Glucose Variability in a 26-Week Randomized Comparison of Mealtime Treatment With Rapid-Acting Insulin Versus GLP-1 Agonist in Participants With Type 2 Diabetes at High Cardiovascular Risk

*The FLAT-SUGAR Trial Investigators**

Diabetes Care 2016;39:973–981 | DOI: 10.2337/dc15-2782

OBJECTIVE

A1C is associated with diabetes complications but does not reflect glycemic variability (GV), which may worsen outcomes by inducing inflammation, oxidative stress, and cardiac arrhythmias. We tested whether a glucagon-like peptide 1 agonist-based regimen can reduce GV and cardiometabolic risk markers while maintaining similar A1C levels in people with insulin-requiring type 2 diabetes and high cardiovascular risk.

RESEARCH DESIGN AND METHODS

After run-in on metformin and basal-bolus insulin (BBI), 102 participants continued metformin and basal insulin and were randomized to exenatide dosing before the two largest meals (glucacon-like peptide-1 receptor agonist and insulin [GLIPULIN group]) or continuation of rapid-acting insulin analogs (BBI group). Indices of GV by continuous glucose monitoring (CGM), hypoglycemia, weight, risk markers, and cardiac arrhythmias were assessed. The primary end point was change in glucose coefficients of variation (CV) by CGM from baseline to 26 weeks.

RESULTS

At randomization, the median A1C was 7.3% (57 mmol/mol) for GLIPULIN and 7.4% (56.3 mmol/mol) for BBI, and glucose CVs were 30.3 for BBI and 31.9 for GLIPULIN. At 26 weeks, A1C levels were similar (7.1% [54 mmol/mol] vs. 7.2% [55 mmol/mol]), whereas mean CV improved with GLIPULIN (−2.4 vs. 0.4, P = 0.047). Other GV indices followed similar nonsignificant patterns of improvement with GLIPULIN. There were no differences in hypoglycemic events during CGM or arrhythmias during electrocardiographic monitoring. On-trial changes in body weight (−4.8 kg vs. +0.7 kg, $P < 0.001$), alanine aminotransferase (P = 0.0002), and serum amyloid A (P = 0.023) favored GLIPULIN.

CONCLUSIONS

GLIPULIN reduced GV, weight, and some cardiometabolic risk markers while maintaining equivalent A1C levels versus BBI and might improve clinical outcomes in a larger trial.

Corresponding author: Jeffrey L. Probstfield, jeffprob@uw.edu.

Received 22 December 2015 and accepted 23 March 2016.

Clinical trial reg. no. NCT01524705, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-2782/-/DC1.

**The members of the Writing Committee of the FLAT-SUGAR Trial are listed in the APPENDIX.*

Intensive insulin therapy in type 1 diabetes and improved glucose control with metformin, sulfonylureas, or insulin in newly diagnosed type 2 diabetes have been shown to reduce microvascular complications in the short-term and macrovascular complications after >10 years of passive follow-up (1–4). These landmark observations helped to establish A1C as the primary biomarker and target for glucose-lowering treatments in both forms of diabetes. Subsequent studies assessing effects of more versus less intense glucose lowering for ~5 years recorded mixed results (5,6), with a cardiovascular benefit emerging in only one study during passive follow-up (7). One potential reason for this discrepancy is that A1C does not reflect glycemic variability (GV), which typically increases with longer duration of type 2 diabetes, mainly due to progressive insulin deficiency (8).

Accumulating data support the possibility that GV is involved in the pathogenesis of vascular complications of diabetes by inducing inflammatory activation and oxidative stress (9). Furthermore, hypoglycemia is strongly associated with GV and may promote cardiac arrhythmias (10) while limiting the ability of insulin therapy to attain desired levels of control of A1C. Introduction of glucagon-like peptide 1 receptor agonists (GLP-1RA), particularly the short-acting agents, exenatide and lixisenatide, have provided us with a new strategy to dampen these fluctuations, especially after meals (11). Finally, introduction of continuous glucose monitoring (CGM) has provided a method to quantify glycemia and GV (12).

These advances improve our ability to test the hypothesis that GV, independent of A1C, contribute to complications of diabetes and allow testing of a new approach to the treatment of high-risk patients with type 2 diabetes. Our study, FLuctuATion reduction with inSUlin and GLP-1 Added togetheR (FLAT-SUGAR), was designed as a proof-of-concept study to determine whether GV can be decreased more by mealtime therapy with exenatide than with a rapid-acting insulin analog while A1C levels are kept equivalent (13). Secondary study questions included whether this approach will alter other indices of GV, hypoglycemia, weight, albuminuria, and other markers of cardiovascular risk, or frequency of cardiac arrhythmias. If positive, results of this study may provide a basis for designing a larger, outcome-driven trial examining the medical risks and benefits of a regimen combining basal insulin with a short-acting GLP-1RA. Because of this long-term objective, the population studied was intended to be similar to that of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (5), in which intensive treatment of a high-risk population with conventional methods, including basal-bolus insulin (BBI), reduced myocardial infarction but led to increased cardiovascular and all-cause mortality.

RESEARCH DESIGN AND METHODS

Study Design

This was an investigator-initiated, multicenter collaboration between academic groups and was funded by pharmaceutical and medical device sponsors. The study was a two-arm comparison of treatment strategies and consisted of a screening period, an 8- to 12-week open-label run-in period, and a 26-week randomized open-label treatment period. A detailed description of methods has been reported previously (13).

Study Population

Selection criteria included *1*) a diagnosis of type 2 diabetes for >12 months and stable glycemic control while using insulin for at least 3 months; *2*) age 40–75 years with a history of a prior cardiovascular event or two or more markers of increased cardiovascular risk; *3*) A1C between 7.5 and 8.5% (58 and 69 mmol/mol); *4*) BMI no higher than 45 kg/m^2; and *5*) fasting C-peptide ≥0.5 mg/mL (0.17 nmol/L). Notable exclusion criteria included *1*) inability or unwillingness to perform self-monitoring of blood glucose (SMBG) a minimum of three times daily, CGM, or Holter monitoring; *2*) inability or unwillingness to discontinue use of all other diabetes treatment agents during the study except subcutaneously injected insulin and 500 mg/day or more of metformin; *3*) creatinine level ≥1.5 mg/dL (132.6 μmol/L) for males or ≥1.4 mg/dL (123.8 μmol/L) for females; *4*) alanine aminotransferase (ALT) level three or more times upper limit of normal; *5*) current symptomatic heart failure, history of New York Heart Association Functional Classification III or IV congestive heart failure at any time or left ventricular ejection fraction <25%, or a history of pancreatitis.

Study Intervention and Adherence

A run-in procedure was used to establish a stable baseline, familiarize candidates with procedures, and identify those unable to adhere to study requirements. During this period, candidates used BBI therapy given by separate injections and performed SMBG with meters and strips (Contour, Bayer) provided by the study. All candidates were given insulin glargine (Lantus, Sanofi) to take once or twice daily and were randomly assigned to one of three rapid-acting insulin analogs (aspart [NovoLog, Novo Nordisk], glulisine [Apidra, Sanofi], or lispro [Humalog, Eli Lilly]) for mealtime administration. Use of metformin was required with dosage increasing to 2,000 mg daily as tolerated. All participants were intended to maintain A1C levels between 6.7 and 8.0% (50 and 64 mmol/mol) during the run-in. Investigators advised insulin changes seeking this range based on SMBG and locally measured A1C values. All participants used CGM (Dexcom Seven Plus or Gen 4) and ambulatory electrocardiographic (Holter) monitoring (Medicomp) for a 7- to 10-day period after at least 8 to 10 weeks of stabilization of glycemic control. The length of the monitoring period for CGM was consistent with scientific evaluation of the sensor and device (14). Participants and investigators were masked to results of these continuous measurements. To be eligible for randomization participants had to demonstrate tolerance of ≥500 mg of metformin daily together with BBI, performance of SMBG at least three times daily, collection of data of adequate quality for at least 85% of the 7- to 10-day period of both CGM and Holter monitoring, and attainment of an A1C level between 6.7 and 8.0% (50 and 64 mmol/mol) at the end of the run-in.

Eligible participants continued metformin and basal insulin and were randomized in equal numbers to continue BBI or to switch to the glucagon-like peptide-1 receptor agonist and insulin (GLIPULIN) regimen, which added the GLP-1RA exenatide and discontinued rapid-acting insulin. For the first month, the dose was 5 μg exenatide (Byetta, AstraZeneca) before the two largest

meals. After the first month, two or three premeal doses of 5 or 10 μg exenatide were administered as long as the cumulative dose did not exceed 20 μg daily. The third dose of exenatide was to be added when judged necessary to maintain A1C in the desired range. Metformin and glargine were continued in both treatment arms, and dosages of glargine and mealtime insulin were titrated at the investigators' discretion to maintain A1C between 6.7 and 7.3% (50 and 56 mmol/mol), a narrower range than in run-in, during 26 weeks of randomized treatment.

Study Outcomes

Primary outcome was the change from baseline to 26 weeks in the coefficient of variation (CV) of glucose values collected by CGM. Other indices of GV calculated from CGM data (12) included SD, interquartile range (IQR), mean amplitude of glycemic excursions (MAGE), continuous overall net glycemic action (CONGA), and mean of daily differences (MODD). The numbers of participants affected by hypoglycemia and number of episodes were also calculated from CGM data. A single episode was defined by four or more consecutive (5-min interval) CGM readings <70 mg/dL (3.9 mmol/L), followed by at least one reading ≥70 mg/dL (3.9 mmol/L) or 10 mg/dL (0.6 mmol/L) above the nadir, whichever was higher. Clinically reported hypoglycemic events were identified by participant report and by review of SMBG meter downloads.

Concurrent with CGM measurements, 7- to 10-day Holter monitoring was performed before randomization and before the 13- and 26-week visits. Other secondary outcomes assessed at baseline and at 13 and 26 weeks are indicated in Table 1. Weight and vital signs were measured at each clinic visit. Adverse events were collected at each contact with participants and recorded according to the Medical Dictionary for Regulatory Activities classification. To further ensure the safety of participants, downloads of CGM values were examined centrally (masked to treatment assignment) to allow notification of site investigators if significant hypoglycemia (>2% of readings <40 mg/dL [2.2 mmol/L]) was identified. Similarly, Holter downloads were examined for predefined critical arrhythmias and other significant abnormalities as described in the design paper (13).

Statistical Analysis

The CV of glucose measured by CGM was calculated as the SD of all values divided by the mean. To estimate a sample size, unpublished data were taken from a previous randomized clinical study of CGM in adults with type 1 diabetes (unpublished data from a privileged communication with R.W. Beck and the JDRF Continuous Glucose Sensor Trial). The control group for the prior study (n = 58) had a baseline A1C between 6.7 and 8.0% (50 and 64 mmol/mol), and masked CGM data were collected at baseline and 6 months. Mean CV at 6 months was 38, with a SD of 8 (values were similar at baseline with a mean of 39 and a SD of 8), and the data showed an approximately normal distribution. Assuming a two-sample two-tailed t test with type I error = 0.05, a sample of 110 participants (55 per group) would give 90% power to detect a difference of a mean change from baseline of 5 CV units (SD = 8) between control and treatment groups. In addition to the conventional two-sample t test, an ANCOVA model, adjusting for baseline value and clinical site, was to be performed. If residual values from the ANCOVA indicated nonnormality in distribution by Shapiro-Wilk testing, a Wilcoxon rank sum test was used instead. Analysis followed the intent-to-treat principle, with all participants analyzed in the group to which they were randomized.

Other indices of GV (SD, IQR, MAGE, CONGA, and MODD) were calculated and analyzed as continuous measures using methods analogous to those described above for CV, including testing for normal distribution. Glycemic patterns were assessed separately by logistic regression, as described previously (13).

RESULTS

Participant Flow and Baseline Characteristics

As summarized previously (13), between August 2012 and January 2014, 12 clinical sites screened 255 individuals, of whom 146 eligible candidates were enrolled to the run-in period, and 102 remained eligible and agreed to be randomized after the run-in (Fig. 1). Characteristics at enrollment were balanced between the randomized groups (13). Overall, 63% were male, 81% were Caucasian, mean age was 62 years, median duration of diabetes was 15 years, and 32% had a prior cardiovascular event. At enrollment mean BMI was 34 kg/m^2, blood pressure was 130/73 mmHg, A1C was 7.9% (63 mmol/mol), and creatinine was 0.9 mg/dL (79.56 μmol/L). Microalbuminuria was present in 18% of participants. The study was completed by 96 (94%) of the randomized participants (47 of 50 on BBI, 49 of 52 on GLIPULIN), and 92 (90%) had complete collection of CGM data before and after 26 weeks of randomized treatment, allowing analysis for the primary end point. Adherence to all protocol-prescribed procedures was excellent.

Changes of A1C, Body Weight, Vital Signs, and Medication Dosage

Mean A1C was similar in the groups at randomization (7.4% [57.4 mmol/mol] for BBI vs. 7.3% [56.3 mmol/mol] for GLIPULIN) and remained so at 13 weeks (7.1% [54.1 mmol/mol] vs. 7.3% [56.3 mmol/mol]) and at 26 weeks (7.2% [55.2 mmol/mol] vs. 7.1% [54.1 mmol/mol]) of randomized treatment (Fig. 2*A* and Table 1).

Mean weight at randomization was slightly higher in the GLIPULIN group (101.3 kg) than in the BBI group (100.1 kg) (Fig. 2*B* and Table 1). Weight increased by 0.7 kg at 26 weeks with BBI but decreased steadily in the GLIPULIN group to a mean reduction of 4.8 kg and a between-group difference of 5.45 kg ($P < 0.001$) at 26 weeks. No between-treatment differences in blood pressure or heart rate were observed.

The mean dose of insulin glargine was higher in the GLIPULIN group than in the BBI group at randomization (57 units/day for GLIPULIN vs. 43 units/day for BBI, P = 0.04), and these doses were little changed at 26 weeks (58 units/day vs. 43 units/day, P = 0.02) (Supplementary Table 1). The mean dose of rapid-acting insulin in the BBI group increased from 36 units/day at baseline to 45 units/day at 26 weeks. Mean total exenatide dose in the GLIPULIN group was 18 μg (5–20 μg/day) daily at 26 weeks (Supplementary Table 1). Of 52 participants in the GLIPULIN group, 29 (56%) never took more than two daily injections of exenatide, whereas 23 (44%) used three injections daily.

Table 1—A1C, weight, and cardiovascular risk markers

	GLIPULIN			BBI			*P* value	
Variable	*n*	Mean (SD)	Median (IQR)	*n*	Mean (SD)	Median (IQR)	*t* test	Wilcoxon
A1C (%)								
Visit 1	52	7.9 (0.3)	7.9 (0.6)	50	7.9 (0.3)	7.8 (0.4)	0.41	0.51
Visit 2	52	7.3 (0.3)	7.3 (0.6)	50	7.4 (0.3)	7.4 (0.3)	0.25	0.22
13 weeks	46	7.3 (0.8)	7.2 (1.2)	45	7.1 (0.6)	7.1 (0.7)	0.17	0.33
26 weeks	45	7.1 (0.6)	7.1 (0.8)	45	7.2 (0.6)	7.1 (0.6)	0.63	0.77
Change from visit 1	45	−0.8 (0.7)	−0.8 (0.9)	45	−0.7 (0.6)	−0.8 (0.7)	0.52	0.56
A1C (mmol/mol)								
Visit 1	52	62.8	62.8	50	62.8	61.7		
Visit 2	52	56.3	56.3	50	57.4	57.4		
13 weeks	46	56.3	55.2	45	54.1	54.1		
26 weeks	45	54.1	54.1	45	55.2	54.1		
Weight (kg)								
Visit 1	52	101.1 (13.7)	100.0 (16.0)	50	99.0 (17.4)	98.2 (18.7)	0.45	0.44
Visit 2	52	101.3 (14.2)	99.2 (16.3)	50	99.7 (17.8)	98.6 (21.1)	0.98	0.65
Baseline	52	101.3 (14.2)	99.2 (16.9)	48	100.1 (17.9)	98.1 (21.8)	0.71	0.57
26 weeks	45	97.3 (14.1)	95.7 (16.0)	45	99.9 (18.1)	99.4 (20.3)	0.46	0.55
Change from baseline	45	−4.8 (3.3)	−4.6 (4.4)	44	+0.7 (3.3)	+1.3 (4.0)	<0.001	<0.001
ACR (mg/g)								
Visit 1	52	35.3 (69.1)	10.7 (19.2)	48	41.7 (152.7)	7.8 (9.0)	0.78	0.02
26 weeks	45	34.2 (73.5)	10.2 (10.4)	43	56.5 (197.3)	8.4 (10.7)	0.48	0.53
Change from visit 1	45	−1.8 (29.5)	−1.8 (7.1)	41	+9.5 (119.3)	−1.0 (6.3)	0.40	0.75
ACR (g/μmol)								
Visit 1	52	4.0 (7.8)	1.2 (2.2)	48	4.7 (17.3)	0.9 (1.0)		
26 weeks	45	3.9 (8.3)	1.2 (1.8)	43	6.4 (22.3)	0.9 (1.2)		
Change from visit 1	45	−0.2 (3.3)	−0.2 (0.8)	43	+1.1 (13.5)	−0.1 (0.7)		
Serum creatinine (mg/dL)								
Visit 1	52	0.9 (0.2)	0.9 (0.3)	50	0.9 (0.2)	0.9 (0.4)	0.36	0.45
26 weeks	45	0.9 (0.3)	0.9 (0.3)	45	0.9 (0.2)	0.9 (0.3)	0.74	0.90
Change from visit 1	45	0.0 (0.2)	0.0 (0.2)	45	0.0 (0.1)	0.0 (0.1)	0.83	0.67
Serum creatinine (μmol)								
Visit 1	52	79.6 (17.7)	79.6 (26.5)	50	79.6 (17.7)	79.6 (35.4)		
26 weeks	45	79.6 (26.5)	79.6 (26.5)	45	79.6 (17.7)	79.6 (26.5)		
Change from visit 1	45	0.0 (17.7)	0.0 (17.7)	45	0.0 (8.8)	0.0 (8.8)		
ALT (units/L)								
Visit 1	52	37.6 (22.8)	34.0 (20.0)	50	32.4 (14.6)	29.5 (16.0)	0.18	0.21
26 weeks	45	28.6 (13.2)	26.0 (17.0)	45	33.4 (17.2)	32.0 (15.0)	0.14	0.17
Change from visit 1	45	−10.7 (16.8)	−8.0 (13.0)	45	+0.9 (10.0)	−1.0 (12.0)	0.0002	0.0001
ALT (μkat/L)								
Visit 1	52	0.63 (0.38)	0.57 (0.33)	50	0.54 (0.24)	0.49 (0.27)		
26 weeks	45	0.48 (0.22)	0.43 (0.28)	45	0.56 (0.29)	0.53 (0.25)		
Change from visit 1	45	−0.18 (0.28)	−0.13 (0.22)	45	0.02 (0.17)	−0.02 (0.20)		
SAA (mg/L)								
Baseline	52	6.1 (6.5)	4.0 (4.5)	49	6.7 (8.8)	4.6 (4.2)	0.71	0.74
26 weeks	45	9.5 (29.8)	3.6 (3.7)	44	10.8 (29.8)	5.7 (4.6)	0.84	0.01
Change from baseline	45	+3.5 (30.2)	−0.4 (2.3)	44	+5.1 (29.6)	0.0 (2.3)	0.80	0.02
CRP (mg/dL)								
Baseline	52	0.35 (0.46)	0.22 (0.30)	49	0.44 (0.63)	0.22 (0.44)	0.37	0.99
26 weeks	45	0.38 (0.68)	0.20 (0.17)	45	0.38 (0.60)	0.19 (0.34)	0.98	0.68
Change from baseline	45	+0.03 (0.74)	−0.02 (0.21)	45	+0.02 (0.55)	0.00 (0.13)	0.95	0.97
Interleukin 6 (pg/mL)								
Baseline	52	2.87 (1.57)	2.60 (1.32)	48	2.72 (1.33)	2.53 (1.50)	0.60	0.56
26 weeks	45	3.39 (2.08)	2.74 (1.41)	45	2.94 (1.30)	2.70 (2.14)	0.22	0.55
Change from baseline	45	+0.56 (2.36)	+0.11 (1.80)	45	+0.30 (1.00)	+0.11 (0.95)	0.50	0.76
8-iso-$PGF_{2\alpha}$ (ng/mg)								
Baseline	52	3,360 (3,277)	1,489 (5,648)	49	3,633 (3,716)	1,849 (5,581)	0.70	0.48
26 weeks	45	3,967 (4,197)	1,625 (5,642)	43	2,583 (3,011)	1,113 (3,129)	0.08	0.16
Change from baseline	45	+654 (5,380)	+389 (7,474)	43	−1,400 (4,320)	−1,076 (4,503)	0.052	0.06

ACR, albumin-to-creatinine ratio; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$.

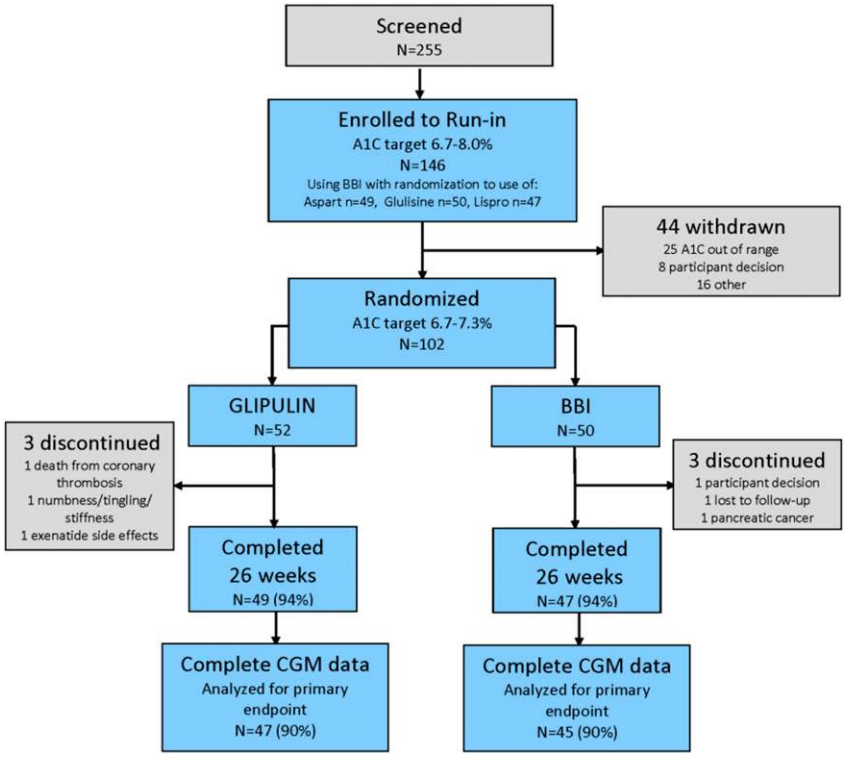

Figure 1—Consolidated Standards of Reporting Trials flow diagram of FLAT-SUGAR enrollment.

Changes of Glucose Profiles Measured by CGM

Means of mean values from CGM recordings for 24-h glucose profiles for all randomized participants are displayed by treatment group in Fig. 3*A*. Profiles for the BBI group at baseline and 26 weeks are nearly superimposable, but the curve for the GLIPULIN group at 26 weeks differed noticeably from that recorded just before randomization. Mean CV before randomization was 30.3 for BBI and 31.9 for GLIPULIN. Group mean change of CV from baseline differed by 2.87, with a greater decrease with GLIPULIN (*t* test, $P = 0.047$) (Fig. 3*B*). An ANCOVA model adjusting for CV before randomization and clinical center did not show a significant between-treatment difference ($P = 0.134$). However, residual CV values did not follow a normal distribution (Shapiro-Wilk , $P = 0.008$), and therefore, the nonparametric Wilcoxon rank sum test was performed. This confirmed a significant difference in CV between the two groups ($P = 0.024$) for the primary end point. Percentages of individuals in each treatment group achieving an improvement from baseline CV of at least 20% were 9% for the BBI and 26% for GLIPULIN ($P = 0.035$).

Other GV indices (SD, IQR, MAGE, CONGA, and MODD) followed a similar, although nonsignificant, pattern of improvement with GLIPULIN (Fig. 3*B*). Percentage of time within the 70–180 mg/dL (3.9–10 mmol/L) range was 71% with BBI treatment and 76% with GLIPULIN at 26 weeks of treatment (Supplementary Table 2*A*).

Hypoglycemia by Clinical Report and by CGM

No episodes of hypoglycemia requiring medical assistance were reported in either group. Analysis of all SMBG values collected by participants during randomized treatment showed that there were no apparent differences in the percentages of measurements at <70 mg/dL (3.9 mmol/L), <60 mg/dL (3.3 mmol/L), or <50 mg/dL (2.8 mmol/L), or >180 mg/dL (10 mmol/L) (Supplementary Table 2*B*). In both groups, >70% of measurements were between 70 and 180 mg/dL and <2% were <70 mg/dL.

Analysis of CGM patterns obtained at 13 and 26 weeks showed that at each time point, 33 of 45 (73%) of the participants using BBI had one or more events with glucose <70 mg/dL (3.9 mmol/L) (as defined in RESEARCH DESIGN AND METHODS), and the mean number of events for each of those affected was 5.2 and 5.4, respectively (Supplementary Table 3). In comparison, 35 and 37 of 47 (74–79%) of those using the GLIPULIN regimen had at least one event, with a mean of 4.8–5.5 events per individual. By CGM at 26 weeks, no statistically significant differences between treatment groups were apparent in percentages of time in which glucose values were <70 mg/dL (3.9 mmol/L), <60 mg/dL (3.3 mmol/L), or <50 mg/dL (2.8 mmol/L), or >180 mg/dL (10 mmol/L) (Supplementary Table 2*B*). Each treatment-group averaged <3% of the time <70 mg/dL (3.9 mmol/L) threshold.

Cardiovascular Risk Markers

With GLIPULIN, significantly greater decreases from baseline were found for ALT (mean ± SD −11 ± 17 vs. −1 ± 12, Wilcoxon, $P = 0.0001$) and serum amyloid A (SAA) (median [IQR]) −0.4 [2.3] vs. +0.0 [2.3], Wilcoxon, $P = 0.02$) (Table 1). In contrast, no between-treatment differences were seen for changes of albuminuria, serum creatinine, serum CRP, serum interleukin 6, or urinary prostaglandin $F_{2\alpha}$.

Arrhythmias by Continuous Electrocardiographic Monitoring

During the entire study (before randomization and at the 13- and 26-week visits), no critical arrhythmias were identified in this clinical arrhythmia-naïve population. A total of 20 abnormal but noncritical episodes were found in each treatment-group during these three intervals of observation. Measurements during randomized treatment (at 13 and 26 weeks) detected 10 episodes of tachyarrhythmias in the BBI group and 9 episodes in the GLIPULIN group. Six episodes of bradyarrhythmias were found with BBI and nine with GLIPULIN (Supplementary Table 4).

Adverse Events

In all, 266 adverse events were reported by 92 participants, 52 of them occurring before randomization (Supplementary Table 5). More of the 214 postrandomization events (131 of 214 [61%]) were reported in the GLIPULIN group. Of 63 events that were considered to be related to the randomized treatment medication, 58 (92%) were in the

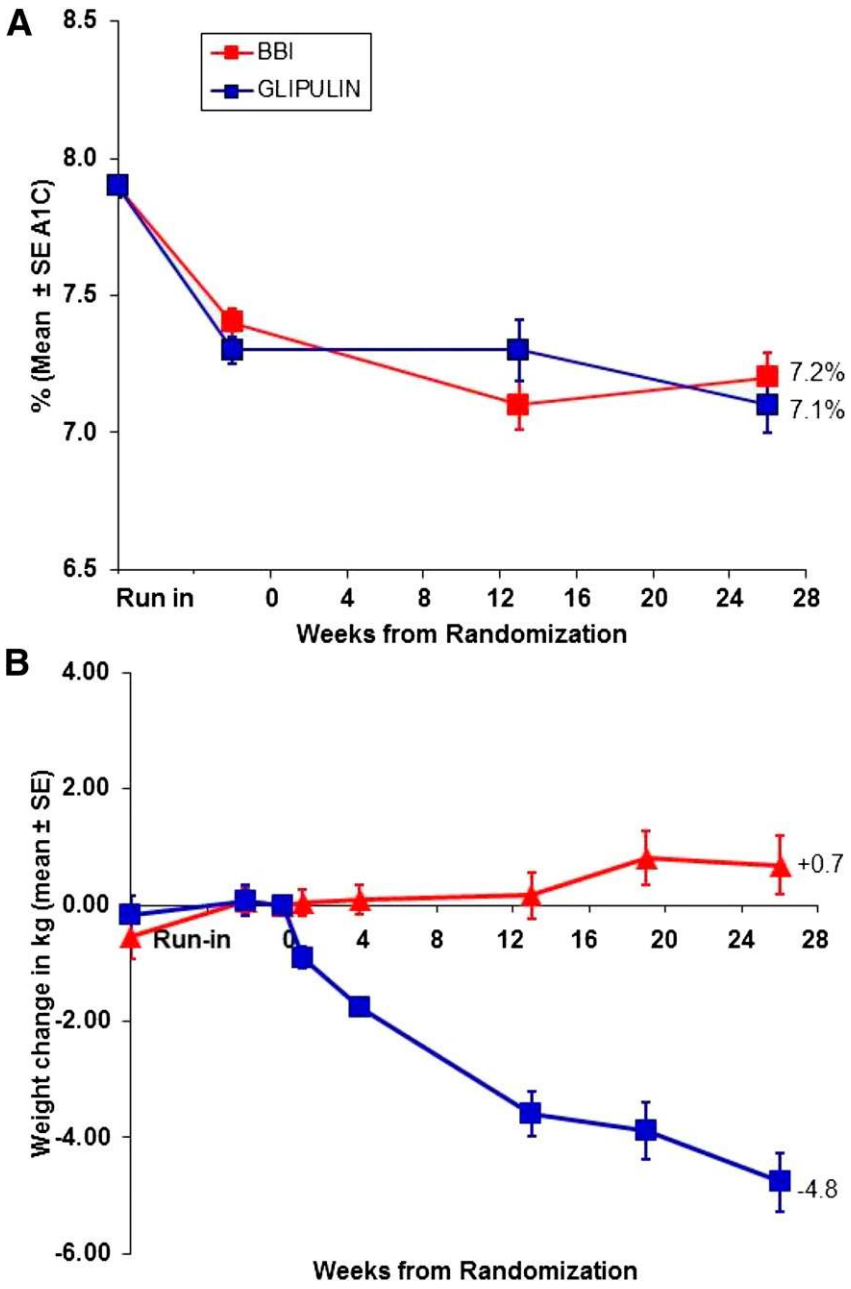

Figure 2—Baseline and on-trial measurements of A1C (*A*) and change in participant weight (*B*) for BBI and GLIPULIN arms.

GLIPULIN group and were gastrointestinal or nervous-system related. Six serious treatment-emergency adverse events were reported in each treatment group. The six participants randomized who did not complete 26 weeks of treatment discontinued due to *1*) numbness, tingling, stiffness, and a death from coronary thrombosis in the GLIPULIN group and *2*) withdrawal of consent, being lost to follow-up, and pancreatic cancer in the BBI group. Thirteen on-treatment adverse events related to the nervous system were reported, 3 in the BBI group and 10 in the GLIPULIN group, with 3 of the 10 were thought to be related to the intervention.

CONCLUSIONS

This proof-of-concept study demonstrated that in a high-risk, long-duration type 2 diabetes population on a background regimen of metformin and basal insulin therapy, a short-acting GLP-1RA exenatide regimen, compared with a rapid-acting insulin analog regimen, significantly reduced the CV of CGM measurements while maintaining similar A1C values near 7% (3.9 mmol/mol). The MAGE also was reduced more with the exenatide-based GLIPULIN group. GV was quite low with both regimens, perhaps due to close observation of study participants and extensive experience of site investigators in the use of insulin. The safety of both regimens, as administered in this study, was further supported by absence of any hypoglycemia requiring third-party assistance. Frequency of glucose values <70 mg/dL (3.9 mmol/L) identified by SMBG did not differ between regimens, but the significance of this is unclear due to the potential for bias in frequency and timing of testing in this unmasked comparison. A more reliable analysis of hypoglycemia was obtained from masked CGM, which showed values were <70 mg/dL (3.9 mmol/L) <3% of the time in both arms. By CGM assessment at 26 weeks, glucose values were between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) 71% of the time with BBI and 75% of the time with GLIPULIN. There was no significant change between baseline and 26 weeks with either regimen.

Lack of significant between-treatment group differences in many of the secondary end points—including other measures of GV, electrocardiographically demonstrated arrhythmias, albuminuria, CRP, interleukin 6, and urinary isoprostanes—may be explained by the relatively modest differences in glycemic patterns and low frequency of hypoglycemia. Secondary end points that did show differences are therefore of particular interest. Whereas body weight changed very little when BBI was continued after randomization, prominent and continuing weight loss accompanied use of the GLIPULIN regimen, with a between-treatment difference at 26 weeks of 5.45 kg. Levels of ALT and of SAA (an established marker of inflammation) were both reduced during treatment with GLIPULIN, observations consistent with a metabolically favorable effect on the liver. However, it is not possible to determine whether these two serum markers were reduced because of the observed reduction of GV, weight loss, other effects of the GLP-1RA, or by some combination of these possibilities. Because weight, ALT, and SAA are all associated with cardiovascular risk, these findings

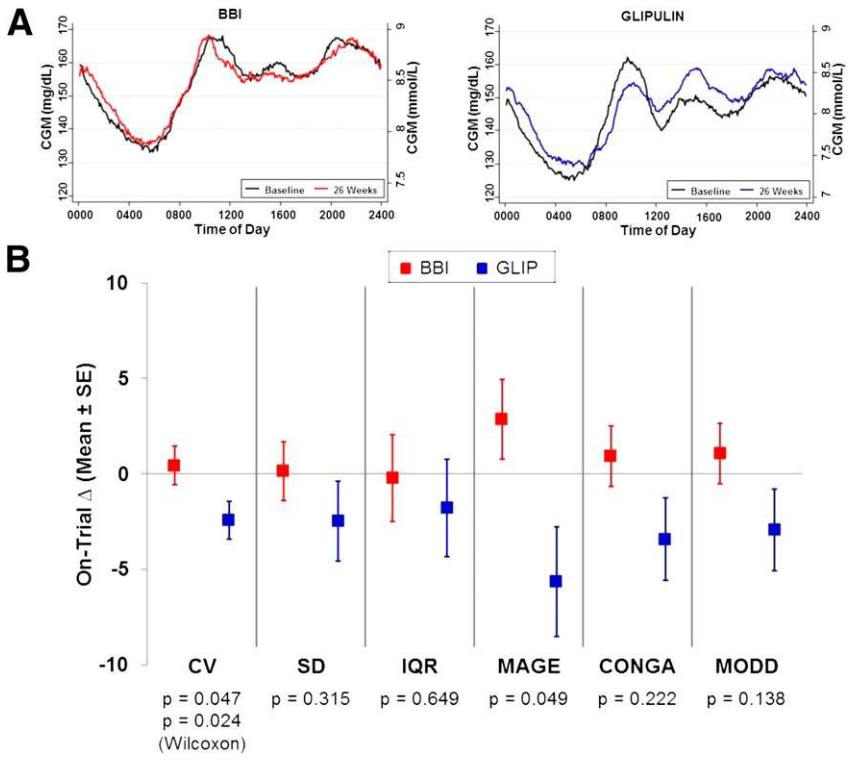

Figure 3—*A*: Means of mean values from continuous glucose measurements per 24-h periods for BBI and GLIPULIN treatment group. *B*: Primary outcome measure of group mean change in CV and differences for other measures of glucose variability between treatment groups.

suggest that longer treatment with the GLIPULIN regimen might lead to medical benefits. Inflammatory markers will be further explored in a future manuscript.

Relationships between glycemic changes, hypoglycemia, and cardiac arrhythmias are of considerable interest in a population like that enrolled in this study. Vital signs measured in the morning at each visit did not differ between treatments, but it is possible that changes in blood pressure or heart rate might have occurred later in the day when the mealtime interventions were given. Predefined analysis of overt arrhythmias reported here did not show any differences between randomized treatments, although any arrhythmia in this clinically arrhythmia-naïve population is of interest. Further analyses are planned to compare QTc and other electrocardiographic findings between treatments and in relation to concurrent glucose patterns.

A recent study by Diamant et al. (15) enrolled patients with type 2 diabetes with A1C levels ≥7.0% (53 mmol/mol) despite use of metformin, with or without a sulfonylurea, together with insulin glargine, but no prior mealtime insulin. After a run-in period in which basal insulin dosage was optimized, 652 participants with A1C still ≥7.0% (53 mmol/mol) were randomized to additional treatment with twice-daily exenatide or thrice-daily insulin lispro for 30 weeks. Both treatment groups attained mean A1C levels of 7.2% (55.2 mmol/mol), very similar to results in our study. As in our study, change of body weight strongly favored exenatide (−4.6 kg), and no between-treatment differences in albuminuria or CRP were observed. Slightly less clinically recognized hypoglycemia was reported with exenatide than with lispro treatment. Our study differed from this earlier report by enrolling a population with a longer average duration of diabetes (median duration of 15 years), in most cases already taking mealtime insulin, and selected for high cardiovascular risk. We collected CGM and Holter data and observed a greater reduction of GV, ALT, and SAA with the exenatide-based regimen.

Our findings, together with those of this earlier report, support two attractive options for further studies. One approach would be to further examine the possibility that GV mediates complications of diabetes by directly comparing the GLIPULIN regimen to a regimen of basal insulin together with a long-acting GLP-1RA. Previous studies have shown that short- and longer-acting GLP-1RAs both have similar effects on body weight; however, longer-acting agents cause greater improvement of fasting plasma glucose and A1C levels, whereas shorter-acting agents more effectively reduce mealtime glycemic increments and thus GV (16,17). Thus, when basal insulin is used to control fasting and between-meal glucose levels for patients with longer-duration diabetes, shorter- and longer-acting GLP-1RAs might both further improve control of A1C but with quite different effects on GV. A study with this design might better isolate effects of GV on cardiovascular risk markers without a confounding difference in change of weight or A1C, thereby allowing further testing of the GV hypothesis.

An alternative follow-up study might test the full clinical potential of the GLIPULIN regimen in attaining A1C levels <7.0% (53 mmol/mol) in a high-risk population with type 2 diabetes. Neither our study nor that of Diamant et al. (15) tested systematic use of a short-acting GLP-1RA with all significant meals, even though mealtime insulin was taken this way, and thus, the added effect of a dose with a midday meal was not obtained. Also, our study did not encourage attainment of A1C levels much below 7.0% (53 mmol/mol), and so little difference in hypoglycemia was seen compared with BBI therapy. Dose-ranging studies suggest that low doses of exenatide (18,19) and lixisenatide (20) both retain the ability to limit mealtime increments of glucose with less frequent gastrointestinal adverse effects than higher doses. Using low doses (e.g., 5 μg) for all administrations, without frequent glucose testing or titration, might prove simpler, safer, and better tolerated than BBI. This approach might improve adherence to treatment by favoring weight loss and reducing frequency of SMBG measurement, and, with systematic titration of basal insulin, might allow more frequent attainment of A1C <7.0% (53 mmol/mol) without problematic hypoglycemia. Use of CGM and Holter

monitoring could assess GV and cardiovascular risks or benefits accompanying this regimen.

Strengths of our study include direct comparison of two treatment regimens for a clinically important population, attainment of a very high rate of adherence to the protocol, direct demonstration of a reduction of GV using CGM, demonstration that Holter monitoring is also feasible in such a study, and confirmation of the efficacy and safety of the newer method of treatment. Our findings were limited by lack of masking of the treatments, inability to distinguish between effects of reduction of GV and other known or potential effects of exenatide on secondary outcomes, and inability to extrapolate the findings to a study population with even longer duration of diabetes and less endogenous insulin reserve, or is less highly selected, expertly supervised, and motivated.

In conclusion, we confirmed efficacy and safety of mealtime exenatide treatment for a high-risk insulin-requiring population and demonstrated a reduction of GV using this approach. Improvement of several measures that are associated with medical risks supports further study of underlying physiologic mechanisms as well as the potential for this regimen to improve medical outcomes in a large and challenging population of patients.

Appendix

Writing Committee. Jeffrey L. Probstfield, University of Washington (co-chair, co-principal investigator); Irl B. Hirsch, University of Washington (co-principal investigator); Barry R. Davis, The University of Texas Health Science Center at Houston; Andrew Ahmann, Oregon Health & Science University; Richard Bergenstal, Park Nicollet; Matthew Gilbert, University of Vermont; Connie Kingry, University of Washington; Dorrine Khakpour, University of Washington; Dejian Lai, The University of Texas Health Science Center at Houston; Sarah L. Pressel, The University of Texas Health Science Center at Houston; Kelley R. Branch, University of Washington; Matthew Riddle, Oregon Health & Science University (co-chair); and Kevin D. O'Brien, University of Washington.

Funding and Duality of Interest. This study is an investigator-initiated clinical trial primarily funded by a grant from Sanofi. A contract was developed between Sanofi and the Clinical Trials Service Unit of the University of Washington, which became the academic sponsor of the study. Supplemental funding was provided later in the study by grants from Bristol-Myers Squibb–AstraZeneca and Sanofi. In-kind donations were provided for the study by several organizations, including Sanofi (donated insulin glargine [Lantus] and insulin glulisine [Apidra] and purchased insulin aspart [NovoLog]), Eli Lilly (donated insulin lispro [Humalog]), Amylin/Bristol-Myers Squibb–AstraZeneca (donated exenatide [Byetta]), Bayer (donated Contour Glucose Meters, strips, and supplies), Becton Dickinson (donated pen needles), Dexcom (donated the various components of the CGM devices [Seven Plus and Gen 4]), and Medicomp (donated Holter monitoring equipment and supported reading of the recordings).

J.L.P. reports honoraria for consulting from Sanofi and research grant support from Sanofi, Bristol-Myers Squibb–AstraZeneca, Eli Lilly, and Bayer. These dualities of interest have been reviewed by the University of Washington. The FLAT-SUGAR Trial Investigators report receiving honoraria for consulting from Roche, Abbott Diabetes Care, and Becton Dickinson and receiving grants from Sanofi and Halozyme. R.B. reports receiving honoraria for consulting and lectures from Abbott Diabetes Care, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb–AstraZeneca, Calibra, Eli Lilly, Halozyme, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, Takeda, and Valeritas. C.K. reports having received grant support from Sanofi and Bristol-Myers Squibb–AstraZeneca. D.K. and K.R.B. report having received grant support from Sanofi. M.R. reports having received grant support from Sanofi, AstraZeneca, Eli Lilly, and Novo Nordisk; honoraria for speaking from Sanofi; and honoraria for consulting from Sanofi, AstraZeneca, Eli Lilly, Elcelyx, Valeritas, and Biodol; these dualities of interest have been reviewed and managed by Oregon Health & Science University. K.D.O. reports having received grant support from Sanofi for this study. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.L.P., I.B.H., B.R.D., C.K., M.C.R., and K.D.O. led the concept development and design of the study. J.L.P., I.B.H., B.R.D., C.K., and K.D.O. were responsible for obtaining funding for the study. J.L.P., I.B.H., B.R.D., A.A., R.B., M.G., C.K., D.K., S.L.P., K.R.B., and K.D.O. provided administrative, technical, or logistic support. J.L.P., I.B.H., B.R.D., A.A., R.B., M.G., C.K., D.K., and S.L.P. were responsible for the provisions of materials, patients, or resources. J.L.P., I.B.H., B.R.D., A.A., R.B., M.G., C.K., D.K., S.L.P., and K.D.O. were responsible for data collection. J.L.P., I.B.H., B.R.D., C.K., D.K., S.L.P., K.R.B., M.C.R., and K.D.O. led the analysis and interpretation of the study. J.L.P., I.B.H., B.R.D., A.A., M.G., C.K., S.L.P., K.R.B., M.C.R., and K.D.O. contributed to the composition of the first draft of the manuscript. J.L.P., I.B.H., B.R.D., C.K., K.R.B., M.C.R., and K.D.O. led critical revision of the article. B.R.D., D.L., and S.L.P. provided statistical expertise and analysis. All authors of the writing committee had access to the results of the analysis, contributed to revisions and made decision to submit for publication. J.L.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015.

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
3. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577–1589
5. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545–2559
6. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560–2572
7. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
8. Hirsch IB. Glycemic variability and diabetes complications: does it matter? Of course it does! Diabetes Care 2015;38:1610–1614
9. Razavi NL, Kitabchi AE, Stentz F, et al. Proinflammatory cytokines in response to insulin-induced hypoglycemic stress in healthy subjects. Metabolism 2009;58:443–448
10. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747
11. Uccellatore A, Genovese S, Dicembrini I, Mannucci E, Ceriello A. Comparison review of short-acting and long-acting glucagon-like peptide-1 receptor agonists. Diabetes Ther 2015; 6:239–256
12. Rodbard D. The challenges of measuring glycemic variability. J Diabetes Sci Technol 2012;6:712–715
13. Probstfield JL, Hirsch I, O'Brien K, et al.; FLAT-SUGAR Trial Investigators. Design of FLAT-SUGAR: randomized trial of prandial insulin versus prandial GLP-1 receptor agonist together with basal insulin and metformin for

high-risk type 2 diabetes. Diabetes Care 2015; 38:1558–1566
14. Garg SK, Voelmle MK, Gottlieb P. Feasibility of 10-day use of a continuous glucose-monitoring system in adults with type 1 diabetes. Diabetes Care 2009;32:436–438
15. Diamant M, Nauck MA, Shaginian R, et al.; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014; 37:2763–2773
16. Drucker DJ, Buse JB, Taylor K, et al.; DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008;372:1240–1250
17. Buse JB, Rosenstock J, Sesti G, et al.; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39–47
18. Poon T, Nelson P, Shen L, et al. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. Diabetes Technol Ther 2005;7:467–477
19. Cervera A, Wajcberg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab 2008; 294:E846–E852
20. Ratner RE, Rosenstock J, Boka G; DRI6012 Study Investigators. Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. Diabet Med 2010; 27:1024–1032