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REVIEW

Rationale for, Initiation and Titration of the Basal Insulin/GLP-1RA Fixed-Ratio Combination Products, IDegLira and IGlarLixi, for the Management of Type 2 Diabetes

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ABSTRACT

Type 2 diabetes (T2D) is a progressive disease affecting glucose regulation and a major cause of morbidity and mortality globally. Many patients are not escalated up the treatment ladder appropriately despite failing to achieve glycemic control, with barriers such as fear of hypoglycemia, weight gain, and treatment burden recognized as factors. Exogenous basal insulin is titrated to address control of fasting plasma glucose and may preserve residual β-cell function, thus promoting a greater endogenous prandial insulin response. Native glucagon-like peptide-1 (GLP-1) is a peptide hormone secreted by the gut in response to nutrient ingestion; it increases insulin secretion, inhibits glucagon secretion, and prolongs gastric emptying, thereby lowering overall food intake. As its glucose-lowering action is glucose dependent, a GLP-1 receptor agonist (GLP-1RA) achieves these benefits with a lower risk of hypoglycemia compared with other diabetes therapies. Two products, an insulin degludec/liraglutide combination (IDegLira) and an insulin glargine/lixisenatide combination (IGlarLixi), were approved for use in adults with T2D by the US Food and Drug Administration in 2016. The efficacy and safety of these two basal insulin/GLP-1RA combination products were studied in the DUAL program (NCTs 01336023, 01392573, 01676116, 01618162, 01952145, and 02298192) and the LixiLan program (NCTs 02058160 and 02058147). Compared with basal insulin, insulin/GLP-1RA fixed-ratio combinations are superior at reducing HbA_{1c} with weight neutrality or weight loss rather than weight gain, as well as reduced hypoglycemia rates, and reduced insulin-dose requirement with IDegLira. A combination of different medications may often be required to achieve glycemic control, and fixed-ratio combination products allow such therapies to be given in simple regimens. Clinical trial data for these products highlight the great potential of these agents, not merely their efficacy and safety but also their ease of use and decreased injection burden for patients.

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INTRODUCTION

Type 2 diabetes (T2D) is a progressive multi-organ disease [1–3] that accounts for approximately 90% of all cases of diabetes; hence, it is a major cause of morbidity and mortality in both high-income and developing countries [4, 5]. T2D is a substantial health-economic burden in the Western world, with over 11% of total global healthcare expenditure attributed to diabetes (types 1 and 2) and one in five US healthcare dollars spent on caring for a person with diabetes [5, 6]. Effective therapies that can improve the health of diabetes patients and reduce the healthcare cost to society are therefore required.

One regimen that has increased in popularity in recent years, because of the complementary actions of its components, is the combination of a basal insulin and glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA). Although this is an effective strategy, it requires multiple injections, which has led to the development of fixed-ratio combination products that require only one injection per day and so could simplify treatment. Our review considers the rationale for such products and the practicalities of initiating and using them for optimal effect in the clinical setting.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. Studies were identified by searching PubMed and abstracts accepted by the American Diabetes Association (ADA), using the names of the combination products and their mono-components as search terms.

RATIONALE FOR BASAL INSULIN + GLP-1RA COMBINATION THERAPIES

T2D Treatment Issues

The main features of T2D are declining β-cell function, global insulin resistance, and loss of the prandial insulin response with a corresponding lack of suppression of postprandial glucagon release [2]. By the time of diagnosis,

β-cell function may have decreased by 50%, and patients with the greatest disease progression before diagnosis may have lost over 80% of their β-cell function [7–9]. The rate of progression of β-cell failure defines the rate of progression of T2D [8], so interventions must be intensified accordingly in a timely manner; hence, patients rarely remain on their initial therapy regimen. Timely intensification of treatment helps patients to maintain glycemic control, which is easier than trying to gain or regain control. This is important because a reduction in glycated hemoglobin (HbA$_{1c}$) is associated with a corresponding reduced risk of both microvascular and macrovascular complications [2, 10]. Even when therapy is intensified, glycemic control can be lost over time because of the progressive nature of the disease. Less than 30% of adults with T2D reach and maintain HbA$_{1c}$ at less than 7.0% (less than 53 mmol/mol) within 3 years of being started on basal insulin [11], and in one study, 57.6% of those who achieved their HbA$_{1c}$ goal did not sustain it [12].

In the past, when basal insulin alone was insufficient to maintain glycemic control, the only effective intensification option for addressing postprandial glucose (PPG) control was to add mealtime bolus insulin, or switch to premixed insulin products. Control of PPG is key because postprandial hyperglycemia contributes to HbA$_{1c}$, especially at lower HbA$_{1c}$ concentrations, and is widely considered to be an independent risk factor for micro- and macrovascular complications [10, 13]. ADA guidelines state that PPG should be less than 180 mg/dL 1–2 h post-meal [13]. Clinicians should be purposeful in titrating insulin dose to achieve a target fasting glucose, but should also know when to look at the contributions of PPG to the HbA$_{1c}$ levels, with bolus insulin or GLP-1RAs considered logical intensifications [14]. There are useful clinical tools to help the clinician in identifying such patients: one is the Accurate Insulin Decisions website [15], which provides guidelines covering when it is appropriate to consider intensifying a patient's insulin therapy, such as a total daily basal dose at or exceeding 0.5 units/kg of basal insulin. Second, the BeAM value (differences between bedtime and morning glucose), which identifies patients

who need tighter PPG control rather than further increases in their basal insulin doses (when the calculated difference is 45–55 mg/dL) [16]. There is a risk that patients who are not correctly identified as needing intensification could continue to have inappropriate "over-basalization" rather than additional therapies.

There are several known perceived barriers to intensification of insulin therapy, including fear of hypoglycemia [17], concerns about weight gain [17], and patient difficulties with adherence, such as when regimen and dosing calculation complexity becomes challenging [17]. With the number of therapeutic options increasing, the wide range of potential combination regimens can be daunting, and this perceived complexity may actually contribute to delays in intensification. There is, therefore, an argument for the development of easy-to-use, well-tolerated therapies combining basal insulin supplementation with a component that can address PPG control while minimizing these barriers.

Pharmacological Logic of Basal Insulin plus GLP-1RA

The progressive nature of T2D means that, eventually, many T2D patients will need exogenous insulin supplementation to maintain glycemic control [18, 19]. Exogenous basal insulin is usually titrated to address control of fasting plasma glucose (FPG) [19]. In addition, supplementing endogenous insulin may suppress insulin release from the β-cell [20] to preserve residual β-cell function [21], promoting a greater endogenous prandial insulin response. Exogenous insulin can also help preserve β-cell function; although there are no data on human patients, mouse models have shown that β-cells can de-differentiate in response to hyperglycemia, with re-differentiation when euglycemia is achieved with exogenous insulin [22].

In healthy individuals, native GLP-1 is a peptide hormone secreted by the gut wall in response to nutrient ingestion, increasing insulin secretion and inhibiting glucagon secretion. GLP-1 also prolongs gastric emptying [23], thereby lowering overall food intake [23],

and this was thought to be the reason why therapeutic agents based on GLP-1 resulted in weight loss [23]. However, while this is true for short-acting GLP-1RAs [24], recent findings have demonstrated that for long-acting GLP-1RAs, weight loss is mediated by regulation of appetite signals in the brain [25]. A GLP-1RA will therefore help optimize the prandial insulin response to control PPG, reduce the insulin dose requirement, and mitigate the weight gain associated with insulin therapy. Unlike other therapeutic options, its glucose-lowering action is glucose dependent, thus GLP-1RA achieves these benefits without the risk of hypoglycemia associated with the use of rapid-acting prandial insulins or sulfonylureas. Long-acting GLP-1RAs can lower FPG in addition to simulating prandial insulin response, whereas short-acting GLP-1RAs act primarily to inhibit gastric emptying, thus lowering PPG at the meal that follows dosing [24].

Owing to their different and complementary modes of action, the combination of basal insulin and GLP-1RAs addresses seven of the eight key defects seen in T2D [8, 9]. Insulin decreases lipolysis in the adipocytes, while GLP-1RAs augment insulin secretion, decrease glucagon secretion from the pancreas, and thus reduce hepatic glucose production. GLP-1RAs also improve insulin sensitivity in muscles by promoting weight loss, thus reducing the lipid levels in muscles, and improving muscle sensitivity to insulin [9]. GLP-1RAs supplement any deficient incretin response in the intestine by binding to and activating GLP-1 receptors throughout the body, and reduce appetite signals in the brain. The only defect that insulin/ GLP-1RA combination products do not address is increased glucose reabsorption from the kidney [8, 9].

Because of these theoretical benefits, many studies have assessed and demonstrated the clinical feasibility and value of treating patients with GLP-1RAs plus basal insulin. These studies have been subject to a recent systematic review in which the majority of them demonstrated improved glycemic control, without hypoglycemia or weight gain, when GLP-1RA was added to basal insulin therapy [26]. With the

clinical benefits of this approach well established, a logical progression has been the development of fixed-ratio combination products that simplify the practical use of the regimen for patients. By combining a basal insulin and GLP-1RA in a single injection pen, patients can potentially benefit from a simplified regimen with reduced frequency of injections.

COMBINATION PRODUCTS

The first fixed-ratio basal insulin/GLP-1RA combination products were approved by the US Food and Drug Administration (FDA) in November 2016 [27, 28]. These products were Xultophy® 100/3.6 (IDegLira) and Soliqua™ 100/33 (IGlarLixi) [27, 28]. Xultophy® was also approved by the European Medicines Agency (EMA) in September 2014 [29], and Soliqua® was approved by the EMA in January 2017 [30].

IDegLira—Novo Nordisk A/S, Bagsværd, Denmark

IDegLira is a fixed-ratio combination of insulin degludec (IDeg) and liraglutide, containing 100 units/mL (U/mL) of IDeg and 3.6 mg/mL of liraglutide in a 3-mL prefilled injection pen [19].

IDeg is a long-acting basal insulin that achieves its protracted action through multihexamer formation in the subcutaneous injection depot [31]. IDeg has a half-life of over 24 h [32], meaning that with once-daily dosing, a steady state is achieved with little pharmacodynamic variability [31]. This results in a predictably flat and stable glucose-lowering action with a low risk of hypoglycemia compared with insulin glargine 100 units/mL (IGlar U100) [33, 34]. Recently, IDeg was shown to be superior to IGlar U100 in terms of rates of severe hypoglycemia in the DEVOTE study, rate ratio 0.60 (95% CI 0.48, 0.76), $p < 0.001$ for superiority [35]. The DEVOTE study also showed that IDeg was non-inferior to IGlar U100 with regard to incidence rates of major adjudicated cardiovascular events (MACE); hazard ratio 0.91 (95% CI 0.78, 1.06), $p < 0.001$ for non-inferiority [35].

Liraglutide is a once-daily analogue of human GLP-1 with 97% amino acid sequence homology to endogenous GLP-1 [36]. Liraglutide reduces both FPG and PPG excursions [17] via its glucose-dependent effects on β- and α-cell function [17]. Protraction is achieved through self-association as heptamers in the depot, albumin binding in the circulation, and resistance to dipeptidyl peptidase-4 (DPP-4; an enzyme that rapidly degrades endogenous GLP-1), resulting in a half-life of approximately 13 h, which means that a 24-h action is achieved with once-daily dosing. In the LEADER cardiovascular outcomes trial (CVOT), liraglutide was shown to be superior to placebo when analyzing the incidence rates of MACE; hazard ratio 0.87 (95% CI 0.78, 0.97), $p < 0.001$ for non-inferiority, $p = 0.01$ for superiority [37].

IGlarLixi—Sanofi-Aventis, Bridgewater, NJ, USA

IGlarLixi is a fixed-ratio combination of insulin glargine (IGlar) and lixisenatide, containing 100 U/mL of IGlar and 33 μg/mL of lixisenatide in a 3-mL prefilled injection pen [28, 38, 39]. Two co-formulations were developed: Pen A, with a ratio of 2 U of IGlar and 1 μg of lixisenatide; and Pen B, with a ratio of 3 U of IGlar and 1 μg of lixisenatide [38]. Pen B was approved by the FDA in November 2016 [28]. It is worth noting that the Pen B used during the LixiLan trials had a dose range 30–60 U, whereas the Pen B approved by the FDA allows a starting dose of 15 U.

IGlar U100 is a basal insulin that achieves a protracted action through post-injection precipitation, which retards absorption and results in an action time of approximately 24 h, enabling once-daily dosing in most patients [40–42].

Lixisenatide is a once-daily injectable, synthetic, exendin-derived GLP-1RA for which PPG lowering is brought about mostly through delayed gastric emptying and reduced glucagon release [38, 39]. Lixisenatide is resistant to DPP-4, binds the GLP-1 receptor with high affinity, but has a half-life of only 2–4 h [43]. This relatively shorter half-life means that in the clinical study program, lixisenatide has been dosed before patients' main meals to gain the maximum benefit. In the ELIXA CVOT, lixisenatide was found to be non-inferior to placebo in terms of risk of MACE [44].

These two combination products—IDegLira and IGlarLixi—are both titrated in a similar fashion to a basal insulin, although different titration regimens were used in the clinical development programs. Titration allows a gradual increase in the GLP-1RA dose, thereby enabling the avoidance of nausea, the most common side effect of GLP-1RAs [38]. Healthy eating can also help minimize this side effect and has the benefit of improving glucose further.

Evidence of Clinical Benefit

The clinical utility of these combination products has been established through a series of phase 3 efficacy and safety trials. No new studies of human or animal subjects have been performed by any of the authors for this article.

For IDegLira, these were the "DUAL" trials, with DUAL I–VI studies published; key results are summarized in Table 1. Direct comparisons of results should not be made across these trials as different patient populations were studied in each. IDegLira was initiated with doses of 10 U (10 U insulin degludec/0.36 mg liraglutide) for DUAL I [19], DUAL IV [45], and DUAL VI [46], and 16 U (16 U insulin degludec/0.58 mg liraglutide) for DUAL II [17], DUAL III [47], and DUAL V [48]. IDegLira improved glycemic control and mitigated the primary side effects of insulin and GLP-1RA therapy in patients uncontrolled on oral antidiabetic drugs (OADs; DUAL I main trial and extension, DUAL IV, and DUAL VI), basal insulin (DUAL II and DUAL V), or GLP-1RA therapy (DUAL III) [17, 19, 45–48]. IDegLira resulted in significantly greater HbA_{1c} reductions versus either of its mono-components (DUAL I main trial and extension) [19], and superior HbA_{1c} reductions were observed with IDegLira versus IGlar U100 up-titration (DUAL V) [48] and versus unchanged GLP-1RA therapy (DUAL III) [47]. IDegLira was weight-neutral in patients uncontrolled on OADs, resulted in weight loss in those uncontrolled on basal insulin, and weight gain in those uncontrolled on GLP-1RA. Rates of confirmed hypoglycemia ranged between 1.5 and 3.5 events/patient-year of exposure (PYE) in DUAL I–V, with the highest rates being observed in DUAL III and DUAL IV, in

which background therapy included sulfonylureas [17, 19, 45, 47, 48]. Nausea occurred in no more than 4% of patients receiving IDegLira at any given time in DUAL I–V [17, 19, 45, 47, 48].

IGlarLixi safety and efficacy analyses were previously conducted in the LixiLan-O and LixiLan-L trials [38, 39]. Key results are summarized in Table 2. These two 30-week studies demonstrated superior HbA_{1c} reductions versus lixisenatide in patients uncontrolled on OADs (LixiLan-O) and versus IGlar U100 in patients uncontrolled on basal insulin (LixiLan-L) [38, 39]. Non-inferior HbA_{1c} reductions with IGlarLixi versus IGlar U100 were also seen in patients uncontrolled on OADs (LixiLan-O) [39]. Change in body weight from baseline to end of trial was –0.3 kg and –0.7 kg in LixiLan-O and LixiLan-L, respectively, and rates of documented symptomatic hypoglycemia were 1.4 and 3.0 events/patient-year. In terms of gastrointestinal adverse events, nausea occurred in 9.6% and 10.4% of patients in the LixiLan-O and LixiLan-L trials, respectively (Table 2) [38, 39].

It is worth noting that direct comparisons between the results of the LixiLan and DUAL studies should not be made because of the different study designs, patient populations, interventions, and definitions used. At the time of writing, no head-to-head studies have been conducted. However, there have been previous comparisons of the individual components. A meta-analysis comparing hypoglycemia rates at equivalent HbA_{1c} values in IDeg and IGlar U100 found similar improvements in HbA_{1c} values with significantly fewer overall confirmed hypoglycemic episodes in favor of IDeg [33]. Meanwhile, liraglutide has been shown to reduce HbA_{1c} to a statistically significantly greater extent versus lixisenatide when added to metformin in a 26-week, head-to-head study, with an estimated treatment difference (ETD) –0.62% (95% CI –0.8, –0.4), $p < 0.0001$ [49]. A greater proportion of patients reached either HbA_{1c} less than 7%/less than or equal to 6.5% (less than 53/less than or equal to 48 mmol/mol) with liraglutide versus lixisenatide (74.2% vs. 45.5%/54.6% vs. 26.2% respectively, $p < 0.0001$ for both) [49]. While liraglutide was associated with a greater reduction in mean 9-point self-measured plasma

Table 1 Key efficacy and safety results for IDegLira from DUAL trials I, II, IV, V, and VI [17, 19, 45–48]

FAS/SAS	IDegLira						
	DUAL I [19] n = 833/825	DUAL II [17] n = 199/199	DUAL III [47] n = 292/291	DUAL IV [45] n = 289/288	DUAL V [48] n = 278/278	DUAL VI [46] 1WT n = 210/209	DUAL VI [46] 2WT n = 210/210
Population	Met ± pio Insulin naïve	Basal insulin 20–40 U daily + Met ± SU/glinides	GLP-IRA** + Met ± pio ± SU Insulin naïve	SU ± met Insulin naïve	IGlar U100 20–50 U daily + Met	Met ± pio Insulin naïve	Met ± pio Insulin naïve
Mean baseline HbA$_{1c}$ % (SD)	8.3 (0.9)	8.7 (0.7)	7.8 (0.6)	7.9 (0.6)	8.4 (0.9)	8.2 (0.9)	8.1 (0.9)
Mean EOT HbA$_{1c}$ % (SD)	6.4 (1.0)	6.9	6.4 (0.8)	6.4 (0.8)	6.6 (0.9)	6.1	6.0
Mean ΔHbA$_{1c}$ % (SD)	−1.9 (1.1)	−1.9	−1.3 (0.8)[i]	−1.5 (0.8)	−1.8 (1.1)	−2.0 (1.1)[o]	−2.0 (1.0)[o]
Mean ΔHbA$_{1c}$ mmol/mol	−21*	−21	−14.5	−16	−20*	−22	−22
% patients achieving HbA$_{1c}$ < 7.0%	81[b]	60[f]	75[f]	79[b]	72[m]	90[p]	90[p]
% patients achieving HbA$_{1c}$ ≤ 6.5%	70[b]	45[f]	63[f]	64[b]	55[m]	83.6[p]	85.0[p]
Mean EOT FPG, mg/dL (SD)	101 (32.4)*	112	108 (28.8)*	117*	110 (38.4)	N/A	N/A
Mean ΔFPG from baseline, mg/dL (SD)	−65[a]*	−62 (53)[c]	−54 (41)[i]*	−47 (47)[c]*	−50[a]*	−78[o]	−82[o]
Mean Δweight from baseline, kg (SD)	−0.5 (3.5)[a]	−2.7[c]	+2.0 (3.9)[i]	+0.5[c]	−1.4 (3.5)[a]	−1.0[o]	−2.0[o]
Baseline daily mean insulin dose, U (SD)	N/A	29 (8)	N/A	N/A	31 (10)	11	11
Final daily mean insulin dose, U (SD)	38 (13)[a]*	45[c]	43	28	41[a]	41[o]	41[o]
EOT mean 9-point SMPG, mg/dL (SD)	128 (32)*	135[g]	N/A	N/A	137 (35)	N/A	N/A
Δ mean 9-point SMPG from baseline, mg/dL (SD)	−58[a]*	−58[c]	N/A	−40 (3.8)[c]*	−46 (44.9)[k]	N/A	N/A
Confirmed hypoglycemia rates, events per PYE	1.8[c]	1.5[h]	2.8[n]	3.5[j]	2.2[l]	N/A	N/A
Nocturnal hypoglycemia rates, events per PYE	0.2[c]	0.2[h]	0.5[n]	0.5[j]	0.2[l]	N/A	N/A

Table 1 continued

FAS/SAS	IDegLira								
	DUAL I [19] $n = 833/825$	DUAL II [17] $n = 199/199$	DUAL III [47] $n = 292/291$	DUAL IV [45] $n = 289/288$	DUAL V [48] $n = 278/278$	DUAL VI [46] 1WT $n = 210/209$	DUAL VI [46] 2WT $n = 210/210$		
Nausea, % of participants	9[d]	7	3	5	9	5	5		

Data aligned to number of decimal places across each individual row

ANCOVA analysis of covariance, *BID* twice daily, *EOT* end of trial, *FAS* full analysis set, *FPG* fasting plasma glucose, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *IGlar U100* insulin glargine 100 units/mL, *LOCF* last observation carried forward, *Met* metformin, *MMRM* mixed model for repeated measurement, *N/A* not available, *OAD* oral antidiabetic drug, *OD* once daily, *PG* plasma glucose, *pio* pioglitazone, *PYE* patient-year of exposure, *SAS* safety analysis set, *SD* standard deviation, *SMPG* self-measured plasma glucose, *SU* sulfonylurea, *U* units, *1WT* once-weekly titration, *2WT* twice-weekly titration, % percentage of treatment arm

*If data not available in mg/dL, mmol/L data were converted using http://www.diabetes.co.uk/blood-sugar-converter.html; if HbA1c data only available in %, converted to mmol/mol using http://www.diabetes.co.uk/hba1c-units-converter.html

** Liraglutide OD/exenatide BID

[a] ANCOVA with treatment (stratification factors for DUAL 1) and country as fixed factors, and baseline value as covariate. Analysis done on FAS using LOCF to impute missing values

[b] Logistic regression model (with LOCF for missing values)

[c] FAS using a negative binomial regression model with treatment, stratification factors, and country as fixed factors, and treatment-emergent time period (on or after the first day of treatment and no later than 7 days after the last day of treatment) as offset

[d] Occurred on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment; reported by at least 5% of participants in any one treatment group, data are from the SAS

[e] ANCOVA model with treatment, previous glucose-lowering drugs and country as fixed factors, and baseline value as covariate (plus HbA1c for dose)

[f] Logistic regression model with treatment, region, and previous glucose-lowering drugs as fixed factors, and baseline value(s) as covariate(s)

[g] Area under the profile (calculated using the trapezoidal method) divided by the measurement time

[h] Negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycemic episode was considered treatment emergent as offset. The model included treatment, previous antidiabetes treatment, and region as fixed factors

[i] ANCOVA on the FAS. Treatment, pretrial GLP-1RA and region (Australia, Europe, or North America) were included as fixed effects, with baseline HbA1c as covariate

[j] Negative binomial regression model with treatment, geographical region and pretrial medication as fixed factors, and log of the duration of treatment-emergent time period (on/after the first day of treatment and no later than 7 days after the last day of treatment) as offset

[k] Linear mixed model with an unstructured residual covariance matrix for measurements within patient and with treatment, time point, region and interaction between treatment and time point as fixed effects, and baseline 9-point SMPG profile values as covariates

[l] Negative binomial regression model with a log link function and log of the exposure time as offset, which included treatment and region as fixed factors

[m] Generalized linear model with binomial distribution and identity link, which included treatment as a fixed factor

[n] Negative binomial regression model based on the FAS population, with treatment, pretrial GLP-1RA, and region included as fixed factors, and the logarithm of the time period in which an episode was considered treatment emergent as offset

[o] A standard MMRM with unstructured covariance matrix. The model included treatment, visit, region, and previous OAD treatment as fixed factors, and the corresponding baseline value as a covariate

[p] Logistic regression model on FAS with treatment, region, and previous treatment as fixed factors, and baseline HbA1c as covariate. Confirmed hypoglycemia was defined as episodes in which the PG value was less than 56 mg/dL (regardless of symptoms) or if classified as severe (requiring assistance). Confirmed hypoglycemic episodes with an onset between 00:01 and 05:59 (inclusive) were classified as nocturnal

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Table 2 Key efficacy and safety results for IGlarLixi from LixiLan-O [39] and LixiLan-L [38]

	IGlarLixi	
	LixiLan-O [39] $n = 468$	LixiLan-L [38] $n = 367$
Population	Met ± 2nd OAD	Basal insulin 15–40 U daily ± 1–2 OADs
	Insulin naïve	
Run-in phase	4 weeks	6 weeks
	Met	Met + IGlar U100
Baseline HbA$_{1c}$, % (SD)	8.1 (0.7)	8.1 (0.7)
EOT HbA$_{1c}$, % (SD)	6.5 (0.8)[a]	6.9 (0.9)[a]
Mean ΔHbA$_{1c}$, % (SD)	−1.6 (0.04)	−1.1 (0.06)
Mean ΔHbA$_{1c}$, mmol/mol	−17	−7
% patients achieving HbA$_{1c}$ < 7.0%	74[b]	55[b]
% patients achieving HbA$_{1c}$ ≤ 6.5%	56[b]	34[b]
EOT FPG, mg/dL (SD)	113.4 (6.3)*	122 (41)
ΔFPG from baseline, mg/dL (SD)	−63.0 (1.8)[b*]	−6 (3)[b]
Δweight from baseline, kg (SD)	−0.3 (0.2)[b]	−0.7 (0.2)[b]
Baseline daily mean insulin dose, U (SD)	N/A	27 (8)
Final daily insulin dose, U (SD)	40 (15)[b]	47 (13)[b]
EOT mean 7-point SMPG, mg/dL (SD)	N/A	140 (31)
Δ mean 7-point SMPG from baseline, mg/dL (SD)	−0.69[b*]	−27 (2)[b]
Δ 2-h postprandial glucose from baseline, mg/dL	−102.6 (3.6)[d*]	−85 (6)[d]
Confirmed hypoglycemia rates, events per PYE	1.4[c]	3.03[c]
Nocturnal hypoglycemia rates, events per PYE	N/A	N/A
Nausea, % of participants	9.6	10.4

ANCOVA analysis of covariance, *EOT* end of trial, *FAS* full analysis set, *FPG* fasting plasma glucose, *IGlar U100* insulin glargine 100 units/mL, *IGlarLixi* insulin glargine/lixisenatide combination, *Met* metformin, *N/A* not available, *OAD* oral antidiabetic drug, *PG* plasma glucose, *PYE* patient-year of exposure, *SAS* safety analysis set, *SD* standard deviation, *SMPG* self-measured plasma glucose, *U* units, % percentage of treatment arm

* If data not available in mg/dL, mmol/L data were converted using http://www.diabetes.co.uk/blood-sugar-converter.html

[a] Mixed-effect model with repeated measures with treatment groups, randomization strata of HbA$_{1c}$ (<8.0%, ≥8.0%), randomization strata of second oral glucose-lowering therapy use at screening, visit, treatment-by-visit interaction, and country as fixed effects, and baseline outcome measure value by visit as a covariate

[b] A mixed-effect model with repeated measures with treatment groups, randomization strata of HbA$_{1c}$ (<8.0%, ≥8.0%), randomization strata of second oral glucose-lowering therapy use at screening, visit, treatment-by-visit interaction, and country as fixed effects and baseline outcome, and Cochran–Mantel–Haenszel method stratified by randomization strata

[c] Number of events divided by total PYE. PYE calculated as time from the first to the last injection of investigational drug plus 1 day; documented symptomatic hypoglycemia = typical symptoms of hypoglycemia accompanied by a measured PG concentration of less than 70 mg/dL (3.9 mmol/L) or 60 mg/dL (3.3 mmol/L)

[d] ANCOVA model with treatment groups, randomization strata of HbA$_{1c}$ (<8.0%, ≥8.0%), randomization strata of second oral glucose-lowering therapy use at screening, and country as fixed effects, and baseline 2-h postprandial PG excursion value as a covariate. N is number of patients, where FAS and SAS are not detailed

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glucose (SMPG; $p < 0.0001$), lixisenatide was associated with a smaller PPG excursion versus liraglutide, but only for the first meal eaten after the daily injection ($p < 0.05$), with no statistical difference between the two treatments across all meals [49]. Body weight reductions and adverse events, including hypoglycemic events, were similar for both GLP-1RAs [49]. In an 8-week trial in 2015, Meier et al. demonstrated comparable end-of-trial HbA_{1c} values for lixisenatide 20 µg (6.2% ± 0.4) compared with liraglutide 1.2 mg (6.1% ± 0.3) and liraglutide 1.8 mg (6.1% ± 0.3) [50]. Marginal mean treatment differences were not significant with lixisenatide 20 µg versus liraglutide 1.2 mg [–0.1% (95% CI –0.2, 0.03), $p = 0.17$]; however, liraglutide 1.8 mg had a significant marginal mean treatment difference versus lixisenatide 20 µg [–0.2% (95% CI –0.3, –0.05), $p = 0.007$] [50]. Lixisenatide produced a greater reduction in the incremental area under the curve (AUC) between time points 00:30 and 04:30 (AUC $PPG_{00:30–04:30h}$) compared with liraglutide doses of 1.2 and 1.8 mg (ETD –108.3 h mg/dL and –83.0 h mg/dL, respectively; both $p < 0.001$) [50]. There was no statistically significant difference in FPG reductions between lixisenatide and either dose of liraglutide [50]. In this study, the most common adverse events reported were nausea and symptomatic hypoglycemia. Lixisenatide 20 µg and liraglutide 1.2 mg had similar proportions of patients reporting nausea, 18.8% and 17.0% respectively, while 23.4% of patients on liraglutide 1.8 mg reported nausea [50]. A greater proportion of patients on lixisenatide 20 µg reported symptomatic hypoglycemia than patients on liraglutide 1.2 mg or 1.8 mg (29.2%, 19.1%, and 21.3% of patients, respectively) [50].

PRACTICALITIES (WITH WHOM, HOW, AND WHEN DO I USE COMBINATION PRODUCTS?)

Target Population

Patients who would benefit from intensification include those in whom HbA_{1c} values remain high despite an acceptable FPG (although this was only a requirement in the LixiLan trials, not the DUAL trials), those with glucose variability in the morning, and those whose total daily basal insulin dose is greater than 0.5 units/kg/day. HbA_{1c} values do not give an accurate picture of glycemic variability, and patients can be at goal for FPG levels while still having HbA_{1c} above target. Previous treatment is also a factor as those patients unable to achieve glycemic control on GLP-1RA- or basal insulin-based regimens, especially when PPG increments are limiting HbA_{1c} target achievement, could benefit from switching. In addition, there may be patients who will benefit from the relative simplicity of these products; a patient on a basal–bolus insulin regimen could potentially see their weekly number of total injections decrease from 28 to 7 if switched to a fixed-ratio combination insulin/GLP-1RA product.

Another target population would be one where further intensification of therapy is being delayed because of fears surrounding potential weight gain and hypoglycemic episodes. A regimen that does not increase the daily number of basal insulin injections, while still promoting weight loss and reduced frequencies of hypoglycemic episodes, could be more acceptable, thus improving adherence. This is supported by findings in DUAL V, where the patient-reported outcomes (PROs) questionnaire (i.e., Treatment-Related Impact Measure For Diabetes, or TRIM-D) showed an improvement in overall score for IDegLira compared with IGlar U100, mostly because of the large differences in scores in diabetes management, ETD 7.2 (95% CI 4.2, 10.2), $p < 0.001$, and treatment burden, ETD 3.7 (95% CI 0.7, 6.8), $p = 0.017$ [48]. These outcomes were not reported in the LixiLan-L and LixiLan-O trials, although IGlarLixi is also injected once a day, so one might assume that similar benefits would be felt. The aforementioned benefits are likely to make IDegLira and IGlarLixi, which target several physiological defects of T2D, more attractive options to patients, thereby tackling clinical inertia with insulin intensification. This is important because the earlier in the disease trajectory they are introduced, the greater impact they will have on slowing β-cell deterioration [51, 52]. However, it is worth noting that while both

products are approved for use in the EU in patients with inadequate glycemic control on OADs [29, 30], in the USA both products are only licensed for use in patients with inadequate glycemic control on basal insulin or their respective GLP-1RA mono-components [27, 28].

It is important to acknowledge, however, that while most recent official diabetes treatment guidelines address the mono-components of IDegLira and IGlarLixi, they do not yet specifically cover fixed-ratio combination products [53]. The overall cost of the fixed-ratio combination products should also be taken into account when making the decision to commence a patient on a new or intensified therapy. These medications are expensive; therefore, the insurance status of US patients should be taken into account.

How to Use

IDegLira is given by once-daily subcutaneous injection, with the injection ideally being administered consistently at the same time of day (which can vary from patient to patient), with or without food [19, 27]. Injection sites should be rotated between the thigh, upper arm, and abdomen [27]. The pens are prefilled for single-patient use only. The product is contraindicated in the following patients: those with a personal or family history of medullary thyroid carcinoma, because of its liraglutide component; those with multiple endocrine neoplasia syndrome type 2; those experiencing hypoglycemia episodes; or those with hypersensitivities to IDegLira, IDeg, or liraglutide [27].

The recommended initial dosing of IDegLira is 16 U, which delivers 16 U IDeg and 0.58 mg liraglutide [27]. The maximum dose is 50 U, which delivers 50 U IDeg + 1.8 mg liraglutide [19, 27], the maximum approved dose of liraglutide for T2D. The dose should be titrated according to the mean of three or four consecutive prebreakfast SMPG results using the algorithm shown in Table 3, and according to the individual patient's glycemic target range. It is important to note that maximum dose is not required for efficacy.

Table 3 Titration algorithm for combination products

Mean fasting SMPG	Dosage adjustment
IDegLira	
Above target range	+2 U (2 U IDeg and 0.072 mg liraglutide)
Within target range	No adjustment
Below target range	−2 U (2 U IDeg and 0.072 mg liraglutide)
IGlarLixi	
Above target range	+2 U (2 U IGlar U100 and 0.66 μg lixisenatide) to +4 U (4 U IGlar U100 and 1.32 μg lixisenatide)
Within target range	No adjustment
Below target range	−2 U (2 U IGlar U100 and 0.66 μg lixisenatide) to −4 U (4 U IGlar U100 and 1.32 μg lixisenatide)

IDeg insulin degludec, *IDegLira* insulin degludec/liraglutide combination, *IGlarLixi* insulin glargine/lixisenatide combination, *IGlar U100* insulin glargine 100 units/mL, *SMPG* self-measured plasma glucose, *U* units

The most common side effects occurring in more than 5% of patients treated with IDegLira include nasopharyngitis, headache, nausea, diarrhea, raised lipase, and upper respiratory tract infections [27]. If patients consistently require doses under 16 U or over 50 U of IDegLira, then switching to alternative therapies should be considered. There are very few significant drug interactions, details of which can be found in the Highlights of Prescribing Information [27].

IGlarLixi is given by once-daily subcutaneous injection [38, 39], with the injection being administered within 1 h of the first meal of the day [28]. The pen is prefilled for single-patient use only. Injection sites should be rotated between the thigh, upper arm, and abdomen [28]. IGlarLixi is contraindicated in patients experiencing hypoglycemia episodes, or those with hypersensitivities to IGlarLixi,

IGlar U100, or lixisenatide [28]. There are no thyroid-related contraindications with products containing lixisenatide, unlike liraglutide. Antibiotics, certain analgesics, or other medications that are particularly dependent on threshold concentrations for efficacy, or for which a delay in effect is undesirable, should be administered at least 1 h before or 11 h after IGlarLixi injection.

Other basal insulin or GLP-1RA therapies should be discontinued before initiating IGlarLixi. The recommended initial dosing of IGlarLixi for patients previously uncontrolled on lixisenatide or on less than 30 U basal insulin is 15 U, which delivers 15 U IGlar and 5 µg lixisenatide, and for patients previously uncontrolled with 30–60 U of basal insulin, the recommended starting dose of IGlarLixi is 30 U, which delivers 30 U IGlar and 10 µg lixisenatide [28]. The maximum dose is 60 U IGlar + 20 µg lixisenatide [28]. The dose should be titrated once a week using the algorithm shown in Table 3, according to the individual patient's glycemic target range.

IGlarLixi should be administered up to 1 h before the first meal daily, although the maximum dose is not required for efficacy. The most common side effects include nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, and headache [28]. If patients consistently require doses of IGlarLixi under 15 U or over 60 U, switching to alternative therapies should be considered.

There are few significant drug interactions, details of which can be found in the Highlights of Prescribing Information [28].

Storage Information

Both IDegLira and IGlarLixi should be stored in a refrigerator at 36–46 °F (2–8 °C) before use, and should not be frozen. After the first injection, IDegLira can be stored either at room temperature (59–86 °F; 15–30 °C) or in the same refrigerator as before first use for 21 days, away from direct heat or light. Each pen should be used for a maximum of 21 days [27]. After the first injection, IGlarLixi should be stored at room temperature (below 86 °F; 30 °C) for

14 days, away from direct light. The pen should be discarded 14 days after the first use [28].

Advice for Demonstrating Injection Technique

Many patients are intimidated by the prospect of initiating or changing injection therapy, so they often welcome a practical demonstration by their diabetes healthcare provider. Given the titration methods used for IDegLira and IGlarLixi, a demonstration will be especially beneficial if the patient has not used a basal insulin before. Educational videos demonstrating injection techniques can be found online. A checklist of items to explain or show to the patient may also be helpful, and can be found in the Supplementary Material.

CONCLUSIONS

Type 2 diabetes is a progressive, multi-system disease that affects a large proportion of the global population. Because of its complex pathophysiology, a combination of different medications may often be required to achieve glycemic control, and fixed-ratio combination products allow such therapies to be given in simple regimens. Basal insulin/GLP-1RA fixed-ratio combination products can help in this respect by addressing seven of the eight key defects found in advanced T2D [7, 8]. Compared with basal insulin, insulin/GLP-1RA fixed-ratio combinations are superior at reducing HbA_{1c} [17, 38, 47], with the added advantage of weight neutrality or weight loss rather than weight gain, as well as reduced hypoglycemia rates, and reduced insulin-dose requirement with IDegLira. These fixed-ratio products are a relatively new addition to our armamentarium and their clinical scope is still under investigation. However, the combination of basal insulin and GLP-1RAs is well studied [54] and makes pharmacological sense. Clinical trial data of these products highlight the great potential of these agents, not merely of their efficacy and safety but also their ease of use and decreased injection burden for patients.

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