Hypoglycemia Risk Related to Double Dose Is Markedly Reduced with Basal Insulin Peglispro Versus Insulin Glargine in Patients with Type 2 Diabetes Mellitus in a Randomized Trial: IMAGINE 8

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Abstract

Background: Basal insulin peglispro (BIL) has a peripheral-to-hepatic distribution of action that resembles endogenous insulin and a prolonged duration of action with a flat pharmacokinetic/pharmacodynamic profile at steady state, characteristics that tend to reduce hypoglycemia risk compared to insulin glargine (GL). The primary objective was to demonstrate that clinically significant hypoglycemia (blood glucose ≤54 mg/dL [3.0 mmol/L] or symptoms of severe hypoglycemia) occurred less frequently within 84 h after a double dose (DD) of BIL than a DD of GL.

Methods: This was a randomized, double-blind, two-period crossover study in patients with type 2 diabetes (T2D) previously treated with insulin (N=68). For the first 3 weeks of each of the two crossover periods, patients received an individualized dose of BIL or GL once nightly (stable dose for 2 weeks/period). Then, during a 7-day inpatient stay with frequent blood glucose monitoring and standardized meals, one DD of study insulin was given. Glucose was infused if blood glucose was ≤54 mg/dL (3.0 mmol/L) or for symptoms of severe hypoglycemia.

Results: Within 84 h after the DD, a significantly smaller proportion of patients experienced clinically significant hypoglycemia with BIL compared to GL (BIL, 6.6%; GL, 35.5%; odds ratio for BIL/GL 0.13 [95% confidence interval 0.04–0.39]; P<0.001). Adverse event profiles were similar for the two insulins. Serum alanine aminotransferase and triglyceride levels were significantly higher with BIL versus GL.

Conclusions: BIL has a markedly lower risk of hypoglycemia than GL when replicating a double-dose error in patients with T2D.

Keywords: Fasting blood glucose, Hypoglycemia, Type 2 diabetes, Basal insulin peglispro (BIL), Insulin therapy.

Introduction

Among patients taking insulin to treat type 2 diabetes (T2D), forgetting injections is a frequent reason for noncompliance with prescribed insulin regimens.1 When patients are uncertain if they have missed a dose, they may administer another, resulting in a double dose (DD) if in fact the dose has not been missed. There are no published data on the frequency of double dosing errors in particular, but recent publications have documented other types of insulin-related...
dosing errors that occur frequently in patients with diabetes, such as not eating soon enough after dosing or mixing up insulin products. The consequences of any insulin dosing error can be severe: overdose of insulin can induce complications of hypoglycemia, including nausea, dizziness, loss of consciousness, and death.

In cases of insulin-induced hypoglycemia, hepatic glucose production is reduced, while glucose uptake is stimulated. This study defined hypoglycemia events in a manner consistent with American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) standards, focusing primarily on documented symptomatic events. Severe hypoglycemia was defined as a hypoglycemic episode requiring assistance of another person to actively administer carbohydrates, glucagon, or other resuscitative actions. In alignment with a very recent article in Diabetes Care, events with blood glucose (BG) <54 mg/dL (3.0 mmol/L) were labeled as “clinically significant.” Events with BG ≤70 mg/dL (3.9 mmol/L) were also analyzed in this study.

Counter-regulatory responses are triggered when BG is low and result in release of glucagon, epinephrine, cortisol, and growth hormone. Acute recovery depends on the effects of glucagon and epinephrine to stimulate hepatic glucose release, while no counter-regulation acutely mitigates the increase in glucose disposal. Therefore, excess peripherally-acting insulin may not be countered, whereas the hepatic effects can be mitigated through stimulation of glucagon and epinephrine secretion, suggesting a potential benefit of a hepato-preferential insulin. Hypoglycemia recovery has been reported to be normal with basal insulin peglispro (BIL) in patients with type 1 diabetes (T1D).

BIL is distinguished from existing basal insulins such as insulin glargine (GL) by a peripheral-to-hepatic distribution that is more like endogenous insulin. BIL has a prolonged duration of action with a flat pharmacokinetic (PK)/pharmacodynamic (PD) profile at steady state. These characteristics may help minimize hypoglycemia risk versus GL even in circumstances like dosing errors leading to administration of a DD. BIL was extensively studied in phase III (in patients with T1D or T2D) and showed superior efficacy with less glucose variability and less nocturnal hypoglycemia than GL. BIL is a full insulin agonist, but, like some analogs, has reduced potency, resulting in higher concentrations to compensate.

This study simulated an inadvertent DD administration of long-acting insulins, evaluating the safety of a DD of BIL versus a DD of GL in patients with reasonably well-controlled T2D. The analyses tested the hypothesis that BIL, with its flatter PK/PD profile, might be beneficial in avoiding hypoglycemia in the case of insulin overdose.

**Patients and Methods**

**Study design**

This was a phase III, randomized, double-blind two-period crossover study in patients with T2D (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/dia). The trial ran from May 2014 to July 2015 at three study centers in two countries and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guide-
inpatient periods, and physical activity during the inpatient periods was limited. BG was monitored frequently during the inpatient periods, and standardized meals were provided (~45%–55% carbohydrate, 25%–35% fat, and 15%–25% protein [meals for each inpatient day were identical within each study site]; patients were encouraged to consume 100% of all meals.

On days 1, 2, and 4–6 of the inpatient periods, patients received a standard dose of study insulin (the fixed post-randomization dose). To achieve a bedtime target glucose of 120 mg/dL (6.7 mmol/L), short-acting insulin lispro and/or glucose was infused (from 5:00 to 9.30 p.m.) on days 1 and 3 before study insulin administration, enabling similar glucose control in all patients before single and DD in both arms (Supplementary Fig. S2). On day 3 of the inpatient periods, patients received a DD of BIL or GL. If glucose concentrations fell below 100 mg/dL (5.6 mmol/L) at any time, the BG measurement was repeated according to the guidance in Supplementary Table S1. Glucose was infused and oral glucose administered as a drink, typically juice, when measured BG was ≤54 mg/dL (3.0 mmol/L) or symptoms of severe hypoglycemia (such as seizure, unconsciousness, difficulty speaking, confusion or disorientation, and fainting, but not dizziness, headache, increased appetite, sweating, or tremor) were present.

**Study objectives**

The primary objective of the study was to demonstrate that clinically significant hypoglycemia (BG ≤54 mg/dL [3.0 mmol/L] or symptoms of severe hypoglycemia) occurred less frequently within 84 h after DD of BIL than DD of GL. Other objectives were to compare BIL versus GL for the incidence of clinically significant hypoglycemia within 12 h after DD, the incidence of hypoglycemia with BG ≤70 mg/dL (3.9 mmol/L) after DD, and the time to, duration of, and mean nadir BG (defined as the minimum BG that was also ≤70 mg/dL [3.9 mmol/L] and within 84 h of the DD). The PK of BIL and GL after DD were also evaluated.

**Sample size**

The sample size was based on an adaptive design. There was one blinded sample-size reestimation, in which the incidence of clinically significant hypoglycemia was estimated based on historical and simulated data. It was determined that 40–60 patients would need to complete the study to ensure at least 90% statistical power to demonstrate that the incidence with BIL was significantly less than the incidence with GL. Using the interim blinded data, the sample size for completers was recalculated as 49 (95% confidence interval CI) 23–750). Based on the study design and the reestimation, a conservative approach was taken, and 60 patients were targeted to complete the study.

**Randomization and blinding**

Patients who met all criteria were eligible to be randomized to double-blind treatment at the baseline visit. Randomization was stratified by study site and baseline insulin dose (≤0.6 and >0.6 U/kg/day). Assignment to treatment groups was determined by a computer-generated random sequence. Patients, investigators, and sponsor personnel were all blinded to study drug assignments.

**Bioanalytical assays**

Serum samples were analyzed for BIL using a validated ELISA method that was specific for BIL and did not detect endogenous insulin. The lower limit of quantification was 20.00 pM, and the upper limit of quantification was 500.00 pM.

Serum samples for GL were analyzed using a nonspecific validated radio immunoassay method. The concentrations determined with this assay included concentrations of GL, endogenous insulin, and the GL metabolites M1 and M2. The lower limit of quantification was 50 pM, and the upper limit of quantification was 2000 pM.

GL concentrations were reported by correcting for the presence of endogenous insulin using c-peptide correction as described by Owens.

**Analysis methods**

All analyses were assessed using the full analysis set (all randomized patients who received at least one dose of study medication); only data collected while patients were on treatment were included. All hypoglycemia events were included in analyses. The incidences of hypoglycemia and other repeated binary outcomes were analyzed by the generalized linear mixed model. The treatments were compared by Prescott’s exact test as needed. Continuous outcomes were analyzed by the mixed-model repeated measures model.

**Results**

A total of 68 patients were randomized in a 1:1 ratio to two treatment sequences, BIL/GL (34 patients) and GL/BIL (34 patients; Supplementary Fig. S3). Patient characteristics were similar between the two treatment sequences (Table 1). The average dose of basal insulin after the 5-day taper period was ~41 units (0.45 U/kg) and remained similar for the duration of the study, as steady insulin doses were required per protocol. The incidence of self-reported hypoglycemia (BG <70 mg/dL [3.9 mmol/L]) 2 weeks before randomization for all 63 patients randomized and treated in either treatment group was 19%. Immediately before randomization (baseline), mean FBG was ~123 mg/dL (6.8 mmol/L) for the 63 randomized patients treated during the study.

The incidence of clinically significant hypoglycemia was significantly lower within 84 h following a DD of BIL than a DD of GL (Table 2 and Fig. 1A). Because there was a slight imbalance between the treatment groups in FBG before the DD, post hoc analyses that adjusted separately for mean daily BG and mean FBG before the DD were conducted; the results (data not shown) were consistent with the primary result. Overall, during this time, four patients had a total of nine clinically significant hypoglycemic events while being treated with BIL, whereas 22 patients had a total of 52 events while being treated with GL. Clinically significant hypoglycemia within 12 h after a DD of BIL also occurred significantly less frequently compared to that within 12 h after a DD of GL (Table 2).

The incidence of hypoglycemia with BG ≤70 mg/dL (3.9 mmol/L) was significantly less frequent with BIL...
compared to GL within 12 or 84 h following a DD (Table 2). The daily incidence of hypoglycemia was significantly less frequent with BIL versus GL following a standard dose and on the first, second, and third days following a DD (Fig. 1B). The incidence of hypoglycemia following a DD of GL was elevated on the first and second subsequent days compared to the incidence following a standard dose of GL, but similar on the third day. The incidence of hypoglycemia following a DD of BIL remained elevated compared to a standard dose of BIL on all 3 days assessed, and on all 3 days following the DD, the incidence of hypoglycemia with BIL was significantly lower than the incidence with GL.

The majority of clinically significant hypoglycemic events across both BIL and GL (including events with BG $\leq 54$ mg/dL [3.0 mmol/L] or with symptoms of severe hypoglycemia) reported up to 84 h post-DD occurred between bedtime and waking (data not shown).

A greater percentage of GL-treated patients (82%) reached nadir glucose compared to BIL-treated patients (43%), and GL-treated patients reached nadir significantly sooner (mean 28 h) than BIL-treated patients (mean 36 h); the estimated hazard ratio for time to nadir glucose for BIL/GL was 0.32 (95% CI 0.21–0.48); $P < 0.001$. The least-squares (LS) mean nadir BG was significantly higher after a DD of BIL than after a DD of GL (62 and 56 mg/dL [3.42 and 3.10 mmol/L], respectively; $P < 0.001$). On days 1–3 after the DD (inpatient days 4–6, respectively), LS mean fasting plasma glucose values were 102.0, 100.9, and 102.2 mg/dL (5.7, 5.6, and 5.7 mmol/L), respectively, in BIL-treated patients, and 85.6, 86.2, and 86.3 mg/dL in GL-treated patients.

### Table 1. Demographics and Baseline Characteristics (All Randomized Patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>BIL/GL (N = 34)</th>
<th>GL/BIL (N = 34)</th>
<th>Total (N = 68)</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.8 (8.1)</td>
<td>57.7 (5.9)</td>
<td>58 (6.7)</td>
<td>0.959</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>24 (70.6)</td>
<td>24 (70.6)</td>
<td>48 (70.6)</td>
<td>$&gt;0.999$</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.493</td>
</tr>
<tr>
<td>White</td>
<td>32 (94.1)</td>
<td>34 (100.0)</td>
<td>66 (97.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (5.9)</td>
<td>0 (0.0)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino, n (%)</td>
<td>4 (11.8)</td>
<td>5 (14.7)</td>
<td>9 (13.2)</td>
<td>$&gt;0.999$</td>
</tr>
<tr>
<td>Countries, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>$&gt;0.999$</td>
</tr>
<tr>
<td>Germany</td>
<td>29 (85.3)</td>
<td>29 (85.3)</td>
<td>58 (85.3)</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>5 (14.7)</td>
<td>5 (14.7)</td>
<td>10 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>14.8 (6.0)</td>
<td>12.7 (7.2)</td>
<td>13.8 (6.7)</td>
<td>0.188</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>30.7 (4.6)</td>
<td>30.4 (4.3)</td>
<td>30.5 (4.4)</td>
<td>0.792</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>89.4 (14.6)</td>
<td>92.5 (16.6)</td>
<td>90.9 (15.6)</td>
<td>0.415</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>7.4 (0.7)</td>
<td>7.1 (0.8)</td>
<td>7.3 (0.8)</td>
<td>0.080</td>
</tr>
<tr>
<td>mmol/mol</td>
<td>58 (7.6)</td>
<td>54 (9.2)</td>
<td>56 (8.6)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise specified.

$P$-values for the comparisons between treatment groups are from Fisher’s exact test for categorical outcomes (Chi-square test was used for country) and two-sample t-test for the continuous outcomes.

BIL, basal insulin peglispro; BMI, body mass index; GL, insulin glargine; HbA1c, glycated hemoglobin; SD, standard deviation.

### Table 2. Incidence of Hypoglycemia During Inpatient Study Periods

<table>
<thead>
<tr>
<th></th>
<th>GL</th>
<th>BIL</th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant hypoglycemia (BG $\leq 54$ mg/dL [3.0 mmol/L] or symptoms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 h after DD</td>
<td>14 (22.6)</td>
<td>18</td>
<td>N/C$^a$</td>
<td>0.002$^b$</td>
</tr>
<tr>
<td>84 h after DD</td>
<td>22 (35.5)</td>
<td>52</td>
<td>4 (6.6)</td>
<td>0.13$^c$ (0.04–0.39)</td>
</tr>
<tr>
<td>Total hypoglycemia (BG $\leq 70$ mg/dL [3.9 mmol/L])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before DD$^d$</td>
<td>25 (39.7)</td>
<td>N/A</td>
<td>3 (4.8)</td>
<td>0.08 (0.02–0.24)</td>
</tr>
<tr>
<td>12 h after DD$^d$</td>
<td>40 (64.5)</td>
<td>99</td>
<td>12 (19.7)</td>
<td>0.12 (0.05–0.27)</td>
</tr>
<tr>
<td>84 h after DD$^d$</td>
<td>51 (82.3)</td>
<td>322</td>
<td>26 (42.6)</td>
<td>0.15 (0.08–0.31)</td>
</tr>
</tbody>
</table>

$^a$Not calculated because only one event occurred in the BIL group.

$^b$P-value from nonparametric Prescott’s exact test for sensitivity analysis.

$^c$Odds ratio and P-value are from a generalized linear model: [Response = treatment + period + sequence + baseline basal insulin dose stratification factor.] The within-patient error was modeled as unstructured variance–covariance structure.

$^d$Odds ratio and P-value for each period are from generalized linear model: [Response = treatment + dosing + sequence + period + interaction of treatment and dosing (Type III sums of squares) + baseline basal insulin dose stratification factor.] The within-patient error was modeled as compound symmetry variance–covariance structure.

BG, blood glucose; BIL, basal insulin peglispro; CI, confidence interval; DD, double dose; GL, insulin glargine; n, patients with event; N/A, not available; N/C, not calculated; OR, odds ratio.
dL (4.8, 4.8, and 4.8 mmol/L), respectively, in GL-treated patients ($P < 0.001$ for all).

Figure 1C and D plots arithmetic mean (±standard error) serum concentration profiles over 24 h poststandard doses and DDs of BIL and GL, respectively (standard doses were given in the evenings of inpatient days 1, 2, 4, and 5; DD was given in the evening of inpatient day 3). The serum-concentration profile of BIL at steady state (following dosing the evening of inpatient day 1) was relatively flat. Serum BIL concentrations increased after the DD administered the evening of inpatient day 3 and remained elevated but relatively flat during the periods 24–48 h and 48–72 h after the DD (PK samples collected beginning the evenings of inpatient days 4 and 5, respectively). Serum GL concentration increased rapidly following study-drug dosing, reaching a peak 5 h after each dose (including the DD). Effects of the DD on GL exposures waned over 2 days, and concentrations returned to pre-DD levels at day 5 (2 days after the DD).

Supplementary Table S2 summarizes treatment-emergent adverse events (TEAEs). No statistically significant treatment differences were observed for any specific TEAEs. No injection site reactions were reported as TEAEs. One patient in each treatment group reported a serious adverse event (BIL: erosive gastritis; GL: otitis media); neither event was considered related to study drug.

Serum alanine aminotransferase (ALT) and triglycerides were significantly increased with BIL treatment compared to GL treatment (Supplementary Table S3). No patient had a
study-emergent ALT and/or aspartate aminotransferase (AST) ≥3× upper limit of normal (ULN) and/or total bilirubin level ≥2× ULN during the study.

Discussion

To our knowledge, this is the first study to investigate the glycemic effect of a DD of basal insulins. In this double-blind randomized study of hypoglycemic safety in insulin-treated patients with T2D, a significantly smaller proportion of BIL-treated patients had hypoglycemia (clinically significant [with BG ≤54 mg/dL (3.0 mmol/L)] or with BG ≤70 mg/dL [3.9 mmol/L]) compared to GL-treated patients when carefully monitored for up to 84 h following a DD. Fewer episodes of hypoglycemia during the 12 h immediately following a DD of BIL would be expected to reduce the number of emergency room visits or urgent interventions required during the night for patients at home, a clinically important benefit.

The pharmacologic properties of BIL are felt to be responsible for the lower incidences of hypoglycemia observed in comparison to GL during this study. The long half-lives of these basal insulins may intuitively predict prolonged durations of effects, especially if larger-than-usual doses are administered. However, at steady-state conditions, the insulin concentrations in the body are expected to fluctuate minimally; therefore, it is notable that a surprising difference in incidence of hypoglycemia was observed even after administration of a standard dose of study drug (Fig. 1B).

It is important to note that while the incidence of total hypoglycemia after the DD of BIL was increased compared to the relatively low incidence after a standard dose, the absolute incidence remained lower than that with GL for the 3 days following the DD. The relative increases in hypoglycemia after the DD were consistent with increased insulin concentrations, although the magnitude of the changes in insulin concentrations did not fully explain the increases in hypoglycemia. We hypothesize that the advantage in the observed incidence of hypoglycemia with BIL compared to GL, both before and after a DD, may have been due to the BIL mechanism of action of reduced peripheral action.

The primary difference observed between the study insulins was that after a DD, both the concentrations and glucose effects of BIL marginally fluctuated, whereas GL concentrations doubled. A crossover euglycemic clamp study of BIL versus GL in patients with T1D demonstrated that the suppression of glucose production by the liver is similar at equipotent doses of BIL and GL, but a markedly lower glucose disposal rate occurs following BIL.

The hepato-preferential activity of BIL may explain the lower occurrence of hypoglycemia with BIL versus GL following the DD. Insulin concentrations following the DD peaked more quickly with GL than with BIL and were elevated for up to 2 days with GL and up to 3 days with BIL following a DD (Fig. 1C, D). The serum concentrations, as well as the incidences of hypoglycemia within the first 3 days following the DD (Fig. 1B), were consistent with the known profiles of the study insulins. The 84-h observation period was thereby sufficient to assess hypoglycemic risks.

Medication errors occur frequently in insulin-treated patients with T2D, and patients with diabetes who receive insulin are frequently hospitalized for a variety of reasons, which may include dosing errors. The general incidence of patients affected by inadvertent insulin dosing errors is unknown, but one study found increasing incidences of unintentional insulin dosing errors that were attributed primarily to the rapidly rising prevalence of T2D and the growing use of insulin among these patients. The fact that patients with T2D tend to have relatively poor compliance with medications over the long term, as well as the possibility that patients may misdose insulin, may affect a clinician’s approach to insulin therapy for individual patients with T2D.

Our study was reflective of patients accidentally taking an extra dose of long-acting insulin during their usual course of care. The use of inpatient hospital stays ensured patient safety under study conditions intended to mimic accidental DD administration. We believe that the inpatient setting was also less confounded by the variability introduced in ambulatory settings, such as meal delays, skipped meals, or increased physical activity, each of which would independently contribute to the incidence of hypoglycemia.

Koehler et al. reported on insulin overdoses in patients with T1D under continued fasting and hypoglycemic clamp conditions. In contrast, our design incorporated standardized meals, more closely replicating everyday life for patients with T2D. By maintaining patients on once-daily insulin regimens before and after the DD, we simulated patients unknowingly misosing. Safety precautions were sustained through protocol-mandated intervention to prevent glucose levels below 54 mg/dL (3.0 mmol/L).

Because the insulin doses were fixed for each patient, glucose levels could not be targeted, resulting in an imbalance between the treatment groups in FBG preceding administration of the DD. However, correcting for this imbalance in post-hoc analyses did not change the conclusions of the analyses of hypoglycemia. Due to the very long half-life of BIL, the inpatient periods allowed patients to be observed following the DD for up to 2 days after Tmax, but not until BIL concentrations returned to pre-DD levels (~1 week). On inpatient day 5, which was 2 days after the DD, BIL concentrations remained elevated compared to those measured after standard doses, while GL concentrations had returned to those measured after standard doses; despite this, the incidence of hypoglycemia (BG ≤70 mg/dL [3.9 mmol/L]) with BIL was lower than with GL.

While mean 24-h glucose profiles by treatment group would have been informative, data collected during individualized inpatient glucose monitoring prevented investigation of differences between the treatment groups. Finally, patients with T1D are more likely to adjust eating patterns and prandial insulin dosages than are patients with T2D. Hence, in patients with T1D, the analyses of the basal insulins would be confounded by these interventions, and because our study was conducted in patients with T2D, the findings may not be applicable in patients with T1D.

Based on these study results, we believe that among patients with T2D accidentally administered an extra dose of basal insulin, the incidence of clinically significant hypoglycemia would be significantly lower with BIL than with GL. These findings are likely attributable to the prolonged, flat PK/PD profile and/or the reduced peripheral activity of BIL compared with GL. Our data also suggest that if an extra
dose of basal insulin is administered, BG monitoring should be extended through the second night after dosing with GL and at least through the third night after dosing with BIL.

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Author Disclosure Statement

C.H., Q.Z., L.F., and P.G. are employees of Eli Lilly and Company. N.P. is retired from Eli Lilly and Company. T.F. is a member of advisory panels for Eli Lilly, Sanofi, and Boehringer Ingelheim; has received research support from Takeda, AstraZeneca, Novartis, Boehringer Ingelheim, Sanofi, and Novo Nordisk; and is a member of the speaker bureaus of AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, Berlin-Chemie, Novartis, and Boehringer Ingelheim. T.H. is a member of advisory panels for Novo Nordisk and has received speaker honoraria and travel grants from Eli Lilly, Mylan, and Novo Nordisk; his institution has received research funds from Adocia, AstraZeneca, Becton Dickinson, Biocon, Boehringer Ingelheim, Dance Pharmaceuticals, Eli Lilly, Grünenthal, Gulf Pharmaceuticals, Johnson & Johnson, Marvel, MedImmune, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi, Senseonics, and Zealand Pharma. L.P.-M. is an employee of Profil and has no competing interests to report. E.W. has no competing interests to report.

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