Hypoglycemia with New-Generation Basal Analog Insulins: A Descriptive Critical Review

Mazen Alsahli*, James R Thrasher and John E Gerich

1University of Toronto Faculty of Medicine, Toronto, Canada
2Arkansas Diabetes and Endocrinology Center, Little Rock, Arkansas, USA
3University of Rochester School of Medicine, Rochester, New York, USA

Abstract

Optimizing the treatment of people with diabetes relies on balancing the benefits of glycemic control with the risk of hypoglycemia. Although insulin is essential for treating patients with type 1 diabetes mellitus, patient and physician concerns regarding an increased risk of hypoglycemia can lead to delays in initiating insulin treatment in patients with type 2 diabetes mellitus. This clinical inertia contributes to reduced glycemic control and poorer outcomes for patients. Advances in insulin agents have reduced the risk of hypoglycemia. In particular, the introduction of insulin glargine, the first basal analog insulin with a 24-hour glucose-lowering profile with no pronounced peak, represented a significant step towards achieving this goal.

To further improve patient management, a number of insulin formulations and molecules are in development and are designed to have pharmacokinetic/pharmacodynamic (PK/PD) profiles allowing closer mimicking of normal physiologic insulin release. Here we review these new agents, and discuss their hypoglycemic risk as reported in clinical trials. In addition, the difficulties in making comparative evaluations from studies with different patient populations and definitions of hypoglycemia are discussed. Solutions to improve future clinical trials are suggested.

In general, the improved PK/PD profiles of new-generation insulins appear to result in better clinical outcomes in terms of hypoglycemia. What is needed are head-to-head trials using standardized methods and criteria to allow clinicians to compare hypoglycemia rates between insulins, and help them to discuss appropriate choices of therapy with their patients.

Keywords: Hypoglycemia; Insulin; Type 1 diabetes; Type 2 diabetes

Introduction

Insulin treatment is essential for individuals with type 1 diabetes mellitus (T1DM). As a result of progressive beta-cell deterioration in type 2 diabetes mellitus (T2DM), most patients with T2DM eventually require insulin to achieve and maintain optimal glycemic targets. Usually, basal insulin is initiated before adding prandial therapy to maintain glycemic control [1]. Optimizing diabetes treatment depends on balancing glycemic control and the risk of hypoglycemia.

As plasma glucose levels decrease, there is a hierarchy of physiologic counterregulatory responses aimed at preventing further decreases and restoring normal plasma glucose levels (Figure 1) [2,3]. When plasma glucose levels decrease to <70 mg/dl (3.8 mmol/l), activation of counterregulation mechanisms begins; i.e., an increase in the secretion of glucagon, catecholamines, cortisol, and growth hormone, and a decrease in insulin secretion. These changes occur before there are any signs or symptoms related to hypoglycemia. As a consequence of these counterregulatory changes, there is an initial increase in hepatic and renal glucose release into the circulation (approximately equal amounts of glucose are released from the liver and kidneys), followed by a decrease in removal of glucose from the circulation. Decreases in plasma glucose to ~60 mg/dl (3.3 mmol/l) usually evoke the so-called autonomic warning symptoms (hunger, anxiety, palpitations, sweating, nausea). If interpreted correctly, these lead the patient to eat and thus prevent more serious hypoglycemia. If plasma glucose levels decrease to ~55 mg/dl (3.0 mmol/l), neuroglycopenic signs and symptoms of brain dysfunction (blurred vision, slurred speech, glassy eyed appearance, confusion) occur. Concentrations of plasma glucose below 30 mg/dl (1.6 mmol/l) - if prolonged - can cause seizures, permanent neurologic deficits, and death [4].

Within a few years of diabetes onset, people with T1DM develop impaired counterregulatory hormone responses, which are manifested first by decreased or absent glucagon responses to hypoglycemia [3]. This is followed by decreased catecholamine responses, and later by variable decreases in growth hormone and cortisol responses. Defective glucose counterregulation plays a major role in the susceptibility to severe hypoglycemia of people with T1DM. In contrast, people with T2DM experience more modest impairment in glucose counterregulation [5].

In addition to impaired glucose counterregulation, people with T1DM and T2DM may suffer from hypoglycemia unawareness [4]. These patients have an often transient loss of the autonomic symptoms warning them of developing hypoglycemia; these symptoms would normally have prompted them to take appropriate action (i.e., food intake before occurrence of severe hypoglycemia with neuroglycopenia). Hypoglycemia unawareness can be reversed in most cases by instigating a management plan that includes strict avoidance of hypoglycemia [6,7].

Although long-term studies suggest that tight glycemic control can reduce diabetes complications [8,9], this tight control increases the risk of hypoglycemia [9-11]. Concerns regarding hypoglycemia can lead to clinical inertia among physicians and barriers to initiating insulin.
among patients. These have clinical consequences, as hypoglycemic events and the fear of future hypoglycemia are associated with reduced adherence to and persistence with treatment [12-15]. In turn, lower adherence is associated with the reduced likelihood to intensify treatment [16], and contributes to suboptimal glycemic control [17].

The majority of people with T2DM will progress to basal insulin therapy when oral antidiabetes drugs (OADs) fail to maintain adequate glycemic control. The relative simplicity of basal insulin regimens alongside the concept of “fix fasting first” makes basal insulin a desirable choice when intensifying treatment. However, as the disease progresses, this is usually insufficient for maintaining glycemic control and postprandial control is generally also required [18]. Various insulin therapies are available, but the introduction of the long-acting basal analog insulin glargine 100 units/ml (Gla-100) resulted in a reduction in rates of hypoglycemia compared with NPH insulin [19,20]. Diabetes treatment is an evolving field of medicine, with new-generation therapies in development.

The efficacy and safety of investigational insulins have been compared with standardized insulin in treat-to-target trials [21]. In these trials, insulin dosages are titrated in patients according to a specific algorithm so they can achieve a determined treatment glycemic goal [22]. At the same time, clinicians are able to determine differences in other treatment effects, like weight gain and hypoglycemia. It should be noted that the results of treat-to-target trials are sensitive to sample size [23]. For this reason, treat-to-target trials are subject to bias, unless a specific algorithm is rigorously enforced.

In this paper, we review the new generation of basal analog insulins in terms of their effect on hypoglycemia rates in clinical trials. A review of current literature and recent conference abstracts was undertaken to gather evidence. PubMed was searched with the search term: “basal insulin” OR “long-acting insulin” OR “ultra-long insulin” OR “long-acting basal” OR “ultra-long acting basal”. Furthermore, abstracts from the annual conferences of the European Association for the Study of Diabetes (EASD) of 2013 and 2014 were searched. Results were taken for any novel long-acting basal insulins with hypoglycemia data.

Pharmacokinetic/Pharmacodynamic Profiles of Novel Basal Analog Insulins

A key goal of insulin therapy is replicating physiologic basal insulin release: the release of insulin averages around 1.3 U/h under normoglycemic physiologic conditions [24]. As the first basal analog insulin with a 24-hour glucose-lowering profile with no pronounced peak [25], Gla-100 represented a significant step towards achieving this goal. Gla-100’s pharmacokinetic (PK) and pharmacodynamic (PD) profile resulted in the first opportunity for basal insulin coverage with once-daily (QD) dosing. Insulin detemir (IDet) has a similar glucose-lowering profile to Gla-100, often allowing basal coverage from a single daily dose, although twice-daily injections are required in up to 57% of patients (Figure 2) [26].

Advances in insulin therapy have included developing new agents or evolving established therapies. Increasing half-lives and improving peak-trough dynamics have provided a number of agents with therapeutic potential in treating hyperglycemia that more closely mimic physiologic insulin release patterns with fewer injections.

Insulin degludec (IDeg) is a new basal analog insulin with a PK/PD profile that extends glucose lowering beyond 24 hours. Upon injection, IDeg di-hexamers assemble to form stable multi-hexamers. These form a soluble depot in the subcutaneous tissue from which IDeg monomers slowly dissociate. Studies to determine the PK/PD profile of IDeg demonstrate an evenly distributed glucose-lowering profile, with a terminal half-life of more than 25 hours under steady state conditions [27] and a duration of action reported to be over 40 hours [28].

A new formulation of Gla-100 is in development (insulin glargine 300 units/ml [Gla-300]), in which the same number of insulin units as Gla-100 is delivered, but in a third of the injection volume. Gla-300 forms crystals at neutral pH when injected subcutaneously; Gla-300 forms a more compact depot of crystals resulting in a lower depot surface area and a slower rate of dissolution. In patients with T1DM, PK/PD studies of Gla-300 have demonstrated a longer, smoother glucose-lowering profile compared with Gla-100, with a terminal half-life of approximately 19 hours and activity up to 36 hours, resulting in tighter glucose control [29-31]. The peak-trough ratio of Gla-300 is low at ~1.7 versus 2.3 for Gla-100, and this helps to minimize glycemic variability [32]. Theoretically, the less pronounced peak of action could result in a more gradual drop in blood glucose, with a reduced risk of hypoglycemia; this would need to be confirmed clinically in phase 3 trials.

Other basal insulins are in development that also have extended terminal half-lives and activity profiles. A PEGylated form of the fast-acting basal insulin lispro LY2605541 (basal insulin peglispro [BIL]) has a functional size of approximately 75 kDa due to the hydrodynamic properties of the polyethylene glycol chain linked to the insulin lispro.
molecule. This results in slowed absorption and possible preferential hepatic activity [33]. BIL is approximately four times larger than unPEGylated lispro, which contributes to the PK/PD profile of BIL. Data from patients with T2DM suggest that a relatively long time is required to achieve steady state: 7-10 days versus 2-4 days for IDeg and Gla-300, respectively [27,29]. BIL has a terminal half-life of 43-hour half-life for HM12470 compared with 2.9 hours for IDeg [36]. Animal studies in mice, rats, and dogs showed a predicted half-life of 24 hours [35].

In earlier-stage clinical development, HM12470 is a long-acting basal analog insulin produced by conjugating an insulin analog to the constant region of a human immunoglobulin fragment using a non-peptidyl linker [36]. Animal studies in rats showed an approximately 43-hour half-life for HM12470 compared with 2.9 hours for IDeg [36]. Animal studies in mice, rats, and dogs showed a predicted half-life of HM12470 of approximately 132 hours and a low peak-trough ratio of 1.6 in humans [36]. This long half-life may allow once-weekly dosing.

BIOD-531 is a concentrated formulation of recombinant human insulin (400 units/ml) with a high dose/volume ratio and more rapid absorption, owing to the addition of EDTA, citrate, and MgSO₄ [37]. Data suggest that BIOD-531 has a rapid onset of action and a duration of action of around 18 hours in non-diabetic obese subjects [38].

### New basal analog insulins and hypoglycemia

As noted above, the clinical use of Gla-100 is associated with a lower risk of hypoglycemia than NPH insulin; this is a result of its longer, more constant PK/PD profile and a reduction in the variability of glucose-lowering effects [19,20]. Data from clinical trials suggest that the newer generation of basal analog insulins, with their extended, smoother PK/PD profiles, may also result in improved rates of hypoglycemia compared with currently available insulins. In this section, we summarize data from clinical trials with these agents in patients with T2DM and T1DM (trials are summarized in Tables 1 and 2, respectively). Data reviewed are restricted to head-to-head phase 3 clinical trials. Note that data on hypoglycemia rates for BIOD-531 and HM12470 are not yet available.

### Hypoglycemia in T2DM

Hypoglycemia is a frequent adverse effect of the treatment of T2DM, with hypoglycemic events commonly occurring at night. As

| Study                  | Investigational vs comparator | Population                                         | n    | Hypoglycemia category                   | Result                                           | RRa/b (95% CI) | P value |
|------------------------|-------------------------------|-----------------------------------------------------|------|----------------------------------------|------------------------------------------------|---------------|---------|
| BEGIN Once Long [46]   | Insulin degludec vs insulin glargine | Adults with T2DM (A1C 7.0-10.0%) taking OADs only | 1030 | - Confirmed hypoglycemia               | 1.52 vs 1.85 episodes/PYE                      | RR=0.82 (0.64-1.04) | 0.106   |
|                        |                               |                                                     |      | - Nocturnal confirmed hypoglycemia     | 0.25 vs 0.39 episodes/PYE                      | RR=0.64 (0.42-0.98) | 0.038   |
|                        |                               |                                                     |      | - Severe*                              | 0.003 vs 0.023 episodes/PYE                    | RR=0.14 (0.03-0.70) | 0.017   |
| BEGIN Once Asia [49]   | Insulin degludec vs insulin glargine | Asian adults with T2DM (A1C 7.0-10.0%) taking OADs only | 435  | - Confirmed hypoglycemia               | 3.0 vs 3.7 episodes/PYE                       | RR=0.82 (0.60-1.11) | 0.2     |
|                        |                               |                                                     |      | - Nocturnal confirmed hypoglycemia     | 0.8 vs 1.2 episodes/PYE                       | RR=0.62 (0.38-1.04) | 0.07    |
| BEGIN Basal-Bolus [47] | Insulin degludec + insulin aspart vs insulin degludec + insulin aspart | Adults with T2DM (A1C 7.0-10.0%) on any insulin regimen with or without OADs | 1006 | - Confirmed hypoglycemia               | 11.1 vs 13.6 episodes/PYE                      | RR=0.82 (0.69-0.99) | 0.0359  |
|                        |                               |                                                     |      | - Nocturnal confirmed hypoglycemia     | 1.39 vs 1.84 episodes/PYE                     | RR=0.75 (0.58-0.99) | 0.0399  |
|                        |                               |                                                     |      | - Severe*                              | 0.06 vs 0.05 episodes/PYE                     | -              | -       |
| BEGIN Flex [48]        | Insulin degludec flexible vs insulin degludec fixed vs insulin glargine | Adults with T2DM taking OADs (A1C 7.0-11.0%) or basal insulin + OADs (A1C 7.0-10.0%) | 687  | - Confirmed hypoglycemia               | 3.6 vs 3.6 vs 3.5 episodes/PYE                 | RR=1.03 (0.75-1.40) | NS      |
|                        |                               |                                                     |      | - Nocturnal confirmed hypoglycemia     | 0.6 vs 0.6 vs 0.8 episodes/PYE                 | RR=0.77 (0.44-1.35) | NS      |
|                        |                               |                                                     |      | - Severe*                              | -                                             | -              | -       |
| EDITION 1 [54]         | Gla-300 vs Gla-100             | Adults with T2DM (A1C 7.0-10.0%) using 342 U/day basal insulin + mealtime insulin | 807  | - Confirmed hypoglycemia               | 81.9% vs 87.8%                                | RR=0.93 (0.88-0.99) | -       |
|                        |                               |                                                     |      | - Nocturnal confirmed hypoglycemia     | 44.6% vs 57.5%                                | RR=0.78 (0.68-0.89) | -       |
|                        |                               |                                                     |      | - Severe*                              | 5.0% vs 5.7%                                  | RR=0.87 (0.48-1.55) | -       |
| EDITION 2 [55]         | Gla-300 vs Gla-100             | Adults with T2DM (A1C 7.0-10.0%) using 342 U/day basal insulin + OADs | 811  | - Confirmed hypoglycemia               | 70.0% vs 77.3%                                | RR=0.90 (0.83-0.98) | -       |
|                        |                               |                                                     |      | - Nocturnal confirmed hypoglycemia     | 28.3% vs 39.9%                                | RR=0.71 (0.58-0.86) | -       |
|                        |                               |                                                     |      | - Severe*                              | 1.0% vs 1.5%                                  | -              | -       |
## Table 1: Hypoglycemia in randomized clinical trials of novel basal analog insulins in T2DM [46-49,54-58,61].

| Study | Investigational vs comparator | Population | n | Hypoglycemia category | Result | RR<sub>a</sub> (95% CI) | P value |
|-------|--------------------------------|------------|---|-----------------------|--------|--------------------------|--------|
| **BEGIN Basal-Bolus Type 1 [28]** | Insulin degludec + insulin aspart vs insulin degludec + insulin aspart | Adults with T1DM (A1C ≤10%) on basal-bolus therapy | 629 | - Confirmed hypoglycemia (PG <54 mg/dl or severe<sup>‡</sup>) | 42.54 vs 40.18 events/PYE | RR<sup>a</sup> 1.07 (0.89-1.28) | 0.48 |
| | | | | - Nocturnal confirmed hypoglycemia | 4.41 vs 5.86 events/PYE | RR<sup>a</sup> 0.75 (0.59-0.96) | 0.021 |
| | | | | - Severe<sup>‡</sup> | 0.21 vs 0.16 events/PYE | RR<sup>a</sup> 1.38 (0.72-2.64) | 0.34 |
| **BEGIN Flex T1 [62]** | Insulin degludec flexible† + insulin aspart vs insulin degludec fixed + insulin aspart vs insulin glargine + insulin aspart | Adults with T1DM (A1C ≤10%) on basal-bolus therapy | 493 | - Confirmed hypoglycemia (PG <54 mg/dl or severe<sup>‡</sup>) | 82.4 vs 88.3 vs 79.7 events/PYE | NS | |
| | | | | - Nocturnal confirmed hypoglycemia | 6.2 vs 9.6 vs 10.0 events/PYE | NS | |
| | | | | - Severe<sup>‡</sup> | 0.3 vs 0.4 vs 0.5 events/PYE | NS | |
| **EDITION 4 [63]** | Gla-300 vs Gla-100 | Adults with T1DM basal insulin + prandial insulin | 549 | - Confirmed hypoglycemia (PG ≤70 mg/dl or severe<sup>‡</sup>) | 78.4 vs 72.5 events/PYE | RR<sup>a</sup> 1.09 (0.94-1.25) | - |
| | | | | - Nocturnal confirmed hypoglycemia | 8.0 vs 8.9 events/PYE | RR<sup>a</sup> 0.90 (0.71-1.14) | - |
| | | | | - Severe<sup>‡</sup> | 6.8% vs 9.5% | - | |
| **Edition 4 JP 1 [64]** | Gla300 vs Gla-100 | Adults with T1DM basal insulin + prandial insulin | 243 | - Confirmed hypoglycemia (PG ≤70 mg/dl or severe<sup>‡</sup>) | 96.7% vs 97.5% | RR<sup>a</sup> 0.99 (0.95-1.04) | - |
| | | | | - Nocturnal confirmed hypoglycemia | 68.9% vs 81.0% | RR<sup>a</sup> 0.85 (0.73-0.99) | - |
| | | | | - Severe<sup>‡</sup> | - | - | |

*Requiring assistance; †dosing schedule creating 8-40 hours between injections.

A1C, glycated hemoglobin; BG, blood glucose; CI, confidence interval; NS, not significant; PG, plasma glucose; PYE, patient year of exposure; OADs, oral antidiabetic drugs; RR<sup>a</sup>, rate ratio; RR<sup>b</sup>, relative risk; T2DM, type 2 diabetes mellitus.
The incidence of severe episodes of hypoglycemia appeared to be similar between groups; however, rates were too low to assess statistically (Table 1).

The BEGIN series of studies also included trials with a 26-week duration. BEGIN FLEX was a 26-week, open-label, three-arm, parallel-group trial, in which patients received IDeg QD flexibly dosed to a pre-specified rotating morning and evening dosing schedule (IDeg FLEX), creating 8-40 hour intervals between doses [48]. IDeg QD was dosed at the evening meal, or Gl-100 dosed at the same time each day. This trial had a treat-to-target design aimed at achieving blood glucose ~70-90 mg/dl (3.9-5.0 mmol/l) [48]. There were no significant differences in terms of confirmed hypoglycemia, confirmed nocturnal hypoglycemia, and/or severe hypoglycemia between the three treatment groups (Table 1).

In the 26-week, open-label BEGIN Once Asia study, patients were treated with either IDeg or Gl-100 QD, with a titration target of blood glucose ~70-90 mg/dl (3.9-5.0 mmol/l) [49]. There were no significant differences in rates of confirmed overall or nocturnal hypoglycemia over the trial period (Table 1).

In February 2015, the FDA approved Gl-300 based on data from the EDITION series of 26-week, phase 3 clinical trials [50]. Around the same time, the European Medicines Agency (EMA) adopted a positive opinion towards Gl-300 [51]. A meta-analysis of the currently available data from the EDITION trials of Gl-300 versus Gl-100 showed similar reductions in A1C (least square [LS] mean change -1.02%) for both formulations [52].

The main secondary outcome in the EDITION 1, 2, and 3 trials was the percentage of participants with one or more confirmed nocturnal hypoglycemic events, defined as a composite of events with an SMBG value ≤70 mg/dl (3.9-5.0 mmol/l) [53] or a severe event (requiring assistance) occurring between 00:00 and 05:59 hours from Week 9 to Week 26 of treatment. Confirmed or severe hypoglycemia events at any time of the night were also assessed over the full 26-week study period and for the first 8 weeks of the study.

EDITION 1 was a randomized, open-label, parallel-group trial in which patients using high daily doses of basal insulin (≥42 U/day) alongside mealtime insulin received Gl-300 or Gl-100 QD titrated to achieve fasting plasma glucose (FPG) ~80-100 mg/dl (4.4-5.6 mmol/l) [54]. There was a significantly lower incidence of confirmed (plasma glucose ≤70 mg/dl) or severe nocturnal hypoglycemic events in the Gl-300 group compared with the Gl-100 group between Week 9 and Week 26 (36% vs 46%, respectively; P=0.0045) as well as over the full 26-week trial period (Table 1) [54]. Over the full 26-week trial period, the incidence of confirmed hypoglycemia (plasma glucose ≤70 mg/dl) was also lower in the Gl-300 group, while there was no statistically significant difference in the incidence of severe hypoglycemic events (Table 1).

### Table 2: Hypoglycemia in randomized clinical trials of novel basal analog insulins in T1DM [26,62-66]

| Study/rott | Insulin Comparator | Patients | No. Events | Events/PMERR | RR | RRa | RRb |
|------------|--------------------|----------|------------|--------------|----|-----|-----|
| **Rosenstock et al., 2013 [65]** | Insulin lispro vs insulin glargine | Adults with T1DM (A1C ≤10.5%) on basal-bolus insulin | 137 | - Total hypoglycemia (BG ≤70 mg/dl or symptoms) 8.74 vs 7.36 events/PMER | RR* 1.12 (1.03-1.23) | 0.037 | |
| | | | | - Nocturnal hypoglycemia 0.88 vs 1.13 events/PMER | RR* 0.75 (0.62-0.90) | 0.012 | |
| **ELEMENT 1 [66]** | Insulin lispro vs insulin glargine | Adults with T1DM (A1C ≤15%) on basal-bolus insulin | 535 | - Total hypoglycemia (BG ≤70 mg/dl or symptoms) 86.5% vs 89.2% | |

*Requiring assistance; †dosing schedule creating 8-40 hours between injections. A1C, glycated hemoglobin; BG, blood glucose; CI, confidence interval; NS, not significant; PG, plasma glucose; PME, patient month of exposure; PYE, patient year of exposure; RRa, rate ratio; RRb, relative risk; T1DM, type 1 diabetes mellitus.
In the EDITION 2 trial, a randomized, open-label, parallel-group study, adults treated with high-dose basal insulin (≥42 U/day) and OADs received either Gla-300 or Gla-100 QD titrated to an FPG target of ≤80-100 mg/dl (4.4-5.6 mmol/l) [55]. The incidence of confirmed (plasma glucose ≤70 mg/dl) or severe nocturnal hypoglycemic events was significantly lower in the Gla-300 group than the Gla-100 group between Week 9 and Week 26 (21.6% vs 27.9%, respectively; P=0.038), as was the incidence over the full study period (Table 1) [55]. The incidence of confirmed (plasma glucose ≤70 mg/dl) or severe hypoglycemic events occurring at any time was lower in the Gla-300 group than the Gla-100 group during the full 26-week study period, similarly to EDITION 1 (Table 1). The incidence of severe hypoglycemia was low in both groups over the 26-week period (Table 1).

In the open-label EDITION 3 trial, insulin-naive participants on OADs were randomized to receive Gla-300 or Gla-100 titrated to an FPG target of ≤80-100 mg/dl (4.4-5.6 mmol/l). There was no significant difference in the incidence of confirmed (plasma glucose <70 mg/dl) or severe nocturnal hypoglycemia between Week 9 and Week 26 (P=0.45) [56]. Over the full 26-week period, the incidence of confirmed (plasma glucose <70 mg/dl) or severe nocturnal hypoglycemia was lower in the Gla-300 group than the Gla-100 group, and the incidence of confirmed (plasma glucose <70 mg/dl) or severe hypoglycemia at any time was numerically lower in the Gla-300 group (Table 1). There was no difference in the incidence of severe hypoglycemia over the whole treatment period between groups (Table 1).

Glaxo-300 has also been compared with Gla-100 in the EDITION JP 2 trial, an open-label study in Japanese patients using basal insulin and OADs [57]. In this study, no main secondary endpoint was defined. However, although not powered to identify statistical differences in hypoglycemia, the incidence of confirmed (plasma glucose <70 mg/dl) or severe nocturnal hypoglycemia was lower in the Gla-300 group than in the Gla-100 group (25.4% vs 43.7%; relative risk 0.58, 95% CI 0.40-0.85) [57]. Confirmed (plasma glucose <70 mg/dl) or severe nocturnal hypoglycemia was also lower over the full 26-week study period; confirmed (plasma glucose <70 mg/dl) or severe hypoglycemia at any time was numerically lower in the Gla-300 group (Table 1). There was no difference in the incidence of severe hypoglycemia over the whole treatment period between groups (Table 1).

A meta-analysis of the EDITION 1, 2, and 3 trials showed a reduction in overall confirmed or severe hypoglycemia when using Gla-300 compared with Gla-100, which was not consistently observed in the individual clinical trials included in the meta-analysis [52].

**LY2605541, basal insulin peglispro:** Data on hypoglycemia in patients receiving BIL are available only from a single phase 2 trial in T2DM [58]. In this 12-week, open-label, three-arm, parallel-group study, patients were treated with basal insulin and OADs and randomized to receive either BIL or Gla-100 QD. Hypoglycemia was defined as any event with a blood glucose measurement ≤70 mg/dl (3.9 mmol/l), and severe hypoglycemia was defined as that requiring assistance from another person with prompt recovery in response to carbohydrate intake. Insulin dose was titrated to a blood glucose target of ≤100 mg/dl (≤5.6 mmol/l), and severe hypoglycemia was defined as that requiring assistance from another person with prompt recovery in response to carbohydrate intake. The efficacy of BIL was similar to that of Gla-100 in terms of A1C reduction and there were no significant differences in terms of incidence of total or nocturnal hypoglycemia events (Table 1). However, when results were adjusted for baseline hypoglycemia, a significant 48% reduction favoring BIL was detected for nocturnal hypoglycemia (P=0.021) [58]. There were no severe hypoglycemic events reported during the study period.

In the EDITION 4 trial, a 26-week, open-label study in which participants were randomized to GLA-300 or Gla-100 QD. The insulin dose was titrated to achieve blood glucose ≤100 mg/dl (≤5.6 mmol/l). There was no statistically significant difference between LY260361 and Gla-100 (Table 1).

Four phase 3 trials comparing BIL to Gla-100 or NPH have been completed as part of the IMAGINE trial series; reporting of results is expected shortly (NCT01582451, NCT01790438, NCT01435616, NCT01468987; https://clinicaltrials.gov).

**New insulin glargine LY2963016:** The EMA recommended approval of LY2963016 as a biosimilar in June 2014 [59], and the FDA tentatively approved the New Drug Application for LY2963016 in August 2014 [60].

In the EDITION 2 trial, a 26-week, phase 3, double-blind, parallel-group study, insulin-naive patients treated with OADs received either LY2963016 or Gla-100 QD. The insulin dose was titrated to achieve blood glucose ≤100 mg/dl (≤5.6 mmol/l). The efficacy of both agents in terms of A1C reduction was similar [61]. With regard to rate of total hypoglycemia (defined as blood glucose ≤70 mg/dl [3.9 mmol/l]), where measures were available, there was no statistically significant difference between LY2963016 and Gla-100 (Table 1).

**Hypoglycemia in T1DM**

The incidence of hypoglycemia in patients with T1DM is generally higher than among those with T2DM. Adults with T1DM have ~2 episodes of mild hypoglycemia per week; the annual prevalence of severe hypoglycemia is ~30%, with several factors, such as long disease duration, increasing its incidence [39,40].

**Insulin degludec:** In their meta-analysis of phase 3 trials of IDeg versus Gla-100, Vora et al. reported that the two agents had similar efficacy in terms of reduction of A1C in T1DM patients [45].

In the BEGIN Basal-Bolus Type 1 study, a 52-week, parallel-group, phase 3 study, T1DM patients previously treated with basal-bolus insulin for ≥1 year received either IDeg or Gla-100 QD with mealtime insulin aspart [28]. Both basal and mealtime insulin were titrated to achieve blood glucose 70-90 mg/dl (3.9-5.0 mmol/l). In this study, rates of confirmed hypoglycemia were similar between patient groups, confirmed nocturnal hypoglycemia was significantly lower with IDeg than with Gla-100, and a similar rate of severe hypoglycemia was observed for both treatment groups (Table 2).

In the BEGIN FLEX T1 trial, patients received mealtime insulin aspart alongside basal analog insulin treatment. The trial had a treat-to-target design with basal analog insulin titrated to achieve blood glucose 70-90 mg/dl (4.0-5.0 mmol/l) and mealtime insulin titrated to achieve ≤90 mg/dl (≤5.0 mmol/l), based on the preceding day’s pre-lunch, pre-dinner, and bedtime SMPG values [62]. After 26 weeks, confirmed hypoglycemia rates were similar and rates of severe events were low in all groups (Table 2). Confirmed nocturnal events were significantly lower with the IDeg FLEX dosage compared with either IDeg (37%, P=0.003) or Gla-100 (40%, P=0.001) [62].

**Insulin glargine 300 units/ml:** Two phase 3 studies have been conducted in otherwise healthy patients with T1DM as part of the EDITION series of clinical trials. Study designs, definitions of hypoglycemia, and titration targets were consistent throughout the series in patients with T2DM and T1DM.

The EDITION 4 trial was a 26-week, open-label study in which participants were randomized to GLA-300 (morning or evening) or Gla-100 (morning or evening) while continuing their mealtime insulin aspart [28]. Both basal and mealtime insulin were titrated to achieve blood glucose 70-90 mg/dl (3.9-5.0 mmol/l). In this study, rates of confirmed hypoglycemia were similar between patient groups, confirmed nocturnal hypoglycemia was significantly lower with IDeg than with Gla-100, and a similar rate of severe hypoglycemia was observed in both treatment groups (Table 2).

In the EDITION 3 trial, phase 3 study, T1DM patients previously treated with basal-bolus insulin for ≥1 year received either IDeg or Gla-100 QD with mealtime insulin aspart [28]. Both basal and mealtime insulin were titrated to achieve blood glucose 70-90 mg/dl (3.9-5.0 mmol/l). In this study, rates of confirmed hypoglycemia were similar between patient groups, confirmed nocturnal hypoglycemia was significantly lower with IDeg than with Gla-100, and a similar rate of severe hypoglycemia was observed for both treatment groups (Table 2).
hypoglycemia was lower in the Gla-300 group than in the Gla-100 group during the first 8 weeks of the study (rate ratio 0.69, 95% CI 0.53-0.91) [63]. Over the whole study period, the incidence of confirmed or severe hypoglycemia at any time was similar between treatment groups (Table 2). Severe hypoglycemia was seen in 6.6% and 9.5% of patients in Gla-300 and Gla-100 groups, respectively. Neither glycemic control nor hypoglycemia differed between insulins or times for morning and evening injection.

Similarly to the EDITION JP 2 trial, EDITION JP 1 was a 26-week, randomized, open-label study conducted with Japanese participants who received either Gla-300 or Gla-100 alongside continued use of mealtime insulin [64]. Gla-300 showed similar efficacy to Gla-100 in terms of lowering A1C. The incidence of confirmed or severe nocturnal hypoglycemia was not significantly different between groups from Week 9 to Week 26; however, the incidence was lowest during the first eight weeks of the study in the Gla-300 group compared with the Gla-100 group, and was lower in the Gla-300 group over the full 26-week study period (Table 2). Severe hypoglycemia was low in both groups (5.7% and 9.9% with Gla-300 and Gla-100, respectively). There was no difference in the incidence of confirmed or severe hypoglycemia experienced at any time between groups (Table 2).

LY2605541, basal insulin peglispro: There are data from one 8-week, phase 2, open-label, randomized, two-arm, cross-over study in patients with T1DM who received either BIL or Gla-100 QD while continuing mealtime insulin [65]. In this study, BIL demonstrated greater improvements compared with Gla-100 in terms of glycemic control. The rate of total hypoglycemia was higher in the BIL group than in the Gla-100 group (Table 2). However, the rate of nocturnal hypoglycemia was lower in the BIL group than in the Gla-100 group (Table 2). The incidence of severe hypoglycemia was similar between the two treatment groups (five patients with six events in the BIL group and three patients with six events in the Gla-100 group).

Two phase 3 trials comparing BIL to Gla-100 or NPH have been completed as part of the IMAGINE trial series, with reporting of results expected shortly (NCT01481779, NCT01454284; https://clinicaltrials.gov).

New insulin LY2963016: The ELEMENT 1 trial was a 52-week, phase 3, open-label, parallel-group study in which patients received either LY2963016 or Gla-100 in combination with mealtime insulin lispro [66]. Insulin doses were titrated to achieve blood glucose ≥2.22 mg/dl (≤6.0 mmol/l). LY2963016 had similar efficacy to Gla-100 in terms of lowering A1C, and the rate of total hypoglycemia was similar between patient groups (Table 2).

Summary

The longer, more constant PK/PD profiles of the new basal analog insulins appear to confer advantages over previous basal analog insulins with respect to reduced hypoglycemia, particularly nocturnal hypoglycemia. However, interpretation of the data is limited by a lack of head-to-head comparisons between these agents and the fact that all data published to date are from trials sponsored by the pharmaceutical company producing the insulin, with no independent meta-analyses currently available. In addition, the trials have been designed specifically to assess the efficacy of novel basal analog insulins in patients with a history of hypoglycemia unawareness or at high risk for severe hypoglycemia should also be undertaken. The difficulty in performing double-blind assessments in insulin trials, due to the different appearances of formulations, is a perennial issue in randomized trials comparing basal analog insulins. However, two of the upcoming phase 3 studies of BIL have a double-blind design (NCT01435616, NCT01454284; http://clinicaltrials.gov/). Whether this represents a crossing of the Rubicon for the design of insulin trials remains to be seen.

Conclusion

The development of the new generation of basal analog insulins represents an additional step towards patients achieving physiologic glycemic control. Improved PK/PD profiles appear to be associated with better clinical outcomes in terms of hypoglycemia. Future head-to-head trials, studies in specific patient populations, and pharmacoeconomic analyses—many of which are already underway—will be key for clinicians and patients to determine appropriate, individualized treatment courses.

Acknowledgments

The contents of this paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication. The authors contributed to the writing of this manuscript, including critical review and editing of each draft, and approval of the submitted version. The authors received writing/editorial support in the preparation of this manuscript provided by Pim Dekker, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

Conflicts of Interest

Alsahli: None

Thrasher: Research grant support from Akeno, Aventis, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Gilead Sciences, GlaxoSmithKline, Medtronic, Merck & Co, Novartis, Nordisk, Pfizer, Sanofi, Speedel Pharma Ltd, and Yamanouchi Pharma America; has served on the speaker bureau for Amylin, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Medtronic, Nordisk, Pfizer, Sanofi, Takeda, and Virus, and is on advisory boards for Medtronic, Pfizer Pharmaceuticals, and Sanofi-Aventis; and has received editorial/publication support from Boehringer Ingelheim and Eli Lilly.

Gerich: Consultant/member of the speaker bureau for Bristol-Myers Squibb, AstraZeneca, Merck, Janssen Pharmaceuticals, Eli Lilly, and Boehringer Ingelheim.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, et al. (2015) Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 38: 140-149.

2. Mitrokou A, Ryan C, Veneman T, Mokan M, Jenssen T, et al. (1991) Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol 260: E67-74.

3. Gerich JE (1988) Lilly lecture 1988. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37: 1608-1617.

4. Alsahli M, Gerich JE (2013) Hypoglycemia. Endocrinol Metab Clin North Am 42: 657-676.
5. Bolli GB, Tsakalian E, Haymond MW, Cryer PE. Gerich JE (1984) Defective glucose counterregulation after subcutaneous insulin in non-insulin-dependent diabetes mellitus. Paradoxical suppression of glucose utilization and lack of compensatory increase in glucose production, roles of insulin resistance, abnormal neuroendocrine responses, and islet paracrine interactions. J Clin Invest 73: 1532-1541.

6. Gerich JE, Mokan M, Veneman T, Korytkowski M, Mitракou A (1991) Hypoglycemia unawareness. Endocr Rev 12: 358-371.

7. Fritzsche A, Slumvoll M, Häring HU, Gerich JE (2000) Reversal of hypoglycemia unawareness in a long-term type 1 diabetic patient by improvement of beta-adrenergic sensitivity after prevention of hypoglycemia. J Clin Endocrinol Metab 85: 523-525.

8. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359: 1577-1589.

9. Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 329: 977-986.

10. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352: 837-853. Erratum in: Lancet 1999; 354: 837-853.

11. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, et al. (2008) Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 358: 2545-2559.

12. Currie CJ, Morgan CL, Poole CD, Sharpin P, Lammert M, et al. (2006) Multivariate models of health-related utility and the fear of hypoglycemia in people with diabetes. Curr Med Res Opin 22: 1523-1534.

13. Leiter LA, Yale J-F, Chiasson J-L, Harris S, Kleinsteiver P, et al. (2005) Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. Can J Diabetes 29: 186-192.

14. Brod M, Rana A, Barnett AH (2012) Adherence patterns in patients with type 2 diabetes on basal insulin analogues: missed, misdosed and reduced doses. Curr Med Res Opin 28: 1933-1946.

15. Wild D, von Maitzahn R, Brohan E, Christensen T, Clauson P, et al. (2007) A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. Patient Educ Couns 68: 10-15.

16. Grant R, Adams AS, Trinacy CM, Zhang F, Kleinman K, et al. (2007) Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care 30:807-812.

17. Nam S, Chiesa C, Stotts NA, Kroon L, Janson SL (2011) Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract 93: 1-9.

18. Woerhe IE, Neumann C, Zschau S, Tenner S, Insigler A, et al. (2007) Impact of fasting and postprandial glycaemia on overall glycoemic control in type 2 diabetes. Importance of postprandial glycaemia to achieve target HbA1c levels. Diabetes Res Clin Pract 77: 290-295.

19. Ratner RE, Hirsch IB, Neffing JL, Garg SK, Mecca TE, et al. (2000) Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 23: 639-643.

20. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators (2003) The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 26: 3080-3086.

21. Strange P (2007) Treat-to-target insulin titration algorithms when initiating long or intermediate acting insulin in type 2 diabetes. J Diabetes Sci Technol 1: 540-548.

22. Garber AJ (2014) Treat-to-target trials: uses, interpretation and review of concepts. Diabetes Obes Metab 16: 193-205.

23. Wangnoo SK, Sethi B, Sahay RK, John M, Ghosal S, et al. (2014) Treat-to-target trials in diabetes. Indian J Endocrinol Metab 18: 166-174.

24. Rizza RA, Gerich JE, Haymond MW, Westland RE, Hall LD, et al. (1980) Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion, and intensified conventional pancreatic insulin therapy. N Engl J Med 303: 1313-1318.

25. Heise T, Pieber TR (2007) Towards peakless, reproducible and long-acting insulin. An assessment of the basal analogues based on isoglycemic clamp studies. Diabetes Obes Metab 9: 648-659.

26. Swinnen SG, Simon AG, Holleman F, Hooekstra JB, Devries JH (2011) Insulin detemir versus insulin glargine for type 2 diabetes mellitus. Cochrane Database Syst Rev 7: CD006383.

27. Heise T, Nosek L, uncertainty, HAsh PR (2012) Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab 14: 944-950.

28. Heller S, Buse J, Fisher M, Garg S, Marre M, et al. (2012) Insulin degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 379: 1489-1497.

29. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, et al. (2015) New insulin glargine 300 Units · mL-1 provides a more even activity profile and prolonged glycoemic control at steady state compared with insulin glargine 100 Units · mL-1. Diabetes Care 38: 637-643.

30. Shrimolo M, Eto T, Irie S, Fukuzaki A, Teichert L, et al. (2015) Single-dose new insulin glargine 300 U/ml provides prolonged, stable glycaemic control in Japanese and European people with type 1 diabetes. Diabetes Obes Metab 17: 254-260.

31. Dahmen R, Bergmann K, Lehmann A, Tiller J, Jax T, et al. (2013) New insulin glargine U300 formulation evens and prolongs steady state PK and PD profiles during euglycaemic clamp in patients with type 1 diabetes (TIDM). Diabetes 62: A113.

32. Steinaesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH (2014) Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. Diabetes Obes Metab 16: 873-876.

33. Beals JM, Cutler GB, Vick A, Koester A, Li S, et al. (2012) LY2605541: Leveraging hydrodynamic size to develop a novel basal insulin. Diabetologia 55: S23.

34. Sinha VP, Howey DC, Choi SL, Mace KF, Heise T (2014) Steady-state pharmacokinetics and glucodynamics of the novel, long-acting basal insulin LY2605541 dosed once-daily in patients with type 2 diabetes mellitus. Diabetes Obes Metab 16: 344-350.

35. Linnebjerg H, Heise T, Zhang X, Seger ME, Coutsant D, et al. (2014) Comparison of duration of action of 2 insulin glargine products, LY2963016 and insulin glargine, in subjects with type 1 diabetes mellitus. Diabetologia 57: S382.

36. Choi I, Hwang S, Kim J, Jung S, Kim D, et al. (2014) Long-acting basal insulin (HM12470) offers once-weekly-dosing potential with a favorable PK, PD and mitogenic profile. Diabetologia 57:1 S381.

37. Kaye J, Krasner A, Canney L, Pichotta P, Simms P, et al. (2013) Novel formulations BIOD-238 and BIOD-250 result in more rapid absorption and declines from peak than Humalog. Diabetologia 56: S413.

38. Morrow L, Horpesch M, Canney L, Pichotta P, Krasner A, et al. (2014) Biphasic pharmacokinetic and pharmacodynamic profiles associated with concentrated insulin BIOD-531 show rapid onset and basal duration of action. Diabetologia 57: S383.

39. Frier BM (2014) Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nat Rev Endocrinol 10: 711-722.

40. Gerich JE (2000) Hypoglycaemia and counterregulation in type 2 diabetes. Lancet 356: 1946-1947.

41. Wei W, Zhou S, Mao R, Pan C, Xie L, et al. (2014) Much ado about nothing? A real-world study of patients with type 2 diabetes switching Basal insulin analogs. Adv Ther 31: 539-560.

42. Morales J, Schneider D2 (2014) Hypoglycemia. Am J Med 127: S17-24.

43. FDA briefing document (2013) NDA 203313 and NDA 203314. Insulin Degludec and Insulin Degludec/Appear.

44. Novo Nordisk (2013) Novo Nordisk receives Complete Response Letter in the US for Tesibati® and Ryzodeg®.

45. Vora J, Christensen T, Rana A, Bain SC (2014) Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. Diabetes Ther 5: 435-446.
46. Zinman B, Phillips-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, et al. (2012) Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 35: 2464-2471.

47. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, et al. (2012) Insulin degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2); a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 379: 1498-1507.

48. Meneghini G, Atkin SL, Gough SC, Raz I, Blonde L, et al. (2013) The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care 36: 858-864.

49. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, et al. (2013) Insulin degludec compared with insulin glargine in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Investig 4: 605-612.

50. Sanofi (2015) FDA accepts Sanofi’s new drug application for basal insulin Toujeo®. Paris, France.

51. EMA (2015) Summary of opinion (post authorization). Toujeo: insulin glargine 300 units/mL.

52. Ritzel RA, Roussel R, Boll GB, Vinet L, Yki-Järvinen H (2014) New insulin glargine 300 U/mL: glycaemic control and hypoglycaemia in a meta-analysis of phase 3a EDITION clinical trials in people with type 2 diabetes mellitus. Diabetologia 57: S394-S395.

53. American Diabetes Association (2015) Standards of medical care in diabetes-2015. Diabetes Care 38: S1-S92.

54. Riddle MC, Boll GB, Ziemer M, Muehle-Bartmer I, Bizel F, et al. (2014) New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a 6-month randomized controlled trial (EDITION 1). Diabetes Care. 37: 2755-2762.

55. Yki-Järvinen H, Bergenstal R, Ziemer M, Wardecki M, Muehle-Bartmer I, et al. (2014) New insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycaemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care 37: 3235-3243.

56. Boll GB, Riddle MC, Bergenstal RM, Ziemer M, Sestakauskas K, et al. (2015) New insulin glargine 300 U/mL compared with glargine 100 U/mL in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 17: 386-394.

57. Terauchi Y, Koyama M, Cheng X, Shimizu S, Hirose T, et al. (2014) Glycaemic control and hypoglycaemia in Japanese people with T2DM receiving new insulin glargine 300 U/mL in combination with OADs (EDITION JP 2). Diabetologia 57: S401.

58. Bergenstal RM, Rosenstock J, Arakaki RF, Prince MJ, Qu Y, et al. (2012) 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 35:2140-2147.

59. European Medicines Agency (2014) Summary of opinion (initial authorisation). Abasria (insulin glargine).

60. Eli Lilly and Company (2014) FDA grants tentative approval for Lilly and Boehringer Ingelheim’s Basaglar™ (insulin glargine injection).

61. Hollander P, Rosenstock J, Bhargava A, Ilag LL, Pollom RK, et al. (2014) Similar efficacy and safety with LY2963016 insulin glargine compared with insulin glargine in patients with type 2 diabetes mellitus: the EDITION 2 study. Diabetologia 57: S388.

62. Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, et al. (2013) Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab 98: 1154-1162.

63. Home PD, Bergenstal RM, Riddle MC, Ziemer M, Rojeski M, et al. (2014) Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL in people with type 1 diabetes (EDITION 4). Diabetologia 57: S69-S70.

64. Matsuhisa M, Koyama M, Cheng X, Shimizu S, Hirose T (2014) New insulin glargine 300 U/mL: glycemic control and hypoglycaemia in Japanese people with T1DM (EDITION JP 1). Diabetologia 57: S400.

65. Rosenstock J, Bergenstal RM, Blevins TC, Morrow LA, Prince MJ, et al. (2013) 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. Diabetes Care 36: 522-528.

66. Blevins TC, Dahl D, Rosenstock J, Ilag LL, Huster WJ, et al. (2015) Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the EDITION 1 study. Diabetes Obes Metab.