except that cardiac disorders and metabolism and nutrition disorders (hypoglycemia and hypovolemia) occurred less commonly with BIL (Supplementary Table 5). Treatment-emergent anti-BIL antibody responses were similar between groups (Table 2).

Adjudicated major adverse cardiac events (MACE), including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death, were similar between BIL and glargine: 2.3% vs. 4.4%, hazard ratio 0.5 (95% CI 0.18–1.43), $P = 0.20$. There were no cases of unstable angina with hospitalization; thus, MACE+ results were equivalent to MACE. Six deaths, three (1.0%) with BIL (cardiac death, cardiac arrest, and pulmonary hypertension) and three (1.9%) with glargine (multiorgan failure, myocardial infarction, and cardiac arrhythmia) occurred. There were no differences in heart rate or systolic or diastolic blood pressure (Table 2).

Triglycerides increased from 0 to 4 weeks and remained overall stable thereafter during BIL treatment, with treatment differences through week 52 (LSM difference [BIL − glargine] 15 mg/dL, $P = 0.026$) (Table 2 and Supplementary Fig. 4*A*). At study end point, after transition off BIL, triglycerides returned to baseline levels in the BIL group and were lower than with glargine (Supplementary Fig. 4*A*). One patient in each treatment group met discontinuation criteria of triglyceride level >600 mg/dL.

HDL cholesterol (HDL-C) decreased from 0 to 4 weeks with BIL and remained

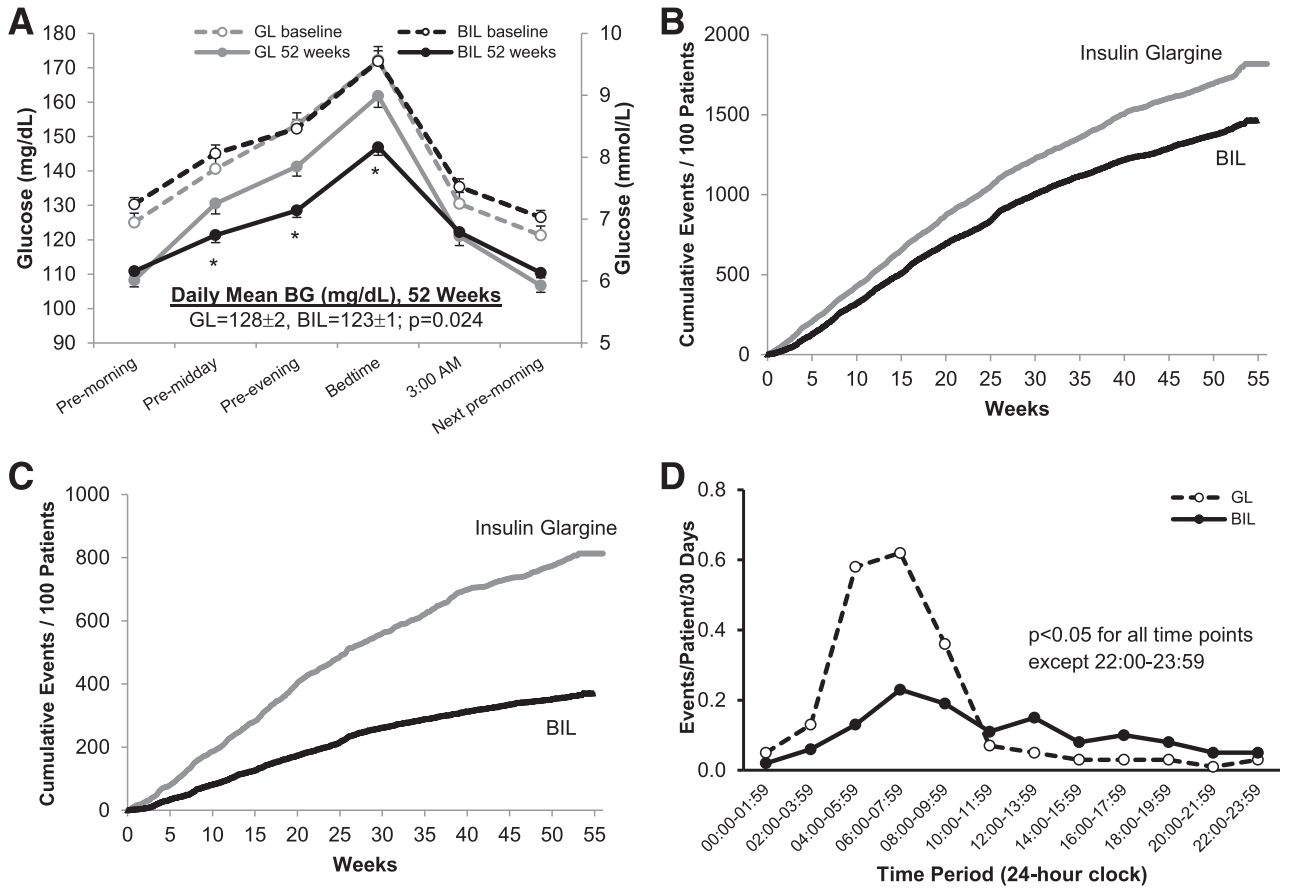

Figure 2—SMBG and hypoglycemia for BIL- and glargine-treated patients. *A*: Six-point SMBG profile at baseline and 52 weeks. Premorning, fasting (premorning meal); Pre-midday, pre-midday meal; Pre-evening, pre-evening meal. Data are LSM ± SE. *$P < 0.05$ for between-treatment group comparisons. *B*: Cumulative total hypoglycemia events/100 patients over time during 52 weeks of treatment. *C*: Cumulative nocturnal hypoglycemia events/100 patients over time during 52 weeks of treatment. For both *B* and *C*, "lines" are continuous data points indicating rates of hypoglycemia throughout 52 weeks of treatment. *D*: Total hypoglycemia by 2-h intervals (0–52 weeks). Data are group mean. GL, insulin glargine. The *P* value is for between-treatment group comparisons.

lower than baseline through week 52, resulting in lower HDL-C (<2 mg/dL) with BIL versus glargine at week 52 (Table 2, Supplementary Fig. 4*B*). At study end point, after transition off treatment, HDL-C was higher with BIL versus glargine (Supplementary Fig. 4*B*). There were no treatment differences in LDL-C at week 26, and LDL-C was lower with BIL at weeks 4 and 52 (Table 2 and Supplementary Fig. 4*C*). There were no differences in total cholesterol between groups during treatment (Supplementary Fig. 4*D*) or non-HDL-C (Table 2). There were no significant differences in the use of lipid-lowering medication or changes to lipid-lowering medications between the treatment groups.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased from baseline with BIL and decreased toward baseline after transition off BIL, with treatment differences at all time points (Table 2, Supplementary Fig. 5). Mean ALT and AST remained within/slightly above reference ranges at all times. Seven (2.3%) BIL- and no glargine-treated patients experienced ALT three or more times the upper limit of normal (ULN). All seven patients had a reduction in ALT less than three times ULN during the study, with four patients continuing treatment and three patients discontinuing BIL and completing study visits. No patients in either group had bilirubin two or more times ULN postbaseline.

A patient subset participated in the MRI addendum (n = 110 BIL, n = 52 glargine). Baseline characteristics, change in HbA_{1c}, and liver/lipid laboratory results in MRI addendum patients were consistent with overall study results. Baseline LFC (10%) was similar between groups (Table 2). With BIL, LFC increased from 0 to 26 weeks and remained stable at week 52. LFC did not change significantly from baseline with glargine (Table 2). LFC change from baseline was higher with BIL versus glargine at weeks 26 and 52 (LSM difference 6.0% and 5.3%, respectively; $P < 0.001$). At 52 weeks, 10 (10.9%) BIL patients versus 1 (2.3%) glargine patient had an absolute increase from baseline of ≥10% in LFC ($P = 0.103$). Change from baseline of the abdominal visceral-to-subcutaneous fat ratio was higher with BIL versus glargine at weeks 26 and 52 (LSM difference 0.04 and 0.06, respectively; $P < 0.001$) (Table 2).

CONCLUSIONS

This is one of the first direct comparisons of two basal insulins in which superiority in glycemic control was demonstrated in a treat-to-target trial. In patients with type 2 diabetes previously treated with basal insulin, switching to

BIL compared with glargine resulted in a clinically significant 0.5% (5.7 mmol/mol) greater HbA_{1c} reduction at 26 weeks (6.6 vs. 7.1% [48.7 vs. 54.4 mmol/mol]). Greater HbA_{1c} reduction with BIL was maintained at 52 weeks. In addition, more BIL-treated patients reached target HbA_{1c} <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol). Despite greater HbA_{1c} reduction, BIL-treated patients experienced statistically and clinically significant reductions in nocturnal hypoglycemia.

The superior HbA_{1c} reduction achieved with BIL is noteworthy, since noninferiority has usually been observed in basal insulin treat-to-target trials (16–18). The FSG levels in glargine-treated patients were well within ranges reported in many treat-to-target trials, whereas BIL-treated patients had greater reduction in FSG compared with glargine (19–21). Not only was HbA_{1c} efficacy in BIL-treated patients superior to glargine-treated patients, but the levels achieved were well below those reported in many major insulin clinical trials (16,18,21,22). The HbA_{1c} levels with BIL treatment were slightly higher than those achieved in the intensive arm of Action to Control Cardiovascular Risk in Diabetes (ACCORD), in which multiple therapies, including bolus insulin, were allowed and the median HbA_{1c} was 6.4% (46 mmol/mol) (23).

Improved glycemic control was achieved without increased rates of total or nocturnal hypoglycemia, important limiting factors in titrating basal insulin to achieve glycemic targets. Nocturnal hypoglycemia was consistently lower in BIL-treated patients, with a clinically relevant 60% rate reduction versus glargine. Total hypoglycemia was also reduced over 52 weeks, and more patients reached HbA_{1c} <7% (53 mmol/mol) without experiencing nocturnal hypoglycemia over 26 and 52 weeks. Reduced nocturnal hypoglycemia with BIL was also seen in insulin-naïve patients with type 2 diabetes (24) and in phase 2 BIL studies (11,25) and may reflect its longer duration of action and lower peak-to-trough ratio, as well as reduced glucose variability versus glargine, with potentially more stable and predictable metabolic control (26).

Basal insulin dose was higher in BIL- versus glargine-treated patients (~13% and ~16% higher at weeks 26 and 52, respectively). With modeling of HbA_{1c} and basal insulin dose, HbA_{1c} reduction per 10 units of basal insulin from 0 to 26 weeks was 0.36% (3.9 mmol/mol) for BIL and 0.30% (3.3 mmol/mol) for glargine, suggesting that BIL was at least as potent as glargine on a per unit basis. These results suggest that BIL may be titrated effectively to reach glycemic targets due to lower nocturnal hypoglycemia rates with less glucose variability and smaller overnight glucose excursions. In addition, potential basal insulin coverage throughout the day with greater reduction in afternoon/evening SMBG levels, when the effects of glargine may be waning, could have also contributed to the greater improvement in glycemic control with BIL compared with glargine in a treat-to-target setting. Although BIL had greater effects on HbA_{1c} and other glycemic measures and patients had higher basal insulin doses, weight was not statistically significantly different with BIL versus glargine at 26 or 52 weeks. This contrasts with a phase 2 BIL study in patients with type 2 diabetes in which weight loss and similar HbA_{1c} was seen, possibly reflecting smaller sample size and 12-week duration, which may have limited titration to optimal basal insulin dose.

Increased mean aminotransferases, within or slightly above reference ranges, were seen with BIL. ALT at or above three times ULN occurred in 2.3% of BIL-treated patients, but no cases were associated with increases in bilirubin at or above two times ULN. Hence, no patients met criteria for Hy's law, a predictor of future risk of severe drug-induced liver injury (27), consistent with other BIL studies (11,24,25).

In the MRI subset, LFC and visceral-to-subcutaneous fat ratio increased in BIL- but not glargine-treated patients at 26 weeks and remained stable in both groups at 52 weeks. This contrasts with the IMAGINE 2 study findings in insulin-naïve patients with type 2 diabetes, where BIL-treated patients had no significant change in LFC, but glargine-treated patients had a reduction in LFC from 13% at baseline to 10% at 52 weeks (24). In the insulin-naïve study, the visceral-to-subcutaneous fat ratio was similar with BIL and glargine over 52 weeks. Prior studies in insulin-naïve patients with type 2 diabetes have shown decreases in hepatic steatosis with 3–7 months of treatment with currently available basal and premixed insulins (28,29).

Conventional insulins may decrease LFC in insulin-naïve patients with type 2 diabetes by decreasing surplus fatty acid delivery to the liver by increasing fat delivery to the peripheral tissues through increased lipoprotein lipase activity and suppression of lipolysis in the adipose tissue. An animal model has recently demonstrated that hepatic triglyceride synthesis is primarily dependent on fatty acid delivery and independent of hepatic insulin action or changes in hepatic insulin signaling (30).

Baseline LFC (10%) in the current study of patients previously treated with basal insulin was similar to the reduced LFC level seen after 26 and 52 weeks in the glargine arm of the IMAGINE 2 insulin-naïve type 2 diabetes study (24). In the current study, baseline LFC may have already been decreased due to prior treatment with conventional basal insulins, primarily glargine; thus, glargine treatment during the study had no further effect on LFC. In contrast, switching from a conventional basal insulin to BIL, with limited peripheral access, may have led to reduced suppression of peripheral lipolysis and relatively higher fatty acid delivery to the liver and increased LFC, which remained stable through 52 weeks. Further research will help to understand the underlying mechanisms and clinical consequences of these LFC differences with BIL in patients previously treated with conventional basal insulins.

Increased triglycerides with BIL remained stable through 52 weeks and decreased after stopping BIL, consistent with other BIL studies in patients with type 1 diabetes or type 2 diabetes previously treated with insulin (11,25). In insulin-naïve patients with type 2 diabetes, triglyceride levels were essentially unchanged with BIL and decreased with glargine over 26 weeks of treatment (24). Insulin glargine and other conventional insulins have been associated with a reduction in triglyceride levels (31–33). Increased triglycerides in the current study were accompanied by a <2 mg/dL decrease in HDL, a decrease in LDL-C at week 52, and no differences in non-HDL-C with BIL versus glargine. As discussed above, we hypothesize that the reduced peripheral

action of BIL may increase relative fatty acid delivery to the liver and, hence, increase hepatic triglyceride reesterification and VLDL secretion. Nonalcoholic fatty liver disease and visceral adiposity have been associated with cardiovascular risk factors (34). In BIL phase 3 type 2 diabetes studies, including IMAGINE 5, there were no significant differences in blood pressure between BIL and glargine (24,35). In the BIL phase 2 and 3 program, there were no significant differences in incidence rates of MACE+, MACE, or all-cause death between BIL and comparator (36).

Potential study limitations include the open-label design, which may increase risk of bias. Of note, the treat-to-target SMBG FBG levels and dosing algorithm adherence were not significantly different in the BIL and glargine groups. The BIL phase 3 program includes three double-blind studies including IMAGINE 2 (24). Although this global study involved eight countries, the study population was primarily white. The study patients overall had reasonably controlled diabetes at baseline given the eligibility criteria of HbA_{1c} $\leq$9% for safety reasons, as these patients were to continue a basal insulin regimen with glargine or switch to new therapy with BIL. The BIL phase 3 clinical program includes patients with higher baseline HbA_{1c} levels (such as the IMAGINE 2 study) as well as patients being treated with other diabetes regimens.

This 52-week, treat-to-target study in patients with type 2 diabetes previously treated with basal insulin demonstrates that switching to BIL provides superior glycemic efficacy with clinically significant reductions in HbA_{1c} with lower risk of nocturnal and total hypoglycemia and lower glucose variability. Increases were seen in aminotransferases, triglycerides, and LFC in comparison with glargine. The conversion from a conventionally acting basal insulin to BIL, a hepatopreferential insulin with reduced peripheral action, may account for these findings.

NOTE ADDED IN PROOF

Since this article was accepted for publication, Eli Lilly and Company has announced plans to cease development of basal insulin peglispro (https://investor.lilly.com/releasedetail.cfm?ReleaseID=945541). This decision is based on unresolved questions regarding changes in liver fat that developed during the late stages of drug testing.

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