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

**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.

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...
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%, 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 3 consecutive mornings was ≥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-treat 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
After 8 weeks of therapy, LY2605541 resulted in better daily mean (± SE) BG (144.2 ± 2.5 mg/dL) compared with GL (151.7 ± 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 eight-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 ~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 meal-time insulin dose was ~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.

Table 1—Patient demographics and disease characteristics

<table>
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<tr>
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<th>LY2605541/GL</th>
<th>GL/LY2605541</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>n = 69</td>
<td>n = 68</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>—</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (4.3)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (1.4)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>65 (94.2)</td>
<td>64 (94.1)</td>
<td></td>
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<tr>
<td>Hispanic or Latino</td>
<td>9 (13)</td>
<td>6 (8.8)</td>
<td>0.586</td>
</tr>
<tr>
<td>Country of residence</td>
<td></td>
<td></td>
<td>0.532</td>
</tr>
<tr>
<td>Israel</td>
<td>7 (10.1)</td>
<td>4 (5.9)</td>
<td></td>
</tr>
<tr>
<td>U.S.</td>
<td>62 (89.9)</td>
<td>64 (94.1)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.8 ± 11.3</td>
<td>39.5 ± 12.3</td>
<td>0.181</td>
</tr>
<tr>
<td>Men</td>
<td>41 (59.4)</td>
<td>45 (66.2)</td>
<td>0.481</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.0 ± 15.7</td>
<td>83.1 ± 17.0</td>
<td>0.965</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 4.4</td>
<td>27.1 ± 4.6</td>
<td>0.582</td>
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<tr>
<td>A1C (%)</td>
<td>7.73 ± 1.07</td>
<td>7.76 ± 0.95</td>
<td>0.890</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>16.8 ± 11.7</td>
<td>19.1 ± 11.5</td>
<td>0.258</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD or n (%). GL/LY2605541, patients who received 8 weeks of treatment with insulin GL, followed by 8 weeks of treatment with LY2605541, GL/LY2605541/GL, patients who received 8 weeks of treatment with LY2605541, followed by 8 weeks of treatment with insulin GL.
LY2605541 vs. glargine in type 1 diabetes

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LY2605541</th>
<th>Insulin GL</th>
<th>LS mean (90% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily SMBG (mg/dL), mean ± SE</td>
<td>161.3 ± 2.9</td>
<td>144.2 ± 2.5</td>
<td>151.7 ± 3.1</td>
<td>-9.9 (-14.6 to -5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG (SMBG) (mg/dL), mean ± SE</td>
<td>187.4 ± 5.6</td>
<td>153.7 ± 4.1</td>
<td>154.8 ± 5.0</td>
<td>-3.4 (-14.2 to 5.4)</td>
<td>0.464</td>
</tr>
<tr>
<td>FPG (laboratory) (mg/dL), mean ± SE</td>
<td>197.8 ± 7.6</td>
<td>149.9 ± 6.8</td>
<td>178.6 ± 7.7</td>
<td>-26.3 (-44.1 to -8.3)</td>
<td>0.017</td>
</tr>
<tr>
<td>FBG interday variability, mean ± SE</td>
<td>61.7 ± 2.0</td>
<td>48.6 ± 1.8</td>
<td>56.9 ± 2.2</td>
<td>-8.5 (-12.4 to -4.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SMBG variability, mean ± SE</th>
<th>21.2 ± 1.6</th>
<th>17.6 ± 1.1</th>
<th>21.8 ± 1.6</th>
<th>-3.4 (-6.5 to -0.4)</th>
<th>0.061</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%), mean ± SE</td>
<td>7.70 ± 0.09</td>
<td>7.07 ± 0.07</td>
<td>7.22 ± 0.08</td>
<td>-0.18 (-0.25 to -0.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cholesterol (mg/dL), mean (± SD)

| 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|

Triglycerides, mean ± SD

| 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|
| Nightly events | 0.46 ± 1.13 | 0.88 ± 1.22 | 1.13 ± 1.42 | 0.75 (0.62–0.90) | 0.012|

GF, 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 ≥3% 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...
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, O; LY2605541, □. A: Mean (± SE) A1C throughout the two treatment periods. B: Mean (± SE) weight throughout the two treatment periods.

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, O; 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 eight-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 inter- 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-acting 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 GL-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 decrease 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.

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L.A.M. is an employee of and holds stock in Proli Institute for Clinical Research, which was contracted with Eli Lilly and Company to perform clinical research activities for this study.


D.C.H. is a retired employee of Eli Lilly and Company and holds stock in Eli Lilly and Company.

No other potential conflicts of interest relevant to this article were reported.

J.R., R.M.B., and L.A.M. participated in conducting the study, in the data analysis, and in writing the manuscript, and approved the final manuscript. T.C.B. participated in the data analysis and in writing the manuscript and approved the final manuscript. M.J.P., V.P.S., and D.C.H. participated in the study design, in the data analysis, and in writing the manuscript, and approved the final manuscript. Y.Q. participated in the study design, designed and conducted the statistical analyses, participated in the data analysis and in writing the manuscript, and approved the final manuscript. S.J.J. participated in the study design, in conducting the study, in the data analysis, and in writing the manuscript, and approved the final manuscript. J.R. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**References**

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

**L.Y2605541 vs. glargine in type 1 diabetes**