Type 2 diabetes remains common worldwide, and its prevalence is increasing regardless of age, sex, ethnicity, education, or income (1,2). Furthermore, numerous large observational studies have demonstrated that many patients with type 2 diabetes have suboptimal glycemic control and that intensification is delayed, even when clinically indicated (3–7). Recently, data from 11,525 patients with A1C levels \( \geq 8\% \) in a large U.S. insurance claims database were examined (8). Less than half had their treatment intensified using either additional oral antidiabetic agents or injectables within 12 months.

**Reasons for Lack of Glycemic Control**
Clinical inertia (i.e., resistance to initiating or intensifying diabetes treatments in patients who are not at their A1C goal [9]) has been discussed for more than a decade as a reason for poor glycemic control (10,11) and remains a clinically important topic today (12,13). Both patient- and clinician-related factors have been identified as contributing to clinical inertia. These include concerns about weight gain, pain from injections, pain from required blood glucose monitoring, and potential negative impacts of complex regimens that...
involve multiple daily injections on patients’ adherence and quality of life (13–15). In addition, hypoglycemia historically has been a leading barrier to initiating insulin for patients (16) and clinicians (17) alike, as a result of the detrimental impact of hypoglycemia on patients’ quality of life and fear of adverse side effects associated with hypoglycemia (18,19).

Unfortunately, despite considerable evolution in treatment options, hypoglycemia is still considered a leading impediment to better diabetes management. For example, a meta-analysis of 46 published studies involving 532,542 patients on various treatments indicated that the overall prevalence of mild hypoglycemia was 45% (95% CI 34–57%) and of severe hypoglycemia was 6% (95% CI 5–7%), corresponding to 19 [95% CI 0–51.08] and 0.80 [95% CI 0–2.15] episodes per person-year, respectively (20). In an Internet survey of 1,984 patients in the United States, 62.9% of respondents reported having experienced hypoglycemia, and 36.9% reported weight gain (21). Other studies have also demonstrated that severity and frequency of hypoglycemia affect patients’ perceptions of their disease, with nocturnal hypoglycemia having a greater effect than daytime events (22). Hypoglycemia has such an impact on patients’ quality of life and ability to achieve good glycemic control that it has been suggested as an important endpoint in clinical trials of new glucose-lowering medications (23).

Importance of Earlier Intensification of Therapy
The latest guidelines recommend intensifying therapy for patients who have been above their glycemic target for >3 months despite proper dosing of their current medications (24). Long-term (~20 years) follow-up of patients from the landmark U.K. Prospective Diabetes Study demonstrated the benefits of early intensive therapy compared to conventional treatment in type 2 diabetes in significantly reducing the risk of myocardial infarction (~15%), microvascular disease (~24%), and any diabetes-related endpoint (~9%) (25). Retrospective studies have found that patients affected by clinical inertia had a shorter mean time to progression of diabetic retinopathy (P = 0.02), were nearly five times more likely to experience progression of retinopathy (adjusted incidence rate ratio 4.92 [95% CI 1.11–21.77]) (26), and were at significantly increased risk for myocardial infarction, stroke, and heart failure by 67, 51, and 64%, respectively (hazard ratios [HRs] 1.67 [95% CI 1.39–2.01], 1.51 [95% CI 1.25–1.83], and 1.64 [95% CI 1.40–1.91], respectively) compared to patients who had more timely intensification of therapy (27).

Availability of New Therapeutic Agents to Treat Diabetes Uncontrolled With Oral Agents
Historically, because insulin was for many years the major next step in intensification when diabetes was uncontrolled on multiple oral agents, insulin therapy became somewhat synonymous with intensification (28). Therefore, many of the barriers to intensification have centered on those associated with insulin use. The introduction of basal insulin analogs such as insulin degludec and insulin glargine have reduced the risk of hypoglycemia in type 2 diabetes compared to human insulin. A meta-analysis showed that insulin glargine U100 used once daily had a lower risk of overall symptomatic (11%, P = 0.0006), nocturnal (26%, P <0.0001), severe (46%, P = 0.0442), and nocturnal severe (59%, P = 0.0231) hypoglycemia compared to NPH insulin (29). A later trial showed that insulin degludec has a lower risk of overall confirmed (rate ratio [RR] 0.83 [95% CI 0.70–0.98]), nocturnal confirmed (RR 0.64 [95% CI 0.48–0.86]), and severe (RR 0.14 [95% CI 0.03–0.70]) hypoglycemia than insulin glargine U100 in insulin-naive patients with type 2 diabetes (30).

A plethora of newer medications for type 2 diabetes have provided alternatives to intensification with insulin. This includes drugs of the incretin class (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptide-4 [DPP-4] inhibitors) and sodium–glucose cotransporter 2 (SGLT2) inhibitors. However, the optimal choice for intensification after failure to achieve glycemic control on oral agents remains unclear, and treatment must be individualized (24).

The complex pathophysiology of type 2 diabetes has meant that treatments such as GLP-1 receptor agonists have generated considerable interest as a result of their robust reduction of A1C, ability to lower postprandial glucose, and weight-sparing effect. Furthermore, treatment with GLP-1 receptor agonists addresses multiple aspects of the underlying abnormalities in type 2 diabetes (e.g., declining β-cell function leading to reduced insulin secretion, excessive secretion of glucagon from pancreatic α-cells leading to undesirable hepatic glucose output, insulin resistance in both liver and peripheral tissues [31], and components of the metabolic syndrome [32]). Although there was initial concern about an increased risk of acute pancreatitis associated with their use, subsequent analyses have failed to confirm such a risk (33).

Combining a basal insulin analog with a GLP-1 receptor agonist in a single formulation is a logical way to take advantage of the best attributes of each component, while simultaneously minimizing side effects associated with each when used alone (34–37). In particular, the basal insulin analog component allows for control of fasting plasma glucose (FPG) levels, whereas the GLP-1 receptor agonist provides additional control of postprandial glucose, with more substantial reductions observed with short-acting GLP-1 receptor agonists (31). From a safety perspective, benefits of the combination include
### Table 1. Comparison of Randomized, Controlled Trials Evaluating Co-Formulations of a Basal Insulin and a GLP-1 Receptor Agonist

| Patients | DUAL I Extension (34) | DUAL IV (40) | DUAL VI (41) | LixiLan-O (37) |
|----------|-----------------------|--------------|--------------|----------------|
| n        | 1,663                 | 435          | 420          | 1,170          |
| Type 2 diabetes | Insight-naive       | Insight-naive | Insight-naive | Insight-naive |

#### Screening criteria

| Oral agents at screening | Met ± Pio | SU ± Met | Met ± Pio | Met ± SU, glinide, DPP-4 inhibitor, or SGLT2 inhibitor |
| A1C (%)                  | 7.0–10.0  | 7.0–9.0  | 7.5–10.0† or 7.0–9.0‡ | 7.5–10.0 (metformin only) 7.0–9.0 (metformin + other oral agent) |
| BMI (kg/m²)              | ≤40       | ≤40       | ≤40         | Not specified |
| FPG (mg/dL)              | N/A       | N/A       | N/A         | ≤250           |

#### Comparison treatments

| Comparison treatments | IDeg + Met ± Pio | IDeg + SU ± Met | IDegLira 1WT + Met ± Pio | iGlarLixi + Met |
|-----------------------|------------------|-----------------|--------------------------|------------------|
|                       | IDegLira + Met ± Pio | IDegLira + SU ± Met | IDegLira 2WT + Met ± Pio | iGlar + Met |
|                       | IDeg + Met + Pio  | Placebo + SU ± Met | Lira + Met ± Pio         | Lixi + Met     |

#### Blinding

| Blinding              | Open-label | Double-blinded | Open-label | Open-label |
|-----------------------|------------|----------------|------------|------------|

#### Duration (weeks)

| Duration (weeks) | 26 main phase + 26 extension | 26 | 32 | 30 |

#### Run-in period before randomization

| Run-in period before randomization | None | None | None | 4 weeks |

#### Baseline characteristics*

| Age (years) | 54.9–55.1 | 59.4–60.0 | 56.6–57.0 | 58.2–58.7 |
| A1C (%)     | 8.3       | 7.9       | 8.1–8.2   | 8.1 |
| BMI (kg/m²) | 31.2–31.3 | 31.2–32.0 | 32.4–32.5 | 31.6–32.0 |
| Duration of diabetes (years) | 6.6–7.2 | 9.0–9.3 | 7.2–7.4 | 8.7–8.9 |

#### Completers (n [%])

| Completers (n [%]) | IDegLira: 621 (74.5) | IDeg: 305 (73.7) | IDegLira: 251 (86.9) | iGlarLixi: 440 (93.8) |
|                    | Lira: 285 (68.7) | Placebo: 111 (76.0) | IDegLira 1WT: 191 (91.0) | iGlar: 440 (94.2) |
|                    | IDegLira 2WT: 204 (97.1) | iGlarLixi: 440 (93.8) | Lira, liraglutide 6 mg/mL; Lixi, lixisenatide; Met, metformin; Pio, pioglitazone; SU, sulfonylurea. |

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*Range of mean values across treatment groups. †For patients treated with just metformin. ‡For patients treated with metformin plus another eligible glucose-lowering therapy. 1WT, once weekly titration; 2WT, twice weekly titration; IDeg, insulin degludec U100; iGlar, insulin glargine U100; Lira, liraglutide 6 mg/mL; Lixi, lixisenatide; Met, metformin; Pio, pioglitazone; SU, sulfonylurea.
A reduced rate of hypoglycemia and a weight- and insulin-sparing effect compared to basal insulin alone, and reduced gastrointestinal side effects compared to a GLP-1 receptor agonist alone (34–37).

Two basal insulin/GLP-1 receptor agonist combination products were approved by the U.S. Food and Drug Administration in November 2016: IDegLira (Xultophy 100/3.6, a titratable, fixed-ratio combination of insulin degludec and the GLP-1 receptor agonist liraglutide) and iGlarLixi (Soliqua 100/33, a titratable, fixed-ratio combination of insulin glargine U100 and the GLP-1 receptor agonist lixisenatide) (24). Administering these products as a co-formulation also offers the convenience and simplicity of delivering both products in a single, easy-to-teach and use pen injection device.

Studies have shown that the pharmacokinetic effects of the component products are preserved in co-formulation for IDegLira (38). No similar studies have yet been published for iGlarLixi, but its prescribing information states that co-formulation has no impact on the pharmacodynamics of insulin glargine or the pharmacokinetics of lixisenatide (39). In this article, we review the results of key clinical trials of each product, including the Dual Action of Liraglutide and Insulin Degludec (DUAL) I (34), DUAL IV (40), and DUAL VI (41) trials for IDegLira and the Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed Ratio Combination Compared to Insulin Glargine Alone and Lixisenatide Alone on Top of Metformin in Patients With Type 2DM (LixiLan-O) trial for iGlarLixi (37) in insulin-naive patients who intensified therapy as a result of poor glycemic control on oral agents and discuss how these products can be initiated and titrated for patients with poorly controlled type 2 diabetes in regular clinical practice.

**TABLE 2. Comparison of Dosing and Titration in Randomized Trials Evaluating Co-Formulations of a Basal Insulin and a GLP-1 Receptor Agonist**

|          | DUAL I (34) | DUAL IV (40) | DUAL VI (41) | LixiLan-O (37) |
|----------|-------------|--------------|--------------|----------------|
| **Starting dose** |              |              |              | iGlarLixi: 10 units |
| IDegLira: 10 units |              |              |              | (iGlar 10 units + 5 μg Lixi) |
| (10 units IDeg + 0.36 mg Lira) |              |              |              |                      |
| IDeg: 10 units |              |              |              | IGlar: 10 units |
| Lira: 0.6 mg/day |              |              |              | Lixi: 10 μg |
| **FPG target (mg/dL)** | 72–90       | 72–108       | 72–90        | 80–100          |
| **Titration** |              |              |              | iGlarLixi: titration once weekly adding 2 units if FPG was >100 mg/dL or adding 4 units if FPG was >140 mg/dL |
| IDegLira: twice weekly based on the mean of three consecutive fasting SMBG results; adjustments occurred in 2-unit increments |              |              |              | IGlar: as above, but dose capped at 60 units |
| IDeg: no limit to titration |              |              |              | Lixi: 10 μg for the first 2 weeks, followed by 20 μg thereafter |
| Lira: increased by 0.6 mg weekly to a maximum dose of 1.6 mg/day |              |              |              |                      |
| **Mean daily dose at end of trial** | IDegLira: 39 units | IDegLira: 28 units | 41 units | iGlarLixi: 39.8 units |
| (39 units IDeg + 1.4 mg Lira) |              | (28 units IDeg + 1.0 mg Lira) | (41 units IDeg + 1.48 mg Lira in both arms) | IGlar: 40.3 units |
| IDeg: 62 units |              |              |              | Lixi: not reported |
| Lira: 1.8 mg |              |              |              |                      |

1WT, once weekly titration; 2WT, twice weekly titration; IDeg, insulin degludec U100; IGlar, insulin glargine U100; Lira, liraglutide 6 mg/mL; Lixi, lixisenatide.
All of the trials were randomized, parallel-group, and of open-label design, with the exception of DUAL IV, which was a double-blinded trial (40). The trials enrolled patients who had not been previously treated with insulin or a GLP-1 receptor agonist and ranged in duration from 26 to 52 weeks, with the 52-week trial (DUAL I) including both a 26-week main phase and a 26-week extension (34). Oral agents being used at screening were to be continued in all of the DUAL trials; however, in the LixiLan-O trial, all oral agents other than metformin were discontinued at randomization. The mean duration of diabetes among randomized patients varied across the trials, ranging from 6.6 to 9.3 years (Table 1 [34,37,40,41]). The mean age of patients, mean A1C, and mean BMI were similar across the trials.

It is important to note that, in the absence of a head-to-head trial, no indirect comparisons should be made between the DUAL and LixiLan trials because of the above-mentioned differences in their designs.

### Dosing and Titration of IDegLira

**IDegLira** is provided in a fixed-ratio combination of insulin degludec 100 units/mL to 3.6 mg/mL of liraglutide; 1 unit contains 1 unit of insulin degludec + 0.06 mg liraglutide. It is recommended that IDegLira be dosed at the same time each day, with or without food (42). Across the three DUAL trials, the starting dose was 10 units for IDegLira (10 units insulin degludec + 0.36 mg liraglutide) (Table 2 [34,37,40,41]). Dosing was adjusted in 2-unit increments based on the mean of three consecutive fasting self-monitoring of blood glucose (SMBG) measurements to a target of 72–90 mg/dL (DUAL I and VI) (41). One unit of pen A delivers 1 unit insulin glargine U100 and 0.5 µg lixisenatide, and each unit of pen B delivers 1 unit of insulin glargine U100 and 0.33 µg lixisenatide. For twice-daily basal insulin or insulin glargine U300, the total daily dose previously used should be reduced by 20%. For any other basal insulin, the same rule should be applied as for insulin glargine U100. To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns (i.e., macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications. GLP-1 receptor agonist– and insulin-naive patients.

### Table 3. Titration of IDegLira and iGlarLixi

| Label | United States and Europe | Europe | United States | Europe |
|-------|--------------------------|--------|---------------|--------|
| Previous regimen | Basal insulin (<50 units) or GLP-1 receptor agonist* | Oral agents only† | Basal insulin (<60 units) or Lixi | Basal insulin | Oral agents only* |
| **Recommended starting dose** | 16 units | 10 units | 15 units for patients previously treated with Lixi or <30 units basal insulin; 30 units for patients previously treated with 30–60 units basal insulin | 20 units using pen A‡ (10–40 pen) for patients on ≥20–<30 units iGlar U100;§ 30 units using pen B‡ (30–60 pen) for patients on ≥30 to <60 units iGlar U100 § | 10 units using pen A‡ (10–40 pen) |
| **Maximum dose** | 50 units | 60 units | 60 units (pen A has a maximum dose of 40 units) |
| **Frequency of titration** | Every 3–4 days | Every week | Not stated |
| **Dose adjustment** | ± 2 units | ± 2–4 units | Not stated |

*U.S. prescribing information specifies liraglutide. In Europe, IDegLira and iGlarLixi are approved for use in GLP-1 receptor agonist– and insulin-naive patients.

†Each pre-filled pen contains 300 units insulin glargine U100 and 150 µg lixisenatide (pen A) or 100 µg lixisenatide (pen B). Each unit of pen A delivers 1 unit insulin glargine U100 and 0.5 µg lixisenatide, and each unit of pen B delivers 1 unit of insulin glargine U100 and 0.33 µg lixisenatide. §For twice-daily basal insulin or insulin glargine U300, the total daily dose previously used should be reduced by 20%. For any other basal insulin, the same rule should be applied as for insulin glargine U100. To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns (i.e., macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications. iGlar, insulin glargine; Lixi, lixisenatide.
In their respective clinical trial programs, the co-formulated products lowered A1C levels significantly more than the basal insulin (34,37), the placebo (40), or the GLP-1 receptor agonist alone (34), and more patients using a co-formulation also reached the target A1C of <7.0% in each of these trials (Table 3 [39,42,45,46]). Mean A1C was -8% at baseline (ranging from 7.9% in DUAL IV to 8.3% in DUAL I), and between 6.0% (in DUAL VI) and 6.5% (in LixiLan-O) at the end of the trials (37). Eligibility criteria for these trials were such that it is unknown whether IDegLira or iGlarLixi would be efficacious in patients with an A1C >10% at initiation. However, mean A1C was ≤7% at end of trial regardless of baseline A1C category for IDegLira (≤7.5, >7.5 to ≤8.5, >8.5 to ≤9.0%, and >9%) and iGlarLixi (<8% and ≥8%) (47,48). Another post-hoc analysis demonstrated that, for IDegLira, the decrease in A1C was measurable within the first 12 weeks of therapy, without weight gain or increased rate of hypoglycemia (49).

A post-hoc analysis of the LixiLan-O and LixiLan-L trials (the latter including insulin-experienced patients), published in abstract form, has indicated that iGlarLixi is associated with less glycemic variability than insulin glargine U100 or lixisenatide alone (50). The co-formulated products also lowered FPG levels to a similar extent as basal insulin alone and to a greater extent than the GLP-1 receptor agonist alone (Table 4 [34,37,40,41]).

Safety Results in the Trials

The safety profiles of both co-formulated products were as expected based on the safety of their individual components in all of the trials. In terms of hypoglycemia, IDegLira was associated with a significantly lower rate of confirmed hypoglycemia and nocturnal hypoglycemia compared to insulin degludec (34) (Table 5 [34,37,40,41,51]). As might be expected, IDegLira had significantly higher rates of confirmed and nocturnal hypoglycemia than either liraglutide alone (34) or placebo (52). The rate of hypoglycemia was higher in the DUAL IV trial than in DUAL I as a result of the concurrent use of sulfonylureas in the former. For iGlarLixi, the rate of confirmed hypoglycemia was numerically higher than that of insulin glargine and about five times greater than for lixisenatide alone (37). Few severe events were reported in any of the trials or treatment groups (Table 5).

In DUAL I and LixiLan-O, IDegLira and iGlarLixi were associated with weight neutrality in patients with diabetes uncontrolled on oral antidiabetic agents, the differences being statistically significant compared to the respective basal insulins alone, which were associated with weight gain in the respective trials (Table 5). Compared to placebo, IDegLira resulted in a small but significant increase in weight (40). Interestingly, titrating IDegLira twice weekly was associated with a twofold greater weight loss than once-weekly titration (41). In both DUAL I and LixiLan-O, the GLP-1 receptor agonists were associated with a much greater weight loss than their respective co-formulated products. In DUAL I, IDegLira resulted in a lower insulin and liraglutide requirement compared to either component alone; the daily insulin dose was lower with IDegLira compared to insulin degludec, and the daily liraglutide dose was lower with IDegLira compared with liraglutide after 52 weeks of treatment. In the LixiLan-O trial, in which the maximum insulin dose for both iGlarLixi and insulin glargine was 60 units, no insulin-sparing effect was observed with the co-formulation, and end-of-trial lixisenatide doses were not reported.

Gastrointestinal side effects were among the most frequent adverse events reported in DUAL I and LixiLan-O, with the majority of events observed in the first weeks of treatment (34,37). In the main phase of DUAL I, 9% of IDegLira-treated patients, 4% of insulin...
Degludec-treated patients, and 20% of liraglutide-treated patients experienced nausea (51), whereas during the extension phase, the incidence of nausea was comparable among treatment arms (34). The lack of an initial sharp increase in gastrointestinal events with IDegLira treatment compared to liraglutide is likely to be a result of the more gradual titration of liraglutide as a component of IDegLira. Similarly, in LixiLan-O, 9.6% of iGlarLixi-treated patients, 3.6% of insulin glargine-treated patients, and 24.0% of lixisenatide-treated patients experienced nausea (37). Furthermore, in both trials, fewer withdrawals due to gastrointestinal adverse events were observed in the combination arm compared to the GLP-1 receptor agonist arm.

With regard to special safety areas of interest, no instances of pancreatitis or medullary thyroid carcinoma were reported for either product (Table 5). Both products were well-tolerated.

**Summary**

Co-formulations of a basal insulin analog and a GLP-1 receptor agonist retain the clinical advantages (i.e., control of fasting and postprandial glucose) and minimize the side effects of each component when used individually. As a result, they are associated with significantly greater reductions in A1C compared to either of their respective components, lower rates of hypoglycemia and weight reduction compared to their respective basal insulin components, and a lower rate of gastrointestinal side effects compared to their respective GLP-1 receptor agonist components. IDegLira was also associated with an insulin-sparing effect compared to insulin degludec used alone.

Combination products offer the relative convenience of intensification with one daily injection and thus might be an attractive option for patients who are reluctant to initiate a more complex regimen or those who are struggling to adhere to their current regimen. Indeed, in the United States, they are indicated for use in patients with diabetes inadequately controlled on either basal insulin or a GLP-1 receptor agonist alone. Furthermore, when switching from oral antidiabetic agents, titration can be done once or twice weekly using a simple algorithm. The clinical trials discussed here have demonstrated that these co-formulation products can be considered as an intensification option for patients with diabetes not adequately controlled on oral antidiabetic agents.

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**TABLE 4. Comparison of Efficacy Results in Pivotal Trials Evaluating Co-Formulations of a Basal Insulin and a GLP-1 Receptor Agonist**

|                  | DUAL I Extension (34) | DUAL IV (40) | DUAL VI (41) | LixiLan-O (37) |
|------------------|-----------------------|--------------|--------------|----------------|
| **Change in A1C**|                       |              |              |                |
| (percentage points) | IDegLira: –1.84 | IDegLira: –1.5 | IDegLira 1WT: –2.01 | iGlarLixi: –1.6 |
|                   | IDeg: –1.40          | Placebo: –0.5 | IDegLira 2WT: –2.02 | iGlar: –1.3    |
|                   | Lira: –1.21          | ETD: –1.02   | ETD 0.12      | Lixi: –0.9     |
|                   | ETD: –0.46           | (–1.18 to –0.87) | (–0.04 to 0.28) | iGlarLixi vs. IGlar P = NS |
|                   | (–0.57 to –0.34)     | IDegLira vs. placebo P < 0.001 (superior) | IDegLira 1WT vs. 2WT P = 0.012 (noninferior) |
|                   | IDegLira vs. IDeg P < 0.0001 (noninferior) | ETD –0.65 (–0.76 to –0.53) | iGlarLixi vs. Lixi P < 0.0001 |
| **A1C responders <7.0% (%)** | IDegLira: 78.2 | IDegLira: 79.2 | IDegLira 1WT: 89.9 | iGlarLixi: 73.7 |
|                   | IDeg: 72.5           | Placebo: 72.8 | IDegLira 2WT: 89.5 | iGlar: 59.4    |
|                   | Lira: 56.5           | P < 0.001    | P = NS        | Lixi: 32.0     |
|                   | P < 0.0001 for all comparisons |                          | P < 0.0001 for all comparisons |
| **Change in FPG** |                       |              |              |                |
| (mg/dL)           | IDegLira: –62.1      | IDegLira: –46.8 | IDegLira 1WT: –78.0 | iGlarLixi: –62.4 |
|                   | IDeg: –61.2          | Placebo: –5.6 | IDegLira 2WT: –81.9 | iGlar: –59.0   |
|                   | Lira: –30.2          | ETD: –41.50  | ETD 3.96      | Lixi: –27.0    |
|                   | (–81.0 to –0.90)     | (–48.94 to –34.07) | ETD 3.50 (–7.6 to 0.7) | iGlarLixi vs. IGlar P = 0.1 |
|                   | IDegLira vs. IDeg P = 0.11 | IDegLira vs. placebo P < 0.001 | IDegLira 1WT vs 2WT P = 0.194 |
|                   | ETD: –30.1           | (–34.6 to –25.6) | ETD –35.4     | iGlarLixi vs. Lixi P < 0.0001 |
|                   | IDegLira vs. Lira P < 0.0001 |                          |                           |

Values are reported as mean (95% CI). 1WT, once weekly titration; 2WT, twice weekly titration; IDeg, insulin degludec U100; IGlar, insulin glargine U100; Lira, liraglutide 6 mg/mL; Lixi, lixisenatide.
### TABLE 5. Comparison of Safety Results in Randomized Trials Evaluating Co-Formulations of a Basal Insulin and a GLP-1 Receptor Agonist

|               | DUAL I (34) | DUAL IV (40) | DUAL VI (41) | LixiLan-O (37) |
|---------------|-------------|--------------|--------------|----------------|
| **Hypoglycemia** |             |              |              |                |
| Confirmed* (events/patient-year) | IDegLira: 1.78 | IDegLira: 3.52 | IDegLira 1WT: 0.16 | iGlarLixi: 1.4 |
|               | IDeg: 2.79  | IDegLira: 2.79 | IDegLira 2WT: 0.76 | iGlar: 1.2     |
|               | Lira: 0.19  | Placebo: 1.35 | Lixi: 0.3   | Lixi: 0.3      |
| RR 0.63 (0.50–0.79) | RR 3.74 (2.28–6.13) | RR not calculated¶ |                |
| IDegLira vs. IDeg | P <0.0001  | IDegLira vs. placebo | Treatment contrast NR |
| RR 8.52 (6.09–11.93) | RR <0.01 |                |                |
| IDegLira vs. Lira | P <0.0001  |                |                |
| **Nocturnal† (events/patient-year)** | IDegLira: 0.22 | IDegLira: 0.49 | IDegLira 1WT: 0.02 | iGlarLixi: 0 |
|               | IDeg: 0.37  | Placebo: 0.32 | IDegLira 2WT: 0.23 | iGlar: 1      |
|               | Lira: 0.018 |                | Lixi: 0      | Lixi: 0       |
| RR 0.68 (0.44–1.06) | RR 2.22 (0.99–5.00) | RR not calculated¶ |                |
| IDegLira vs. IDeg | P =0.09  | IDegLira vs. placebo |                |
| RR 11.99 (4.85–29.63) | RR <0.053 |                |                |
| IDegLira vs. Lira | P <0.0001  |                |                |
| **Severe‡ (n)** | IDegLira: 3 | IDegLira: 2 | IDegLira 1WT: 0 | iGlarLixi: 0 |
|               | IDeg: 2     | Placebo: 0   | IDegLira 2WT: 1 | iGlar: 1      |
|               | Lira: 2     |                | Lixi: 0      | Lixi: 0       |
| **Change in body weight (kg)** | IDegLira: –0.4 | IDegLira: +0.5 | IDegLira 1WT: –1.0 | iGlarLixi: –0.3 |
|               | IDeg: +2.3  | Placebo: –1.0 | IDegLira 2WT: –2.0 | iGlar: +1.1   |
|               | Lira: –3.0  |                | Lixi: –2.3   | Lixi: –2.3    |
| ETD –2.80     | ETD +1.48 (0.90–2.06) | ETD –1.4 (–1.9 to –0.9) |                |
| IDegLira vs. IDeg | P <0.0001  | iGlarLixi vs. iGlar |                |
| ETD +2.66     | ETD +1.09 (0.22–1.96) | iGlarLixi vs. iGlar |                |
| IDegLira vs. Lira | P =0.014 | iGlarLixi vs. iGlar |                |
| P <0.0001     |                |                |                |
| **Adverse events|| | | | |
| **Nausea events (%)** | IDegLira: 9 | IDegLira: 4.5 | IDegLira 1WT: 5.3 | iGlarLixi: 9.6 |
|               | IDeg: 4     | Placebo: 3.4 | IDegLira 2WT: 5.2 | iGlar: 3.6    |
|               | Lira: 20 (51) |                | Lixi: 24     |                |

TABLE CONTINUED ON P. 157 →
Acknowledgments

Medical writing and submission support were provided by Gary Patronek and Germanicus Hansa-Wilkinson of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc.

Funding

Medical writing and submission support for this manuscript were funded by Novo Nordisk. Novo Nordisk also reviewed the manuscript for medical accuracy.

Duality of Interest

C.H.W. is an advisor/consultant for AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi Aventis and has served on speakers bureaus for AstraZeneca, Boehringer Ingelheim, Insulet, Janssen, Novo Nordisk, and Sanofi Aventis. C.C. is an advisor to Boehringer Ingelheim, Eli Lilly and Company, Janssen, Novo Nordisk, and Sanofi Aventis. D.K.’s salary and benefits are supplemented by the National Institutes of Health. She is an advisor to Abbott, Dexcom, Eli Lilly and Company, Intarcia, Janssen, Novo Nordisk, and Sanofi Aventis; serves on speakers bureaus for Abbott, AstraZeneca, Boehringer Ingelheim/Lilly, Dexcom, Eli Lilly and Company, Janssen, Novo Nordisk, and Valeritas; receives research support from AstraZeneca, Dexcom, Eli Lilly and Company, the Helmsley Foundation, Lexicon, and Novo Nordisk; and is a stock shareholder in Dexcom.

Author Contributions

All authors contributed to the conception of the work, drafting and/or critically revising the article, and sharing in the final responsibility for the content and the decision to submit it for publication. C.H.W. is the guarantor of this work and, as such, takes responsibility for the integrity and accuracy of this review.

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