Better Glycemic Control and Weight Loss With the Novel Long-Acting Basal Insulin LY2605541 Compared With Insulin Glargine in Type 1 Diabetes

A randomized, crossover study

Julio Rosenstock, md[1]
Richard M. Bergenstal, md[2]
Thomas C. Blevins, md[3]
Linda A. Morrow, md[4]
Melvin J. Prince, md[5]

Yongming Qu, phd[5]
Vikram P. Sinha, phd[5]
Daniel C. Howey, md[5]
Scott J. Jacober, do[5]

OBJECTIVE—To compare effects of LY2605541 versus insulin glargine on daily mean blood glucose as part of a basal-bolus regimen for type 1 diabetes.

RESEARCH DESIGN AND METHODS—In this randomized, Phase 2, open-label, 2×2 crossover study, 137 patients received once-daily basal insulin (LY2605541 or glargine) plus mealtime insulin for 8 weeks, followed by crossover treatment for 8 weeks. Daily mean blood glucose was obtained from 8-point self-monitored blood glucose profiles. The noninferiority margin was 10.8 mg/dL.

RESULTS—LY2605541 met noninferiority and superiority criteria compared with insulin glargine in daily mean blood glucose (144.2 vs. 151.7 mg/dL, least squares mean difference = -9.9 mg/dL [90% CI -14.6 to -5.2], $P < 0.001$). Fasting blood glucose variability and A1C were reduced with LY2605541 compared with insulin glargine (both $P < 0.001$). Mealtime insulin dose decreased with LY2605541 and increased with insulin glargine. Mean weight decreased 1.2 kg with LY2605541 and increased 0.7 kg with insulin glargine ($P < 0.001$). The total hypoglycemia rate was higher for LY2605541 ($P = 0.04$) and the nocturnal hypoglycemia rate was lower ($P = 0.01$), compared with insulin glargine. Adverse events (including severe hypoglycemia) were similar, although more gastrointestinal-related events occurred with LY2605541 (15% vs. 4%, $P < 0.001$). Mean changes (all within normal range) were higher for alanine aminotransferase, aspartate aminotransferase, triglycerides, and LDL-cholesterol and lower for HDL-cholesterol with LY2605541 compared with insulin glargine (all $P < 0.02$).

CONCLUSIONS—In type 1 diabetes, compared with insulin glargine, LY2605541, a novel, long-acting basal insulin, demonstrated greater improvements in glycemic control, increased total hypoglycemia, and reduced nocturnal hypoglycemia, as well as reduced weight and lowered mealtime insulin doses.

Diabetes Care 36:522–528, 2013

The quest to prolong the action of insulin, which led to modern basal insulins, began in the 1930s with development of protamine zinc insulin (1,2). Basal insulins, such as protamine zinc, lente, isophane (NPH insulin), and ultralente insulins, were originally developed as suspensions to prolong action by delaying absorption (3,4). More recently, insulins glargine (GL) and detemir were developed to prolong subcutaneous absorption by altering amino acid structure (GL) or adding fatty acylated side chains (detemir) (4,5). Insulin degludec, a basal insulin in development, has the goal to achieve an effect longer than 24 h by prolonging subcutaneous absorption (6). Longer-acting insulins may be expected to reduce the need for twice-daily injections, variability, and the risk of hypoglycemia, as well as to provide minimal peak activity. Despite these refinements, current basal insulins cannot restore physiologic distribution of the twofold portal to systemic insulinemia because of subcutaneous systemic absorption, which results in similar portal and systemic levels. Thus, reduced hepatic insulin action must be balanced with excess peripheral insulin action to maintain glucose homeostasis.

LY2605541 is a novel, long-acting basal insulin consisting of insulin lispro covalently modified with a 20-kDa polyethylene glycol moiety. It is a solution-based basal insulin with a time-action profile that is believed to be modulated indirectly through slowed depot absorption and reduced clearance due to increased molecular size. LY2605541 has a duration of action of more than 36 h with low variability, acting considerably longer than insulin glargine (7).

This exploratory Phase 2 clinical trial was designed to determine if LY2605541 was noninferior to insulin GL for reduction of daily mean blood glucose (BG) in patients with type 1 diabetes on a basal-bolus regimen and to compare safety and efficacy of LY2605541 and insulin GL.

RESEARCH DESIGN AND METHODS—This Phase 2, multinational (Israel and U.S.), outpatient, open-label, randomized, two-arm crossover study compared LY2605541 with

insulin GL in patients with type 1 diabetes who had used GL once daily along with mealtime insulin, before the study. The primary objective was to determine if LY2605541 was noninferior to GL for daily mean BG after 8 weeks. The study was conducted from 4 February 2010 to 20 January 2011 in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Study inclusion criteria included type 1 diabetes duration ≥1 year, receiving GL treatment (maximum daily dose, 1 unit/kg) for ≥6 months, age 18 to 65 years, BMI 19 to 45 kg/m^2, and hemoglobin A_{1c} (A1C) ≤10.5%. Exclusion criteria included treatment with GL twice daily in the past 30 days, treatment with oral or injectable diabetes medication other than insulins within the past 3 months, use of an insulin pump, more than one episode of severe hypoglycemia within the past 3 months or diagnosis of hypoglycemia unawareness, New York Heart Association class III or IV cardiac functional status, fasting triglycerides >500 mg/dL, liver disease or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels twofold the upper limit of normal (ULN) or more, renal transplantation or serum creatinine >2.0 mg/dL, participation in a weight loss program, or more than one emergency department visit or hospitalization due to poor glucose control in the past 6 months.

Patients administering GL at any time other than prebreakfast were converted to a prebreakfast basal injection 2 weeks before randomization. Prebreakfast dosing was chosen to elicit potential differences in fasting BG (FBG) due to differences in the half-lives of LY2605541 and GL. Patients continued to use their prestudy mealtime insulin throughout the study.

The study randomization scheme in this open-label trial was stratified within each country by A1C (≤ 8.5%, >8.5%) and baseline basal insulin dose (≤0.4, >0.4 unit/kg). Patients were randomized to receive basal insulin (LY2605541 or GL) once daily plus mealtime insulin for 8 weeks, followed by crossover treatment for 8 weeks and a 4-week follow-up period (Supplementary Fig. 1).

Clinic visits occurred every 2 weeks, with telephone visits interspersed. Patients recorded their self-monitored FBG daily. Eight-point self-monitored BG (SMBG) profiles (measured premeal, 2 h postmeal, bedtime, and 3 A.M.) were collected three times in the week before each clinic visit.

Hypoglycemia was defined as BG concentration ≤70 mg/dL, or if BG was not determined, as experiencing signs or symptoms associated with hypoglycemia (8). Severe hypoglycemia was defined as experiencing signs or symptoms of hypoglycemia with severe neurologic impairment requiring assistance from another person, with recovery after carbohydrate intake, glucagon administration, or intravenous glucose.

Initially, starting doses of LY2605541 were derived from patients' prior basal insulin doses using a conversion factor of 6 nmol LY2605541/unit of GL. After a prespecified interim analysis to assess LY2605541 dose conversion and adjustment, this was changed to 7 nmol LY2605541/unit of GL. LY2605541 concentration was approximately 1,000 nmol/mL, therefore LY2605541 doses were rounded to the nearest 10 nmol (the nearest 10 μL or volumetric unit) to allow accurate administration using a regular 100-unit syringe.

GL was initially transitioned to LY2605541 over 5 days. The total LY2605541 dose was administered each morning along with a full GL dose on the first morning. GL dose was tapered by 25% of the original dose on subsequent days and discontinued on the fifth day. After the interim assessment, this regimen was altered to taper GL over 4 days (75%, 50%, 25%, and 0% GL dose on days 1, 2, 3, and 4, respectively). To transition from LY2605541 back to GL, LY2605541 treatment was stopped, and 2 days later, GL was resumed in 25% daily increments over 4 days.

LY2605541 dose was increased at weekly intervals using the following algorithm: If the mean FBG of three consecutive mornings was 131 to 180 mg/dL, the LY2605541 dose was increased by 10 nmol (10 μL, 1 volumetric "unit"), and if >180 mg/dL, the LY2605541 dose was increased by 20 nmol (20 μL, 2 volumetric "units"). After the interim analysis, these increments were changed to 2 and 4 volumetric "units," respectively. The GL dose was adjusted at weekly intervals using the same algorithm with 2- and 4-unit increments throughout the study. If more than one episode of hypoglycemia occurred in a week, the GL dose was decreased by 2 units or the LY2605541 dose was decreased to 80% of the pre-event dose on the first day and then 90% thereafter.

Prandial insulin adjustments were made as needed, according to the clinical judgment of the treating investigator, with the goal of maintaining preprandial BG between 90 and 130 mg/dL.

Blood samples were tested for the presence of antibodies against LY2605541 and categorized as negative or positive at baseline and at weeks 8 and 16. Percent binding <1.16% was classified as negative.

Statistical methods

SAS Drug Development system (SAS Institute, Cary, NC) was used to perform all statistical analyses. All analyses were based on a slightly modified intent-to-treatment principle in which all patients who took at least one dose of the study medication were included. All tests were performed for two-sided tests at α = 0.1 and the corresponding 90% CIs were calculated. No adjustments for multiplicity were performed. The baseline value for all variables was the last nonmissing value before or at randomization, except that for the analysis of the change in body weight, the value at the beginning of each period was used as the baseline. Assuming no true treatment difference and the SD of within-patient difference of 35.8 mg/dL, the 108 patients who completed the study provided at least 90% power to show noninferiority of LY2605541 to GL at a noninferiority margin of 10.8 mg/dL with the two-sided α = 0.1. If the upper limit of the 90% CI for the least squares (LS) mean difference between treatments was <10.8 mg/dL, LY2605541 was to be declared noninferior to GL. If it was <0 mg/dL, then LY2605541 was to be declared superior.

Daily mean BG was calculated from the three SMBG profiles performed before each visit. Three measures were used to quantify glucose variability: interday FBG (SD of the daily FBG measurements between this visit and the previous visit), interday SMBG variability (average of the interday SDs of the glucose at 8 individual points), and intraday BG variability (SD of SMBG profiles). Rates of hypoglycemia events adjusted for 30 days were calculated by the number of hypoglycemia events divided by patients' duration in the study, multiplied by 30.

All continuous variables, including the primary analysis variable, were analyzed using Grizzle's model (9), specifically, mixed-model repeated measures with independent variables of treatment, sequence, period, week since the beginning of each period, dose conversion (preinterim analysis, postinterim analysis), baseline A1C group, baseline basal

insulin dose group, interaction between treatment and week, and a random effect for patient. To account for possible carry-over effect, body weight and A1C were also analyzed and plotted by sequence and period. Binary variables were analyzed using method of Nagelkerke et al. (10). Sequence groups were compared using the Fisher exact test. Hypoglycemia rate per patient for 30 days was analyzed using a negative binomial model with treatment, treatment sequence, period, and dose conversion as independent variables, and the unstructured variance-covariance was used to model the within-patient correlation.

RESULTS—Of 138 patients randomized to treatment, 137 received at least one dose of study drug and 108 completed the study. Patient decision was the most common reason for discontinuation from both sequence groups (Supplementary Fig. 2). Patient demographics for the two treatment sequence groups were well balanced (Table 1).

After 8 weeks of therapy, LY2605541 resulted in better daily mean ($\pm$ SE) BG (144.2 $\pm$ 2.5 mg/dL) compared with GL (151.7 $\pm$ 3.1 mg/dL; Table 2, Fig. 1). The LS mean difference (LY2605541 minus GL) was -9.9 mg/dL (90% CI -14.6 to -5.2 mg/dL, $P < 0.001$; Table 2). Because the upper limit of the 90% CI was less than 0, LY2605541 was demonstrated to be both statistically noninferior and superior to GL in controlling daily

mean BG. At 8 weeks, interday FBG variability was significantly lower with LY2605541 than with GL ($P < 0.001$), as were interday ($P = 0.061$) and intraday SMBG variabilities ($P = 0.004$).

The 8-point glucose profiles after 8 weeks are depicted in the insert in Fig. 1. FBG from SMBG profiles was not significantly different between LY2605541 and GL. Laboratory fasting plasma glucose, which was measured $\sim$90 min later than FBG from SMBG, was significantly lower with LY2605541 than with GL (Table 2). LY2605541 treatment also resulted in significantly lower A1C (Table 2). During the first treatment period, both sequence groups showed similar reduction in A1C. During the second period, A1C levels rose slightly with GL but continued to fall with LY2605541 (Fig. 2A).

After 8 weeks of treatment, the mealtime insulin dose was $\sim$24% lower with LY2605541 than with GL treatment (Table 2). The basal insulin doses were adjusted to optimize the SMBG FBG measurements using the algorithm noted above. The basal insulin dose for LY2605541 (Table 2) is presented in units per kilogram based on the definition of 1 unit = 9 nmol (7).

Patients had a mean weight loss of 1.20 kg ($P < 0.0001$) during LY2605541 treatment and a mean weight gain of 0.69 kg ($P = 0.0007$) during GL treatment (Fig. 2B). The LS mean difference was -1.89 kg ($P < 0.0001$). Change in weight over time is shown in Fig 2B.

ALT and AST increased during LY2605541 treatment and decreased slightly during GL treatment, resulting in a statistically significant treatment difference after 8 weeks of treatment (Table 2). Mean values for ALT and AST remained in the normal range. At the last visit of the second treatment period, one patient (1.9%) treated with LY2605541 had elevated ALT above three times ULN. This patient entered the study with elevated ALT and AST values of less than two times ULN. The patient's hepatitis serology was negative; a computed tomography scan demonstrated fatty liver.

There were significant differences in lipids after 8 weeks of treatment with LY2605541 or GL. LY2605541 treatment was associated with lower HDL-cholesterol and higher LDL-cholesterol and triglycerides (Table 2). LDL-cholesterol results were not significantly associated with differences in statin use or discontinuation. No other significant differences were observed in laboratory analytes.

Total hypoglycemic event rates (events/30 days) were 12% higher during LY2605541 treatment than during GL treatment during the 8-week treatment period ($P = 0.037$, Table 2). The nocturnal hypoglycemia rate was 25% lower ($P = 0.012$) for LY2605541 compared with GL (Table 2). Incidence of severe hypoglycemia was similar for both basal insulins (5 patients with 6 events with LY2605541 and 3 patients with 6 events with GL).

During LY2605541 treatment, six patients reported eight serious adverse events: severe hypoglycemia ($n = 5$, 6 events), as well as fall and facial bone fracture, both unrelated to hypoglycemia. During GL treatment, four patients reported eight serious adverse events: severe hypoglycemia ($n = 3$, 6 events), urosepsis, and urinary tract infection.

Treatment-emergent adverse events (TEAEs) were similar between groups, with 68 patients (54.8%) reporting one or more TEAEs during LY2605541 treatment and 62 patients (47.7%) reporting one or more TEAEs during GL treatment ($P = 0.691$). TEAEs that occurred in $\geq$5% of patients included upper respiratory tract infection in 12 (8.8%; $P = 1.00$ for between-treatment comparison), headache in 9 (6.6%; $P = 1.00$), and nasopharyngitis in 7 (5.1%; $P = 1.00$).

Events related to skin and subcutaneous tissue were more common during LY2605541 treatment ($n = 9$ [7.3%])

Table 1—Patient demographics and disease characteristics

	LY2605541/GL $n = 69$	GL/LY2605541 $n = 68$	P
Ethnicity			1.00
American Indian or Alaskan Native	—	1 (1.5)	
Asian	—	1 (1.5)	
Black	3 (4.3)	2 (2.9)	
Multiple	1 (1.4)	—	
Caucasian	65 (94.2)	64 (94.1)	
Hispanic or Latino	9 (13)	6 (8.8)	0.586
Country of residence			0.532
Israel	7 (10.1)	4 (5.9)	
U.S.	62 (89.9)	64 (94.1)	
Age (years)	36.8 $\pm$ 11.3	39.5 $\pm$ 12.3	0.181
Men	41 (59.4)	45 (66.2)	0.481
Weight (kg)	83.0 $\pm$ 15.7	83.1 $\pm$ 17.0	0.965
BMI (kg/m^2)	27.5 $\pm$ 4.4	27.1 $\pm$ 4.6	0.582
A1C (%)	7.73 $\pm$ 1.07	7.76 $\pm$ 0.95	0.890
Duration of diabetes (years)	16.8 $\pm$ 11.7	19.1 $\pm$ 11.5	0.258

Values are shown as mean $\pm$ SD or n (%). GL/LY2605541, patients who received 8 weeks of treatment with insulin GL, followed by 8 weeks of treatment with LY2605541; LY2605541/GL, patients who received 8 weeks of treatment with LY2605541, followed by 8 weeks of treatment with insulin GL.

Table 2—Clinical assessments: values at baseline, after 8 weeks of treatment, and for LS mean difference of change from baseline

| | | After 8 weeks of treatment | | | |
	Baseline	LY2605541	Insulin GL	LS mean (90% CI)*	P
Daily SMBG (mg/dL), mean ± SE	161.3 ± 2.9	144.2 ± 2.5	151.7 ± 3.1	−9.9 (−14.6 to −5.2)	<0.001
FBG (SMBG) (mg/dL), mean ± SE	187.4 ± 5.6	153.7 ± 4.1	154.8 ± 5.0	−4.3 (−14.2 to 5.4)	0.464
FPG (laboratory) (mg/dL), mean ± SE	197.8 ± 7.6	149.9 ± 6.8	178.6 ± 7.7	−26.3 (−44.1 to −8.3)	0.017
FBG interday variability, mean ± SE	61.7 ± 2.0	48.6 ± 1.8	56.9 ± 2.2	−8.5 (−12.4 to −4.5)	<0.001
SMBG variability, mean ± SE					
Interday	21.2 ± 1.6	17.6 ± 1.1	21.8 ± 1.6	−3.4 (−6.5 to −0.4)	0.061
Intraday	62.5 ± 1.6	52.2 ± 1.8	58.0 ± 2.2	−6.1 (−9.5 to −2.7)	0.004
A1C (%), mean ± SE	7.70 ± 0.09	7.07 ± 0.07	7.22 ± 0.08	−0.18 (−0.25 to −0.10)	<0.001
Cholesterol (mg/dL), mean ± SE					
HDL	60.3 ± 1.5	54.1 ± 1.5	59.2 ± 1.5	−5.4 (−7.3 to −3.1)	<0.001
LDL	96.1 ± 2.7	102 ± 3.1	92.4 ± 2.7	8.5 (2.7–14.3)	0.016
Triglycerides (mg/dL), mean ± SE	91.2 ± 4.4	113 ± 7.1	85.0 ± 4.4	29.2 (19.5–39.0)	<0.001
ALT (IU/L), mean ± SD	20.9 ± 10.8	27.4 ± 22.3	19.5 ± 9.7	8.6 (5.1–12.1)	<0.001
AST (IU/L), mean ± SD	21.1 ± 8.8	23.4 ± 11.9	20.1 ± 6.6	3.7 (1.9–5.6)	0.001
Rate of hypoglycemic events†					
Total events	3.78 ± 3.92	8.74 ± 7.70	7.36 ± 6.80	1.12‡ (1.03–1.23)	0.037
Nocturnal events	0.46 ± 1.13	0.88 ± 1.22	1.13 ± 1.42	0.75‡ (0.62–0.90)	0.012
Insulin dose (units/kg/day), mean ± SD					
Basal	0.36 ± 0.14	0.42 ± 0.18	0.43 ± 0.19	—	—
Mealtime	0.23 ± 0.17	0.19 ± 0.14	0.24 ± 0.18	−0.06 (−0.08 to −0.03)	<0.001

FPG, fasting plasma glucose. *Mean difference of change from baseline, which is based on mixed-model repeated-measures analyses. †Rate of events across 8 weeks of treatment, per 30 days. ‡These values are the ratios of the LY2605541 negative binomial mean to the insulin GL negative binomial mean.

compared with GL treatment ($n = 2$ [1.5%]), but the difference was not significant ($P = 0.222$). The most common TEAEs in this category were pruritus and rash, which occurred in two patients (1.5%) each. Gastrointestinal (GI)-related events were reported by more patients during LY2605541 treatment ($n = 19$ [15.3%]) than during GL treatment ($n = 5$ [3.8%]; $P < 0.001$). No individual GI-related TEAEs occurred in ≥5% of patients. The most prevalent were dyspepsia, nausea, and abdominal distension, which occurred in four patients each during LY2605541 treatment. Mean weight loss was 0.84 kg for LY2605541-treated patients who experienced a GI-related TEAE and 1.33 kg for LY2605541-treated patients who did not.

Pulse rate and blood pressure (BP) responses and comparisons were variable throughout the study. Systolic BP and pulse rate did not differ between treatments after 8 weeks, but diastolic BP was slightly higher for LY2605541 than for GL (75.0 ± 0.9 vs. 73.6 ± 0.8, Δ = 1.32 mmHg; $P = 0.10$).

The percentages of patients who were LY2605541 antibody-negative at baseline and became antibody-positive after 8 weeks of treatment was similar for LY2605541 and GL (Supplementary Table 1). Interpretation of antibody response during treatment period 2 is confounded due to the study's crossover design. Change in the antibody status (negative to positive or positive to negative) had no apparent effect on glycemic response.

CONCLUSIONS—The primary objective of this crossover Phase 2 study
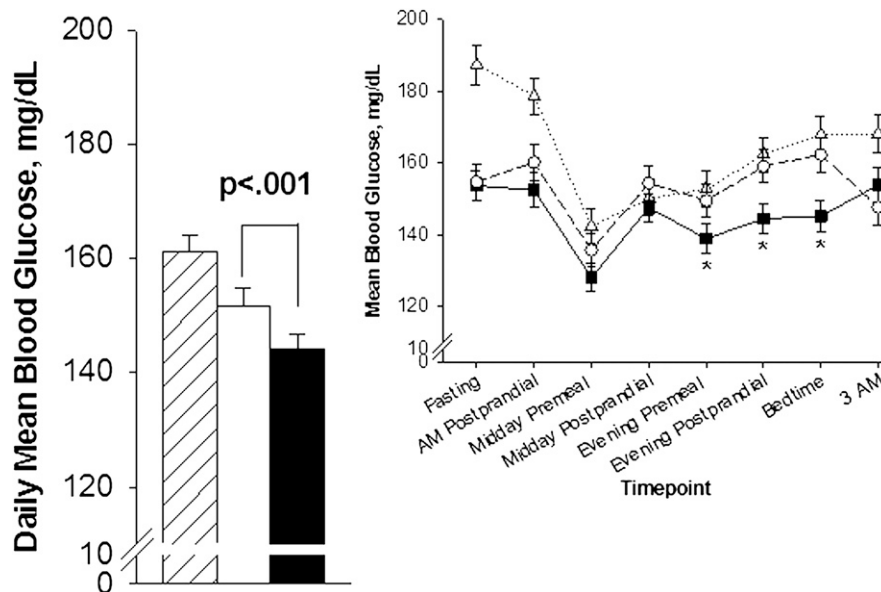
Figure 1—*Daily mean (± SE) BG at baseline and at 8 weeks for LY2605541 (LY) and insulin GL. Baseline for both treatments, ▨; insulin GL, □; LY2605541, ■. Inset graph shows mean (± SE) 8-point SMBG profile at baseline and after 8 weeks of treatment for LY2605541 and GL. Baseline for both treatments, △; insulin GL, ○; LY2605541, ■. *Times at which BG was significantly lower (P < 0.01) after 8 weeks of LY2605541 treatment compared with GL.*
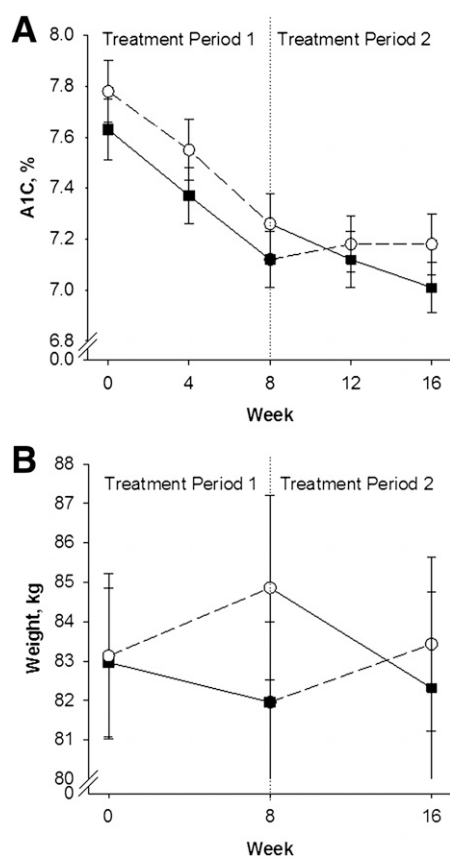
Figure 2—*Mean A1C and weight during treatment with LY2605541 and insulin GL. Patients received treatment with one basal insulin for the first 8-week treatment period and were switched to the other basal insulin for the second treatment period. Insulin GL, ○; LY2605541, ■. A: Mean (± SE) A1C throughout the two treatment periods. B: Mean (± SE) weight throughout the two treatment periods.*

was to compare the effect of two basal insulins, LY2605541 and GL, on mean BG of 8-point SMBG profiles after 8 weeks of treatment when used in basal-bolus insulin regimens in patients with type 1 diabetes. Mean BG was chosen rather than A1C because of the short duration of the study and the likelihood of a carryover effect in A1C. The study demonstrated LY2605541 was noninferior and superior to GL in achieving a lower mean BG after 8 weeks of treatment. LY2605541 also reduced A1C more than GL. Both sequence groups completed the study with mean values at or near guideline-recommended treatment goals for A1C, which attests to the robustness of study implementation.

In addition to improved glycemic control, LY2605541 achieved lower interday and intraday glycemic variability

compared with GL, possibly due to its longer duration and a lower peak-to-trough ratio compared with GL (7). These basal insulins were both administered before breakfast to compare the effect of their duration on fasting glucose. We anticipated that differences in fasting glycemia might be demonstrated because of difference in duration of action, but this was not observed in the fasting glucose from SMBG profiles.

The molar amount of LY2605541 equivalent to 1 unit of insulin was not known before this study. Because the final dose of LY2605541 in nanomoles per kilogram was empirically determined in this trial, and FBG from SMBG was similar between LY2605541 and GL after 8 weeks, the ratio of the basal insulin doses in nanomoles per kilogram at 8 weeks can be used as a reasonable dose conversion factor. This conversion indicates that 9 nmol LY2605541 has approximately the same effect on glycemic measures as 1 unit of insulin glargine. Similar results were seen in the type 2 diabetes trial (11). Thus, for Phase 3 trials, LY2605541 will be formulated at 900 nmol/mL to achieve a U-100 concentration.

The difference in laboratory fasting plasma glucose between treatments in this trial is likely to be artificial and not representative of the patient's glycemic pattern because these measurements were obtained later in the morning (~90 min after the recorded timing of the home-based SMBG FBG values). These laboratory measures were therefore typically obtained more than 24 h after the previous basal insulin dose and would not be representative of the patient's routine, but they do suggest a longer glucose-lowering action of LY2605541.

Patients required ~24% less mealtime insulin during LY2605541 treatment than during GL treatment. This was not a result of a relatively higher dose of LY2605541 compared with GL because fasting glycemia was not different between treatments but presumably is due to better daytime coverage from a longer-lasting basal insulin.

Despite morning administration, which should have minimized nocturnal hypoglycemia for the shorter-acting GL (12), LY2605541 was associated with a lower rate of nocturnal hypoglycemia than GL. However, overall rates of total hypoglycemia were higher during LY2605541 treatment. The higher rate of total hypoglycemia was not a result of a relatively higher dose of LY2605541

compared with GL, because fasting glycemia was not different between treatments and LY2605541 treatment resulted in lower nocturnal hypoglycemia events.

Different treat-to-target algorithms were used for dose titration and for reduction of the two basal insulins after hypoglycemia. The algorithm for LY2605541, while exploratory, was developed based on the pharmacokinetic and pharmacodynamic characteristics of that basal insulin (7). Further clinical experience will be needed to determine the optimal dose adjustment needed in instances of hypoglycemia with LY2605541 as well as the best use of mealtime insulin with this novel long-acting insulin.

Patients treated with LY2605541 lost weight while improving glycemic control. This observation was reaffirmed by sequential observations noted with the crossover design (Fig. 2B). Weight loss with improved glycemic control was also observed in a LY2605541 Phase 2 trial in patients with type 2 diabetes (11).

Patients in this study reported significantly more GI-related adverse events with LY2605541 compared with GL. The converse was noted in a study of LY2605541 in type 2 diabetes (11). Skin disorders were more common with LY2605541 in that study (11), but the difference between treatment groups in skin disorders was less pronounced in this study.

Patients treated with LY2605541 experienced increases in triglycerides and LDL-cholesterol and a reduction in HDL-cholesterol compared with baseline and GL treatment. Triglycerides returned to levels similar to baseline in the follow-up period, and cholesterol was not remeasured. A per-protocol analysis suggested that differences in statin use and discontinuation could not explain the LDL-cholesterol results. The combination of weight loss and lipid changes with improved glycemic control is in contrast to results typically observed with other therapeutically administered insulins. These findings of weight loss and triglycerides changes compared with GL were also observed in the LY2605541 type 2 diabetes study, although changes in LDL- and HDL-cholesterol were not (11).

Mean serum ALT and AST levels also increased from baseline and were higher than with GL, but were within the normal range. This increase in mean levels may reflect a hepatic adaptation reaction to the polyethylene glycolated insulin (13–15). Alternatively, this may reflect an increase

in hepatic fat content, although serum enzyme elevations may not be a reliable indicator of this effect, and a similar magnitude of difference in ALT and AST was observed in the LY2605541 type 2 diabetes study (11). In future studies, additional hepatic monitoring will occur in larger populations with rigorous evaluation of elevations. Hepatic fat content will also be assessed in a subgroup of patients.

The effect of LY2605541 is intriguing in view of long-established precepts of insulin action. Our findings may indicate a significantly different physiological action of LY2605541 compared with other insulins. We speculate that the large molecular (and hydrodynamic) size (16) of this insulin contributes to this aspect of different action. This large size may reduce insulin transport (and thus action) into peripheral target tissues such as adipose tissue. The hepatic sinusoidal endothelium is fenestrated (17) and should permit less impeded transport into the liver. The net effect of these two differential aspects of insulin transport results in a hepatic preferential insulin, as was observed in a somatostatin and glucagon-infused, LY2605541-treated conscious dog model (17). LY2605541 may therefore have the potential to restore a more physiological insulin action and reduce the peripheral hyperinsulinemic action typical of exogenous insulin therapy. With potentially reduced peripheral action, patients converting to LY2605541 may experience decreased lipogenic insulin stimuli, increased lipolysis, and perhaps a transient increase in triglycerides with a concomitant but transient increase in LDL-cholesterol and decrease in HDL-cholesterol. Further, it could be hypothesized that increased lipid oxidation may lead to patients' weight loss. Lipid parameters and potential mechanisms of changes will be assessed in future studies of longer duration.

Results of this study are limited by the inherent nature of an open-label design, which is predominantly exploratory in nature, and of small population size. The short duration and crossover design, although permitting patients to be their own control, may confound observations for safety parameters. The study, however, was well implemented by the investigators, as is evident by end point A1C levels. Dosing variability may have occurred because both basal insulins were administered by vial and syringe, and patients had to reconstitute LY2605541.

In addition, different algorithms were used to adjust doses after hypoglycemia for the two basal insulins. Future Phase 3 studies will address these limitations.

In conclusion, LY2605541 basal insulin therapy for patients with type 1 diabetes has the potential to improve glycemic control, reduce weight, glucose variability, and nocturnal hypoglycemia, and lower prandial insulin requirements. LY2605541 was associated with an increase in total hypoglycemia. The reduction in prandial insulin dose from baseline to end point and the reduction in nocturnal hypoglycemia with LY2605541 suggest prandial insulin may be a major contributor to the increase in total hypoglycemia. Overall Phase 2 findings and preclinical results (18) suggest LY2605541 may have a novel mechanism of action. Phase 3 studies are underway to assess the observed benefits and further evaluate the clinical significance of changes in liver enzymes and lipids.

References
1. Bliss M. *The Discovery of Insulin*. Chicago, IL, University of Chicago Press, 1982

2. Jersild M. Insulin zinc suspension; four years' experience. Lancet 1956;271:1009–1013

3. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. Diabetes Care 1984;7:188–199

4. Bolli GB, Di Marchi RD, Park GD, Pramming S, Koivisto VA. Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia 1999;42:1151–1167

5. Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2004; 64:2577–2595

6. Jonassen I, Havelund S, Ribel U, et al. Insulin degludec is a new generation ultra-long acting basal insulin with a unique mechanism of protraction based on multi-hexamer formation. Diabetes 2010;59(Suppl. 1):A11 [abstract]

7. Sinha VP, Howey DC, Soon DKW, et al. Single-dose pharmacokinetics (PK) and glucodynamics (GD) of the novel, long-acting basal insulin LY2605541 in healthy subjects. Diabetes 2012;61(Suppl. 1):A273 [abstract]

8. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249

9. Grizzle JE. The two-period change-over design and its use in clinical trials. Biometrics 1965;21:467–480

10. Nagelkerke NJD, Hart AAM, Oosting J. The two-period binary response crossover trial. Biom J 1986;28:863–869

11. Bergenstal RM, Rosenstock J, Arakaki RF, et al. A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, versus insulin glargine in basal insulin-treated patients with type 2 diabetes. Diabetes Care 2012;35: 2140–2147

12. Hamann A, Matthaei S, Rosak C, Silvestre L; HOE901/4007 Study Group. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. Diabetes Care 2003;26:1738–1744

13. Au JS, Navarro VJ, Rossi S. Review article: drug-induced liver injury—its pathophysiology and evolving diagnostic tools. Aliment Pharmacol Ther 2011;34:11–20

14. Feldman M, Freidman LS, Brandt LJ. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia, PA, Saunders Elsevier, 2010

15. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006;354:731–739

16. Hansen RJ, Cutler GB Jr, Vick A, et al. LY2605541: Leveraging hydrodynamic size to develop a novel basal insulin. Diabetes 2012;61(Suppl. 1):A228 [abstract]

17. Braet F, Wisse E. Structure and functional aspects of liver sinusoidal endothelial cell fenestrae: a review. Comp Hepatol 2002;1:1 Available at www.comparative-hepatology.com/content/1/1/1

18. Moore MC, Smith MS, Mace KF, et al. Novel pegylated basal insulin LY2605541 has a preferential hepatic effect on glucose metabolism. Diabetes 2012;61(Suppl. 1): A417 [abstract]