Steady-state pharmacokinetics and glucodynamics of the novel, long-acting basal insulin LY2605541 dosed once-daily in patients with type 2 diabetes mellitus

V. P. Sinha, D. C. Howey, S. L. Choi, K. F. Mace & T. Heise

1Eli Lilly and Company, Indianapolis, IN, USA
2Profil, Neuss, Germany

Aims: To assess the pharmacokinetics (PK) and glucodynamics (GD) of LY2605541 in patients with type 2 diabetes mellitus.

Methods: This parallel-group, open-label, dose-escalation study examined the PK and GD of basal insulin LY2605541 after single and multiple-dose administration. Fixed doses of LY2605541 (0.33–1.00 U/kg) were given once-daily (QD) for 14 days to insulin-treated patients with type 2 diabetes. A 24-h euglycaemic glucose clamp was conducted on days 1 and 14.

Results: PK steady state was achieved within 7–10 days and the peak-to-trough fluctuation was <2, translating to a nearly ‘peakless’ glucose infusion rate at steady state and with a duration of action at least 24 h. Across dose levels, $t_{1/2}$ ranged from 44.7 to 75.5 h (≈2–3 days). As steady state was achieved, there were dose-dependent reductions in the prandial insulin dose and in fasting blood glucose, which decreased to 60–100 mg/dl across dose levels. Within-patient variability was <14 and <26% for the area under the concentration versus time curve (AUC) of the 8-point blood glucose profile and fasting blood glucose, respectively. The nocturnal glucose control between 03:00 and 09:00 hours was relatively unchanged. Mild hypoglycaemia was the most common adverse event.

Conclusions: In this Phase I study of fixed LY2605541 doses without titration, LY2605541 was well-tolerated and demonstrated a flat PK and GD profile accompanied by glucose normalization, prandial insulin dose reduction and no severe hypoglycaemia.

Keywords: insulin analogues, pharmacodynamics, pharmacokinetics, type 2 diabetes

Date submitted 6 May 2013; date of first decision 28 June 2013; date of final acceptance 30 September 2013

Introduction

Basal insulin, in combination with oral antidiabetes medications, has been a successful initial therapy option for patients with type 2 diabetes mellitus [1–4]. Its success can be measured by the ability to provide several desirable characteristics, including a solution-based formulation that can readily be integrated into various delivery devices; a prolonged activity profile that supports a once-daily dosing regimen; no pronounced peaks in activity that can induce hypoglycaemia; reproducible absorption from the subcutaneous tissues with minimal variation in blood glucose-lowering activity; and a weight-gain neutral or weight-loss profile. While improvements have been made in the pharmacokinetic/pharmacodynamic (PK/PD) properties of basal insulin over the last decade, currently available basal insulins still do not meet all desired characteristics. In particular, neutral protamine Hagedorn (NPH) insulin exhibits a marked peak in its PK profile [5–7], with the basal insulin analogues, insulin glargine and insulin detemir exhibiting a smaller peak [8]. Additionally, NPH, insulin glargine and insulin detemir do not always cover 24-h insulin needs of patients with once-daily administration [7,9,10]. PD variation is observed in particular with either NPH or glargine [11].

The novel basal insulin analogue, LY2605541, is a long-acting insulin composed of insulin lispro covalently bound, via a urethane bond, to a 20-kDa polyethylene glycol (PEG) chain. LY2605541 has a large functional size and a prolonged duration of action. This extended activity is believed to be mediated through slower absorption and reduced renal clearance [12]. Additionally, the tissue distribution of LY2605541 is believed to be similar to endogenous insulin, with restricted peripheral activity and retained hepatic activity [13].

This study assessed the PK and glucodynamic (GD) profile of LY2605541 after single dose and multiple daily doses in patients with type 2 diabetes previously treated with insulin. Secondary objectives included assessing the safety, tolerability and intra-patient variability of LY2605541 PK and GD parameters.

Patients and Methods

Patients and Study design

This Phase I, open-label, parallel, four-arm, multiple-ascending dose study was completed at a single center in Germany between April 2009 and July 2009. The sample size of eight patients per cohort was expected to provide adequate power
for parameter estimation and is consistent with other Phase I studies evaluating safety, PK and/or GD parameters. The study was approved by an ethical review board. All study procedures were carried out in compliance with the Declaration of Helsinki and Good Clinical Practices. All subjects provided written informed consent.

Eligible patients were men or women, 18–65 years of age (inclusive), with type 2 diabetes mellitus diagnosed at least 1 year prior to enrollment, and who were treated with basal and bolus insulin for at least 3 months prior to screening. Patients were required to have a glycylated haemoglobin (HbA1c) ≤10% and a fasting C-peptide level of ≤1.0 nmol/l at screening to prevent stimulation of endogenous insulin through glucose infusion during the clamp experiments. Patients were excluded if they used a total daily dose of basal insulin that exceeded 0.8 (1)U/kg/day had taken any glucose-lowering medications other than insulin for at least 3 months before the screening visit, had >1 episode of severe hypoglycaemia, or had received chronic systemic glucocorticoid therapy (excluding topical, intra-articular and inhaled preparations) in the past year, or any glucocorticoid therapy within 30 days prior to the screening visit.

Patients were assigned to 1 of 4 treatment cohorts of ascending LY2605541 dose. LY2605541 was administered as mg/kg (nmols/kg) with dose conversion to units (U) as follows: 0.025 mg ≈ 1 nmol and 9 nmols = 1 U of LY2605541. Given this conversion from mg/kg to U/kg, dose levels were 0.33 U/kg (Cohort 1), 0.67 U/kg (Cohort 2), 1.00 U/kg (Cohort 3) and 0.50 U/kg (Cohort 4). The planned dose in Cohort 4 was intended to be 1.33 U/kg; however, this dose was reduced due to the number of events of mild hypoglycaemia in Cohort 3.

Study Procedures

Patients were admitted to the Clinical Research Unit on day 2 and remained resident throughout the dosing period (days 1 through 14), until discharge on day 16. The last dose of basal insulin glargine or insulin detemir on day 2 was required to be administered prior to bedtime (23:00 hours at the latest) in order to safely avoid any carryover effects of long-acting insulin preparations. Patients were allowed to subcutaneously administer short-acting insulin (Humulin®, Eli Lilly and Company, Indianapolis, IN, USA) for mealtime coverage on day 1. LY2605541 was administered subcutaneously, once daily in the morning on days 1–14. Upon discharge, patients were followed on an outpatient basis until at least 30 days after the last dose of LY2605541. Immunogenicity testing was conducted approximately 30 days after the last dose of study drug.

Euglycaemic glucose clamps (24-h duration) were performed on days 1 and 14. Patients were fasted (except for water) from approximately 8 h prior to dosing until completion of the 24-h clamp period. Intravenous (i.v.) insulin infusion of regular human insulin (Humulin®) was started at least 4 h before administration of LY2605541 to achieve a target blood glucose level of 90 mg/dl (5.0 mmol/l). The goal was to achieve this target by at least 2 h before dosing so that the Humulin® infusion rate could be lowered to a level where the blood glucose remained stable and at the same time no glucose infusion was required. The i.v. insulin infusion was stopped completely 15 min before trial drug administration. After the administration of LY2605541, a 20% glucose solution was infused at a variable rate (via Biostator®, Miles Laboratories, Elkhart, IN, USA) in order to maintain blood glucose at the clamp level of 90 mg/dl. The rate of glucose delivery was adjusted by the Biostator in response to changes in blood glucose at 1-min interval until 24-h post dosing.

Fixed meals were administered to patients on all inpatient days, except days 1 and 14. The daily caloric intake was 2200 kcal/day, which was increased to 2600 kcal/day in Cohort 3 to ensure stabilization of blood glucose values. An adjustable dose of short-acting bolus insulin was administered on an individual basis to achieve pre-prandial glucose values between 70 and 180 mg/dl. In the event that blood glucose concentrations fell below 60 mg/dl (confirmed by a repeat measurement), or in the event that a patient experienced symptoms consistent with hypoglycaemia, an adequate portion (at least 10 g) of carbohydrates were administered orally and blood glucose testing was performed for every 20 min until the blood glucose level rose above 70 mg/dl.

Serum samples for PK analysis were obtained on day 1 (pre-dose, 0.5, 2, 4, 6, 12 and 24 hours), day 2 (pre-dose), day 7 (pre-dose, 4, 8 and 12 h), days 10, 13 and 14 (pre-dose, 2, 4, 6, 8 and 12 h), days 15, 17, 19, 21, 23 and 25. Samples were analyzed using a validated LY2605541-specific, enzyme-linked immunosorbent assay (ELISA) method in which the lower limit of quantification was 75 PM and the upper limit of quantification was 900 PM. Samples above the limit of quantification were diluted and reanalyzed to yield results within the calibrated range. Serum samples for GD measures were additionally obtained during the clamp procedure and 8-point glucose profiles were performed daily from day 2 through day 16.

Table 1. Demographic and baseline characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.33 U/kg (n = 8)</th>
<th>0.50 U/kg (n = 8)</th>
<th>0.67 U/kg (n = 8)</th>
<th>1.00 U/kg (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.0 (42–65)</td>
<td>56.5 (50–64)</td>
<td>58.9 (47–65)</td>
<td>55.3 (49–62)</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>8 (100)</td>
<td>6 (75)</td>
<td>8 (100)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 (29.3–36.9)</td>
<td>30.4 (27.5–33.3)</td>
<td>32.0 (28.9–36.2)</td>
<td>30.2 (27.0–33.7)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>97.7 (81.5–123.6)</td>
<td>89.9 (69.5–105.1)</td>
<td>103.6 (89.5–114.5)</td>
<td>96.8 (86.9–106.6)</td>
</tr>
<tr>
<td>Duration of T2DM (years)</td>
<td>13.7 (7.1–21.8)</td>
<td>17.9 (7.3–28.3)</td>
<td>13.4 (9.0–21.3)</td>
<td>19.8 (12.9–39.3)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 (6.3–8.5)</td>
<td>8.2 (6.6–9.6)</td>
<td>8.1 (6.2–9.9)</td>
<td>7.4 (6.1–8.6)</td>
</tr>
</tbody>
</table>

Data are mean (range), with the exception of gender which is presented as number (n) and percentage (%) of male patients. BMI, body mass index; T2DM, type 2 diabetes mellitus; HbA1c, glycylated haemoglobin.
Table 2. Summary of LY2605541 PK parameters following multiple once-daily doses in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>0.33 U/kg n = 8</th>
<th>0.50 U/kg n = 8</th>
<th>0.67 U/kg n = 8</th>
<th>1.00 U/kg n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean (CV%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max,ss} (pmol/l)</td>
<td>40.00 (32)</td>
<td>40.00 (19)</td>
<td>25.75 (25)</td>
<td>54.60 (22)</td>
</tr>
<tr>
<td>C_{ss} (pmol/l)</td>
<td>3.520 (31)</td>
<td>3.210 (28)</td>
<td>6.400 (25)</td>
<td>4.240 (20)</td>
</tr>
<tr>
<td>AUC_{(0–23.97),ss} (pmol.h/l)</td>
<td>24.200 (31)</td>
<td>38.600 (28)</td>
<td>76.800 (25)</td>
<td>53.000 (20)</td>
</tr>
<tr>
<td>AUC_{G,ss} (pmol.h/l)</td>
<td>75.700 (24)</td>
<td>101.000 (22)</td>
<td>169.000 (13)</td>
<td>168.000 (13)</td>
</tr>
<tr>
<td>t_{max,ss} (h)</td>
<td>6.0 (2.0–24.0)</td>
<td>0.009 (0.0–12.0)</td>
<td>7.0 (2.0–12.0)</td>
<td>2.0 (0.0–4.0)</td>
</tr>
<tr>
<td>t_{1/2,ss} (h)</td>
<td>67 (52.7–191.8)</td>
<td>64.5 (42.4–191.5)</td>
<td>44.7 (35.4–62.5)</td>
<td>75.5 (58.8–111)</td>
</tr>
<tr>
<td>PTF</td>
<td>1.56 (22)</td>
<td>1.48 (10)</td>
<td>1.42 (13)</td>
<td>1.49 (7)</td>
</tr>
<tr>
<td>CLss/F (l/h)</td>
<td>3.73 (27)</td>
<td>3.86 (16)</td>
<td>3.54 (20)</td>
<td>3.52 (32)</td>
</tr>
<tr>
<td>Ra</td>
<td>7.48 (46)</td>
<td>7.24 (57)</td>
<td>7.52 (52)</td>
<td>12.2 (44)</td>
</tr>
</tbody>
</table>

AUC_{(0–12),ss}, area under the concentration versus time curve from time zero to time 12 h at steady state; AUC_{G,ss}, area under the concentration versus time curve during 1 dosing interval at steady state; AUC_{(0–23.97),ss}, area under the concentration versus time curve from zero to 23.97 h during a dosing interval at steady state; C_{max,ss}, maximum observed drug concentration at steady state; CV%, coefficient of variation; n, number of subjects; PK, pharmacokinetic; PTF, the peak-to-trough fluctuation ratio calculated based on the equation: C_{max,ss}/C_{min,ss}, where C_{max} and C_{min} are the maximum and minimum drug concentrations in the dosing interval, respectively; Ra, accumulation ratio calculated from AUC_{(0–23.97)}/AUC_{(0–23.97),ss}, half-life associated with the terminal rate constant (λz) in non-compartmental analysis at steady state; t_{max,ss}, time of maximum observed drug concentration at steady state.

*The geometric mean (CV%) C_{max} values on day 1 for the 0.33, 0.5, 0.67, and 1.0 U/kg dose groups were 62.8 (33), 94.9 (49), 1530 (43) and 1310 (62) pmol/l, respectively.

\*Median (range).

Safety was assessed via monitoring of adverse events (AEs), clinical laboratory values, physical examinations and electrocardiograms (ECGs). Additional blood samples were obtained for the determination of fasting blood glucose concentration and C-peptide concentration.

Pharmacokinetic and Glucodynamic Analysis

PK parameters were analyzed by conventional non-compartmental analysis using WinNonlin Enterprise Edition® software (version 5.01, Pharsight Corp., St. Louis, MO, USA). Serum insulin concentrations were used to calculate PK parameters, including maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}) and area under the concentration versus time curve (AUC). PK parameters were individually calculated for each patient. Log-transformed C_{max} and AUC were evaluated using a model to estimate dose-normalized geometric means for day 1, day 14 and ratio of day 14 over day 1 (with corresponding 90% confidence intervals). PK parameter estimates were evaluated to delineate dose proportionality at day 14 [14]. The serum concentration of LY2605541 was compared between days 1, 7 and 14 to assess the accumulation and wash-out effect. Within- and between-patient coefficient variation (CV) in PK parameters was assessed based on steady-state data.

For GD parameters, data were determined from the euglycaemic glucose clamp procedure, where the glucose infusion rate (GIR) over time was measured as a measure of insulin effect. A locally weighted scatterplot smoothing (LOESS) function (smoothing parameter of 0.2) was applied to all individual GIR versus time profiles in each treatment group and/or period using S Plus® software (version 7.0.6, Insightful Corp., Seattle, WA, USA). The mean LOESS fits from all patients in each treatment group was used for the generation of mean GIR plots over time whereas unsmoothed data was used to calculate GD parameters. The primary GD parameters, maximum GIR (G_{max}) and total glucose infusion over the clamp duration (G_{total}) were log-transformed and compared between day 1 and day 14. Fasting and postprandial glucose concentrations were summarized over time to assess the accumulation and wash-out effect of LY2605541 on glucose.

Results

Patient Disposition and Demographics

The demographics and baseline (day 1) characteristics of the study population are summarized in Table 1. A total of 32 patients (30 male and 2 female) with type 2 diabetes were enrolled in the study with 8 patients enrolled into each of four dose cohorts. All patients received study treatment and completed the study. Age and body mass index (BMI) were comparable across all dose cohorts. All patients were Caucasian. The average duration of type 2 diabetes was approximately 16 years (range of 7–39 years).

Pharmacokinetic Evaluations

LY2605541 PK parameters across all dose levels are summarized in Table 2. The concentration-time profile suggests a relatively flat profile in steady state with a peak-to-trough fluctuation at day 14 of <2 across all dose levels. Concentrations increased with steady state being achieved 7–10 days after dosing (figures 1, 2). Trough concentrations at day 7 were higher than those on day 14; however, the average concentrations were in the range of those observed on day 14 indicating that
steady state had been reached by day 7. Monitoring of PK samples for 2 weeks postdosing showed an apparent half-life of 2–3 days (44.7–75.5 h).

A slightly more than proportional increase in PK parameter values was observed across the dose range of 0.33–1.00 U/kg as demonstrated by the ratio of dose-normalized means ($R_{dnm}$) for AUC $[1.12 \ (CI \ 0.93, \ 1.36)]$ and $C_{max} \ [1.09 \ (CI \ 0.91, \ 1.31)]$.

For all PK parameters, the within-patient variability was <35% [AUC(0–23.97) of 34.32% and $C_{max}$ of 29.35%] and the between-patient variability was <25% [AUC(0–23.97) of 24.06% and $C_{max}$ of 21.22%].

Glucodynamic Evaluations

LY2605541 GD parameters are shown in Table 3. Consistent with PK observations, administration of multiple once-daily dosing of LY2605541 resulted in an essentially peakless GIR profile at steady state. The glucose-lowering effect of LY2605541 was evenly distributed over the first and second 12 h after injection with AUC-$G_{tot} \ 0$–$12h$/$AUC-G_{tot} \ 0$–$24h$, being 53.5% (8.97). There was a dose-dependent glucose effect on the GIR (figure 3). The similarity in $G_{tot}$ between the 0.50 and 0.67 U/kg dose likely reflects the between-subject variability in drug concentrations between the two dose groups.

Dose response was demonstrated with regard to glucose infusion rate, fasting blood glucose and bolus insulin requirements. The fasting glucose declined over time with an average change from baseline (day 1) to day 14 of approximately 39 mg/dl (2.2 mmol/l) and was decreased to 60–100 mg/dl (3.3–5.6 mmol/l) across the dose range (figure 4). Further decrease in fasting glucose was prevented by oral carbohydrate intake. Nocturnal glucose control between 03:00 and 09:00 hours was relatively unchanged. The bolus insulin dose declined from study start, with no bolus administrations after day 7 for the 1.00 U/kg cohort.

Within-patient variability was <14 and <26% for the AUC of the 8-point blood glucose profile and fasting blood glucose, respectively.

Safety

Mild hypoglycaemia was the most common treatment-emergent adverse event (TEAE) [44 events (67.7%)] in 38% of patients. All hypoglycaemia events were of mild severity. No local injection site reactions were observed. No serious adverse events (SAEs) were reported. No patients discontinued the study due to an adverse event.

Clinical laboratory tests, vital signs, ECGs and antibodies to LY2605541 did not reveal clinically significant results or changes from baseline. During the course of the study, three patients had elevated alanine aminotransferase (ALT) levels; however, all observed elevations in ALT were below three times the upper limit of normal and all bilirubin levels were normal for these patients.

Discussion

In this Phase I study, LY2605541 was well-tolerated and demonstrated a flat PK and GD profile with no evidence of severe hypoglycaemia. Atypical of insulin dosing, this study was conducted as a ‘fixed’ dose over 14 days; patients were not titrated, nor were doses decreased within a cohort. This allowed investigating the PK and GD properties of LY2605541 without the need to account for dose adjustments or a potential delay in drug response. LY2605541 has a duration of action of >24 h,
Table 3. Summary of LY2605541 GD parameters following single doses and multiple once-daily doses in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>GD parameters</th>
<th>0.33 U/kg</th>
<th>0.50 U/kg</th>
<th>0.67 U/kg</th>
<th>1.00 U/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean (CV%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>R max (mg/min/kg)</td>
<td>0.259 (947)</td>
<td>1.20 (25)</td>
<td>0.143 (1455)</td>
<td>1.72 (82)</td>
</tr>
<tr>
<td>G tot (mg/kg)</td>
<td>122 (911)</td>
<td>920 (37)</td>
<td>54.2 (4540)</td>
<td>1520 (109)</td>
</tr>
</tbody>
</table>

CV%, coefficient of variation; GD, glucodynamic; G tot, total glucose infused over the clamp duration; R max, maximum glucose infusion rate.

Figure 3. Mean locally weighted scatterplot smoothing (LOESS)-fitted glucose infusion rate profiles following single doses and multiple once-daily doses in patients with type 2 diabetes.

Figure 4. Mean fasting blood glucose following multiple once-daily doses in patients with type 2 diabetes.

This study illustrates the favourable characteristics of LY2605541 as a long-acting basal insulin. The apparent half-life of LY2605541 (2–3 days) is considerably longer than that reported for insulin glargine (12.5 h) [15], insulin detemir (6–7 h) [16,17] and insulin degludec (25.4 h) [15]. The long half-life relative to the dosing interval (QD) of LY2605541 explains the low fluctuation in PK levels (i.e. the low peak-to-trough fluctuation <2) in steady state. The long half-life of LY2605541 translates into a prolonged duration of action and long and flat GD profile. While all clamps were stopped after 24 h in this study (and therefore duration of action could not be fully assessed), the mean GD profiles on day 14 were very flat and showed considerably less peak-to-trough fluctuation than observed with insulin glargine or insulin detemir [6,7,18].

Trough concentrations on day 7 were higher than those on day 14. While the reason for this is not clearly understood, a dilution effect is a possibility, due to the large volume of fluid infused on day 14 during the euglycaemic clamp procedure. Further, day 14 PK levels were sampled under clamp conditions with the subjects being supine in contrast to day 7 where subjects were usually sitting for blood draws. Trough levels on days 10 and 13 were also equivalent to those on day 7, indicating that steady state was achieved on day 7.

Administration of LY2605541 produced a long, flat GD profile with small peak-to-trough fluctuations. The GIR profile at steady state mirrored the flat PK profile (concentration vs. time profiles) at steady state. On day 14, the GIR and G tot are indicative of a dose-dependent response with a
GIR ~ 1–2 mg/min/kg in the 0.50–0.67 U/kg dose range of LY2605541. In accordance with the hypothesized mechanism of action, LY2605541 may have restricted peripheral activity, but retains hepatic activity to mimic endogenous insulin distribution [13]. As such, the GIR may not reflect the full effect of LY2605541. Normalization of fasting blood glucose was in a time and dose-dependent manner.

The nocturnal glucose control between 03:00 and 09:00 hours was relatively unchanged, thus potentially providing patients with type 2 diabetes with a lower risk of nocturnal hypoglycaemia. These results are consistent with the GD properties observed in the randomized, controlled study of once-daily LY2605541 versus insulin glargine in patients with type 2 diabetes in which the rate of nocturnal hypoglycaemia was statistically significantly lower with LY2605541 [19]. The GD response for LY2605541 demonstrated low intra-subject variability which is an important consideration for insulin dosing with respect to both reliability and limiting the risk of hypoglycaemia. The intra-subject variability results in this study are consistent with results from the Phase II trial conducted by Bergenstal et al., in which the intra-day blood glucose variability was statistically significantly lower with LY2605541 versus insulin glargine [19]. In terms of PK response, the intra-subject variability (CV%) for C_{max} (21.22%) observed in this trial is lower than both NPH insulin (24%) and insulin glargine (34%), and slightly higher than that of insulin detemir (18%) reported in a randomized, double-blind study comparing the intra-subject variability of the three insulins [11].

LY2605541 was generally well tolerated in patients with type 2 diabetes when administered subcutaneously as multiple doses up to 1.00 U/kg. All events of hypoglycaemia were mild, and no events were prolonged or difficult to manage. Hypoglycaemia appeared to be dose-dependent with 30 events occurring in Cohort 3 (1.00 U/kg). A post hoc analysis of the distribution of hypoglycaemia by time of day did not show any trends in terms of time-related occurrence. The daily caloric intake was increased from 2200 to 2600 kcal/day in Cohort 3 to ensure stabilization of blood glucose values. No bolus insulin doses were administered to patients in Cohort 3 after day 7. This is a clear indication of the strong pharmacological effect of LY2605541 at steady state in high doses which may require a reduction in pre-meal insulin requirements at least in some patients. A similar phenomenon was observed in a clinical study in patients with type 1 diabetes who also had to reduce their average short-acting insulin dose [20].

In conclusion, the use of LY2605541 exhibits desirable characteristics of a long-acting basal insulin, including a prolonged activity profile that supports once-daily dosing, no pronounced peaks in activity and minimal variability. Taken together, these data support the clinical investigation of LY2605541 in a once-daily dosing regimen. Clinical studies assessing the glucose-lowering effects and safety and tolerability of LY2605541 in patients with type 1 and type 2 diabetes are ongoing and LY2605541 is currently in Phase III development.

Acknowledgements
The authors acknowledge the writing and editorial assistance of Stephanie Brillhart, inVentiv Health Clinical (Burlington, MA, USA). This study was funded by Eli Lilly and Company. Dr V. K. S. 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.

Conflict of Interest
The institution of T. H. received research grants from the following pharmaceutical companies: Astellas, Bayer, Becton Dickinson, Biocon, Boehringer Ingelheim, Evolva, Glaxo Smith Kline, Hoffmann LaRoche, Johnson&Johnson, Eli Lilly, Novo Nordisk, Novoxon, Prosidion, Sanofi and Skye Pharma in the past 12 months. In addition, T. H. received travel grants, consulting fees and speaker honoraria from Novo Nordisk and Boehringer Ingelheim. V. P. S. and D. C. H. are former employees, and current stockholders of Eli Lilly and Company. S. L. C. and K. F. M. are employees and stockholders of Eli Lilly and Company, V. P. S., D. C. H., K. F. M. and T. H. designed this study. V. P. S., D. C. H. and K. F. M. conducted this study. V. P. S. performed statistical analysis and data analysis. V. P. S., D. C. H., S. L. C., K. F. M. and T. H. helped in preparation and writing of manuscript and approval of manuscript. S. L. C. performed PK/GD analysis. T. H. carried out data acquisition and interpretation of data.

References


学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具