Insulin degludec/liraglutide: innovation-driven combination for advancement in diabetes therapy

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Introduction: Existing pharmacological therapies with basal insulins are limited by weight gain and hypoglycemia, while those with glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are limited by issues of efficacy when used alone. However, when used in combination they show a complementarity of action, in terms of reducing the incidence of hypoglycemia while providing sufficient glycemic control, that might help counterbalance their individual limitations. Clinical trials have demonstrated better efficacy and safety profile of this combination. Insulin degludec/liraglutide (IDegLira) is a once-daily fixed-dose combination of ultra-long-acting basal insulin degludec (IDeg) and GLP-1 RA, liraglutide.

Areas covered: We reviewed published data regarding chemistry, pharmacokinetics, pharmacodynamics, clinical efficacy and safety of IDeg, liraglutide and the co-formulation. Literature was searched from the electronic medical database PubMed up to December 2013.

Expert opinion: Preliminary studies on IDegLira indicate improved overall glycemic control, better safety profile with reduction in bodyweight and low rate of hypoglycemia compared to IDeg but higher rates of hypoglycemia than liraglutide therapy alone. Further, simplicity of fixed-dose combination offers an additional advantage of improved treatment adherence. IDegLira might be used similar to basal insulins in the current treatment algorithms, but with a greater preference for initiation instead of two or more oral drugs.

Keywords: body weight changes, diabetes mellitus, drug combinations, glucagon-like peptide-1, glycosylated, hemoglobin A, hypoglycemia, insulin, insulin degludec, liraglutide, long acting, type 2
control, it is often associated with weight gain and/or hypoglycemia, consequently delaying its initiation early in the course of diabetes [6,7]. Incretin therapies, on the other hand, are associated with a low incidence of hypoglycemia due to their glucose-dependent mechanism of action and may even help slow disease progression, owing to their favorable effects on markers of β-cell function [8]. However, they are often associated with dose-dependent gastrointestinal side effects including nausea and vomiting, which are usually transient [9-11].

A novel approach that focuses on maximizing the synergies in combining existing monotherapy options is the combination of basal insulin analogs with glucagon-like peptide-1 (GLP-1) receptor agonists (RAs). This approach combines the ability of basal insulin analogs in controlling fasting plasma glucose (FPG), with the potent postprandial effects of GLP-1 RAs while countering the weight gain associated with basal insulin with the weight reduction associated with GLP-1 RAs [3]. Moreover, GLP-1 RAs might reduce the hypoglycemia risk associated with basal insulin [6]. Emerging data from clinical studies indicate that combining a GLP-1 RA with basal insulin improves glycemic control together with better weight management and low rates of hypoglycemia, potentially increasing both patient compliance and treatment satisfaction [12-14]. However, existing long-acting insulins have the limitation of not sufficiently mimicking the basal physiological secretion of endogenous insulin and can result in a peak few hours after administration leading to a risk of hypoglycemia [15]. The availability of ultra-long-acting insulin formulation, insulin degludec (IDeg), with its unique mode of protraction and pharmacokinetic/pharmacodynamic (PK/PD) profiles further the potential of such combinations. They help to mimic endogenous basal insulin secretion as closely as possible in a once-daily injectable formulation [16]. In studies where IDeg was titrated to the same HbA1c levels as insulin glargine, IDeg showed similar long-term glycemic control with lower rates of nocturnal hypoglycemia [17]. While the value of this combinatorial approach is clear, increasing the number of drugs and multiple doses, especially for injectables, can be expected to increase the burden of patients leading to low adherence to therapy and/or adversely impact quality of life [18]. Fixed-dose combinations deliver fixed doses of constituent drugs when administered once, offering an advantage to sequential addition of drugs [19]. Thus, fixed-dose combinations of ultra-long-acting IDeg with GLP-1 RAs such as insulin degludec/liraglutide (IDegLira) represent a new way forward in improving diabetes management.

IDegLira is a fixed-dose, once-daily combination of ultra-long-acting IDeg with liraglutide (Box 1). Liraglutide, a once-daily GLP-1 RA has been shown in the Liraglutide Efficacy and Action in Diabetes (LEAD)-6 trial to be significantly better than exenatide in providing glycemic control [11]. Initial evidence from a large randomized control trial (RCT) has indicated synergistic effects of IDegLira when compared to either IDeg or liraglutide used alone [16]. This combination is clinically significant as it holds the promise of providing better glycemic control without significant weight gain and hypoglycemia and avoiding burdensome or complex intensification of patients’ regimen by the introduction of additional drugs. In light of its clinical potential, the current review provides an overview of this novel combination and suggests its possible role in the management of diabetes.

2. Chemistry

IDegLira is a fixed-dose combination, which consists of IDeg and liraglutide. The fixed-ratio of IDeg liraglutide entails 1 U of IDeg and 0.036 mg of liraglutide that can be administered in one dose step, using a prefilled delivery device. With the maximum allowed dose steps of 50, the combination can be given as 50 U IDeg +1.8 mg liraglutide [20]. However, due to the fixed dose nature of the combination, up on titration of doses, patients are likely to receive varying doses of liraglutide. However, in most cases it makes little or no difference to their combined efficacy or safety profile in relation to hypoglycemia. The drug summary is given in the drug summary box.

IDeg is a basal insulin with an ultra-long duration of action that forms soluble multi-hexamers at the injection site following subcutaneous administration [21]. It preserves the natural amino acid sequence of native human insulin with two modifications that include deletion of residue threonine B30 and addition of C-16 fatty acid (hexadecanedioic acid) to the lysine at positionB29 with a glutamic acid spacer [22]. The chemical name is LysB29 (N- hexadecanoyl-g-Glu) des(B30) human insulin, with chemical formula C_{272}H_{441}N_{65}O_{81}S_{6} and the molecular weight is 6103.97 Da [23].

Liraglutide is a human GLP-1 RA with 97% homology. The peptide precursor of liraglutide is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae). It is engineered by substituting arginine for lysine at position 34 and attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer [22]. The chemical name is LysB29 (N-hexadecanoyl-g-Glu) des(B30) human insulin, with chemical formula C_{272}H_{441}N_{65}O_{81}S_{6} and the molecular weight is 6103.97 Da [23].
acid spacer on the lysine residue at position 26 of the peptide precursor [24,25]. The chemical name of liraglutide is Lys26 (Nε-glutamyl-β-hexadecanoyl)), Arg34-GLP-1 (7-37), with molecular formula C172H265N43O51 and molecular weight 3751.2 Da [24-26].

3. PKs and PDs

The individual PKs and PDs of IDeg and liraglutide have been studied.

The PK profile of IDeg was examined in subjects (n = 12) with type 1 diabetes mellitus (T1DM), receiving once-daily dose (5.0 nmol/kg) of subcutaneous injection for 6 consecutive days. A reproducible, smooth and stable exposure of IDeg is observed over 24 h at steady state [27]. In a RCT conducted in patients with T1DM receiving 0.4, 0.6 or 0.8 U/kg doses of subcutaneous IDeg for 8 days, a half-life longer than 24 h (25.4 h) and detectability in circulation for at least 96 h after the final injection was reported for IDeg. The half-life of IDeg for the three doses was found to be twice as long as that of insulin glargine, resulting in a more evenly distributed and stable PK profile [28]. Evidence from euglycemic glucose clamp studies indicate that at steady state, the total exposure to IDeg was stable and increased proportionally with increasing dose compared to insulin glargine [28,29]. This facilitates the administration of IDeg once daily and shows a peak less than 15 h [24,31]. In a double-blind RCT, Elbrond et al. assessed the PK profile of liraglutide in healthy subjects (eight per dose), subcutaneously administered with eight consecutive dose levels (1.25, 2.5, 5.0, 10.0, 12.5, 15.0, 17.5 and 20.0 µg/kg). The estimated half-life of liraglutide was found to be 11 - 15 h, indicating that once-daily dosing is appropriate. In the dose range 2.5 - 20 µg/kg, concentration of plasma liraglutide increased steadily and tmax was 9.3 - 12 h [31]. In another dose-escalation study in healthy subjects, five consecutive dose levels (1.25, 2.5, 5.0, 7.5, 10.0, 12.5 µg/kg) of liraglutide were administered subcutaneously on day 1 and days 5 - 11. A steady state was observed after three doses and half-life was found to be 12.6 ± 1.1 h in all the dose groups. A dose proportional increase in exposure (AUC and Cmax) was observed with increasing doses of liraglutide [24].

The clinical data on the PK profile of the co-formulation are unavailable in the public domain. However, the combination of IDeg and liraglutide can be expected to be dosed once daily as IDeg with a half-life of 25.4 h caters to basal glycemic needs, while liraglutide with a half-life of 11 - 15 h controls postprandial glucose excursions [24,31]. IDegLira can be administered with the same dose at any time of the day with injection timing varied without compromising glycemic control with lower risk of hypoglycemia compared to insulin glargine administered same time daily. This in turn improves adherence and acceptance of basal insulin therapy in patients with diabetes [32,33].

4. Efficacy and safety

4.1 Basal insulin and GLP-1 RA combination: existing evidence

Basal insulin and GLP-1 RA combinations have been tested in RCTs providing a strong evidence base for the use of this concept in formulating this combination. In a parallel, randomized, placebo-controlled trial that evaluated the efficacy of twice-daily exenatide versus placebo in T2DM patients receiving insulin glargine, significant decrease in HbA1c was observed in group receiving exenatide compared to placebo (1.74 vs 1.04%, between-group difference; p < 0.0001). Compared to 1.0 kg weight gain with placebo, participants receiving exenatide with basal insulin, experienced 1.8 kg weight loss without increased risk of hypoglycemia [14]. In another double-blind, parallel-group, placebo-controlled trial, evaluating efficacy and safety of once-daily lixisenatide (GLP-1 RA) added to basal insulin therapy in T2DM patients, the placebo-corrected change of HbA1c from baseline with lixisenatide was -0.4% (p = 0.0002). More number of patients achieved HbA1c < 7.0% with lixisenatide compared to placebo (28 vs 12%; p < 0.0001). Greater reductions in body weight (placebo corrected, -1.3 kg; p < 0.0001) and insulin dosage (-3.7 units/day; p = 0.012) was observed with lixisenatide [34].

Addition of liraglutide to metformin followed by intensification with basal insulin (detemir) in poorly controlled T2DM patients was evaluated in a 26-week randomized, open-label study. Sixty-one percent of the participants completing the run-in achieved HbA1c < 7% (mean change -1.3%) with liraglutide alone. At week 26, HbA1c further decreased by 0.5% with insulin detemir versus 0.02% increase without insulin detemir (estimated treatment difference -0.52 [95% CI: -0.68 to -0.36]; p < 0.0001). Higher number of patients achieved HbA1c < 7% with insulin detemir versus without detemir (43 vs 17%). Sustained weight loss was observed during the study, however, with higher rates of minor hypoglycemia on treatment with detemir compared to without detemir (9.2 vs 1.3%) [12].

Given the beneficial glycemic effects besides favorable safety profiles the role of basal insulin and GLP-1 RA combinations as the mainstream of future diabetes management protocols might be justified unless the choice of regimen is influenced by final cost. However, the question of best possible combinations from currently existent options is one that deserves close scrutiny as there is wide divergence in the clinical profiles of currently available options. The superior clinical profile of
Liraglutide enhances insulin secretion and inhibits glucagon secretion in a glucose-dependent manner [41]. The efficacy and safety of liraglutide were clinically evaluated in the LEAD studies, including head-to-head comparisons versus exenatide. Data from these trials indicate percentage HbA1c reduction, no weight gain and no hypoglycemia (clinically relevant composite end points) was significantly higher with liraglutide than with all active comparators, including sulfonylureas, thiazolidinediones, insulin glargine and exenatide (Figure 1) [11,42-46]. Thus, liraglutide is ideal for combination with basal insulins due to its safety profile (no hypoglycemia and weight gain), which counters the major concerns associated with insulin use. Issues pertaining to β-cell mass, ductal proliferation, histopathological changes and putative risk of pancreatitis and pancreatic carcinoma have extensively been reviewed by ADA/EASD/International Diabetes Federation and have not found any signal suggesting risk with incretin-based therapies [47]. Furthermore, preclinical data reveal potential benefits of liraglutide treatment, including promotion of β-cell proliferation and reduction of β-cell apoptosis [48,49]. However, data supporting β-cell proliferation with liraglutide in clinical context is limited as the assessment of β-cell function in humans is extremely difficult and therefore one has to look at surrogate markers and the durability of glycemic control as reflection of β-cell protection, which appears to be quite encouraging.

Across all LEAD trials, liraglutide at doses of 1.2 or 1.8 mg once daily, showed significant mean reductions in HbA1c (0.84 – 1.6%) and FPG (0.84 – 2.4 mmol/l), besides sustained weight loss (2 – 3 kg) with lower rate of hypoglycemia [50]. Moreover, significant proportion of patients achieved ADA recommended glycemic targets of HbA1c < 7% with liraglutide (53 – 66%) versus patients on comparator therapies (28 – 53%) [50]. In addition to its benefit on glycemic parameters and body weight, liraglutide has been shown to reduce systolic blood pressure (SBP), which is a surrogate for improved cardiovascular outcome. Furthermore, it favorably impacts lipid profile and several cardiovascular biomarkers including high-sensitive C-reactive protein, B-type natriuretic peptide and plasminogen-activator inhibitor 1 [11,42,45,46,51]. However, on the flip side a minor increase in heart rate by 1 – 3 beats/min has consistently been reported. Over 104 weeks period this increased rate has

Table 1. Summary of rates (number of episodes per patient year of exposure) of overall and nocturnal hypoglycemia across different studies in patients with diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall hypoglycemia</th>
<th>p-value</th>
<th>Nocturnal hypoglycemia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDeg</td>
<td>IGlar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heller et al. [35]</td>
<td>42.54</td>
<td>40.18</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Garber et al. [36]</td>
<td>11.1</td>
<td>13.6</td>
<td>0.0359*</td>
<td></td>
</tr>
<tr>
<td>Zinman et al. [37]</td>
<td>1.52</td>
<td>1.85</td>
<td>0.106</td>
<td></td>
</tr>
<tr>
<td>Birkeland et al. [39]</td>
<td>47.9</td>
<td>66.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinman et al. [37]</td>
<td>0.6§</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9§</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All the values are expresses as number of episodes per-patient year of exposure.
*p < 0.05, †IDeg: 600 µmol/l, §IDeg: 900 µmol/l.
IDeg: Insulin degludec; IGlar: Insulin glargine.
been shown to better out and its overall impact remains to be evaluated [52]. In the LEAD studies, liraglutide when taken as monotherapy or in combination with metformin reduced SBP by 3.6 and 2–3 mmHg, respectively [42,43]. Similarly when compared to twice-daily exenatide, liraglutide treatment was associated with significant reduction in the levels of triglycerides (-7.38 vs -4.14 mg/dl; p = 0.048) and free fatty acids (-3.06 vs -1.80 mg/dl; p = 0.001) [11].

4.4 Insulin degludec/liraglutide

The efficacy and safety of IDegLira were investigated in the clinical development program DUAL™ (Dual Action of Liraglutide and IDEg in type 2 diabetes), involving around 2000 people with T2DM in two Phase IIIa trials [53]. DUAL™ I was a Phase III, open-label, 26-week, randomized, parallel, three-arm, multicenter, multinational treat-to-target trial conducted to compare the efficacy and safety of IDegLira against both IDEg and liraglutide alone in subjects with T2DM inadequately controlled on metformin ± pioglitazone [16]. The primary outcome measure was change in HbA1c from baseline, 0–26 weeks. Secondary outcomes included change in body weight from baseline to 26 weeks, number of hypoglycemic episodes, change in incremental AUC 0–4 h (iAUC0-4 h) from baseline to 26 weeks derived from the glucose concentration profile during meal test, and daily insulin dose required (after study period). Adult subjects with type 2 diabetes, HbA1c ≥ 7 and ≤ 10%, BMI ≤ 40 kg/m² but have not taken sulfonylurea or insulin or incretin therapy in last 90 days were included in the study. IDegLira was given once daily and compared to IDEg or liraglutide (Victoza® 1.8 mg) added alone. IDEgLira and IDEg were titrated to a FPG range 72–90 mg/dl as per the label, and liraglutide was given 0.6 mg initially and titrated in 0.6 mg steps weekly to 1.8 mg. Of the total 1663 adults, mean age of 55 years, diabetes duration of 6.6 years and BMI 31.2 kg/m², 834 were randomized to IDEgLira, 414 to IDEg and 415 to liraglutide arm [16]. Preliminary results of study including a 26-week extension were reported in May 2013.

Decrease in HbA1c values was observed in all the three groups with the largest decrease in IDEgLira group, demonstrating a synergistic effect. The 1.9% decrease observed in IDEgLira group (from 8.3 to 6.4%) was significantly higher (p < 0.0001) than IDEg (−1.4 to 6.9%) and liraglutide groups (−1.3 to 7.0%) [16]. Number of subjects achieving the ADA target (7.0%) and AACE target (6.5%) of HbA1c are higher in IDEgLira group (81, 70%) than IDEg (65, 48%) and liraglutide (60, 41%) groups. A statistically significant difference in mean FPG levels (end of 26 weeks) was observed between

![Graph showing efficacy of liraglutide: change in HbA1c levels in LEAD studies.](image-url)

**Figure 1. Efficacy of liraglutide: change in HbA1c levels in LEAD studies.**

HbA1c: Glycated hemoglobin; LEAD: Liraglutide Efficacy and Action in Diabetes.
Table 2. Key results of DUAL™ I trial.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IDegLira versus insulin degludec estimate [95% CI]</th>
<th>p-value</th>
<th>IDegLira versus liraglutide estimate [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c Change, % -points</td>
<td>-0.47 [-0.58; -0.36]</td>
<td>&lt; 0.0001</td>
<td>-0.64 [-0.75; -0.53]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FPG change (mg/dl)</td>
<td>-3.1 [-7.4; 1.2]</td>
<td>NS</td>
<td>-31.8 [-36.1; -27.5]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>-2.2 [-2.64; -1.80]</td>
<td>&lt; 0.0001</td>
<td>2.44 [2.02; 2.86]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>0.68 [0.53; 0.87]</td>
<td>0.0023</td>
<td>7.61 [5.17; 11.21]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mean prandial increment (mg/dl)</td>
<td>-8.2 [-11.3; -5.1]</td>
<td>&lt; 0.0001</td>
<td>-1.1 [-2.0; 4.2]</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Hypoglycemia: PG < 56 mg/dl and/or requiring assistance; Rate ratio: Insulin degludec/liraglutide/Comparator; p < 0.05 two-sided.

FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; IDegLira: Insulin degludec/liraglutide; NS: Not significant.

IDegLira (100 mg/dl) and liraglutide groups (131 mg/dl) (difference: -31.8 mg/dl, p < 0.0001) but not with the IDEg group (104 mg/dl, difference: -3.1 mg/dl). The nine-point glucose profiles showed lower mean prandial increments with IDegLira and liraglutide groups compared to IDEg group. Compared to IDEg and liraglutide groups, significant reduction (-2.22 kg, p < 0.0001) or gain (2.44 kg, p < 0.0001) in body weight was observed in IDegLira group (-0.5 kg) at the end of 26 weeks (Table 2) [16].

All three groups were generally well tolerated. Compared to IDEg group, significantly lower rate of hypoglycemia (32%, p = 0.0023) was observed in IDegLira group, whereas only few subjects in liraglutide group reported hypoglycemia compared to the IDegLira group (p < 0.0001). Lower incidence of GI side effects were reported in IDegLira compared to liraglutide (nausea: 8.8 vs 19.7%; vomiting: 3.9 vs 8.5%). Results of DUAL™ I study suggest a contribution of IDEg component toward efficacy and liraglutide toward safety of IDegLira administration, complementing the effects of one with the other. The difference in HbA1c and FPG levels between IDegLira and IDEg is smaller, indicating significant contribution of IDEg (Table 2) toward efficacy. Similarly, the difference in weight gain and positive rate ratio in hypoglycemia observed in IDegLira compared with liraglutide indicates an overall contribution of liraglutide toward safety (Table 2).

DUAL™ I study demonstrates substantial improvement in glycemic control in subjects with T2DM than any other combinations of long-acting insulin and GLP-1 RA [16]. In RCTs studying addition of long-acting insulin to existing GLP-1 RA therapy, and GLP-1 RA to existing long-acting insulin therapy, HbA1c reductions (from baseline) of 0.5 – 1.35% [12,54] and 0.77 – 1.7% [14,55], respectively, were reported. The safety of combination therapy in these studies was comparable to DUAL™ I study, with weight reductions of 0.2 – 1.18 kg from baseline and no or similar hypoglycemia between the groups. Results of DUAL™ I study showed a marked difference of 1.9% in HbA1c reduction, the primary outcome of importance for patients with T2DM compared to other combination studies [16]. In addition, the proportion of patients achieving the ADA target of HbA1c (< 7%) is substantially higher in DUAL™ study (81%) compared to the above studies (36 – 76% of patients). The clinical significance of DUAL™ I results is that the ADA target of HbA1c is achieved not only in significant number of patients with T2DM uncontrolled on 1 – 2 OADs, but also with minimal hypoglycemia and weight change.

Further, to investigate the additional impact of liraglutide component of IDegLira on glucose control, the second II Phase IIIa trial, DUAL™ II was conducted [53]. DUAL™ II was a 26-week randomized double-blinded trial comparing IDegLira with liraglutide in people with type 2 diabetes inadequately controlled on basal insulin in combination with 1 – 2 OADs and higher baseline HbA1c levels [20]. In this study, the maximum dose of IDEg was fixed to the same amount in both the arms (50 units) to assess the lira component of IDegLira. Compared to IDEg, once daily IDEgLira demonstrated a significant reduction in HbA1c (1.90 vs 0.89%), body weight (2.7 kg from baseline vs no weight change with IDEg) and low rate of hypoglycemic incidence, comparable to IDEg (25 vs 24%) [20]. In addition, three Phase IIIb trials; DUAL™ III, DUAL™ IV and DUAL™ V on IDEgLira have started. DUAL™ III, an ongoing study will investigate the superiority in HbA1c reduction of combination product compared with unchanged GLP-1 RA therapy (GLP-1 RA switch) [56]. DUAL™ IV study evaluated the superiority in HbA1c reduction of combination product compared with placebo (SU add-on), study results are awaited [57]. DUAL™ V, an ongoing study will evaluate the superiority of IDEgLira in uncontrolled patients failing on basal insulin therapy with insulin glargine [58].

5. Regulatory affairs

The two global Phase IIIa trials on IDEgLira are completed by Novo Nordisk. The marketing authorization application for the approval of IDEgLira has been submitted to the European Medicines Agency (EMA) in May 2013 based on the results of these two Phase IIIa trials [53]. The individual component, IDEg (Tresiba™) is approved by EMA for use in European Union (EU) since January 2013. Liraglutide (Victoza™) is approved, both in US and EU. It is expected that Novo
Nordisk will introduce IDegLira as a prefilled delivery device on a technology platform similar to FlexTouch® [53].

**6. Conclusion**

Hypoglycemia and weight gain, the risks associated with insulin therapy hinder the optimal use of insulin in patients with T2DM. While incretin therapy is relatively safe with comparable glycemic efficacy that is provided by basal insulin, they are often associated with gastrointestinal side effects such as nausea and vomiting. Combination of basal insulin with GLP-1 RA has shown the potential of complementing each other and overcoming their respective efficacy and safety issues. IDegLira is a fixed-dose combination of ultra-long-acting IDeg and liraglutide. The combination provides basal and postprandial glycemic control with no weight gain and low rates of hypoglycemia. Preliminary clinical data suggest that IDegLira provides robust glycemic control significantly better than existing basal insulin therapy while addressing their safety concerns. Its flexibility of use, once-daily dosing coupled with its clinical profile makes IDegLira the drug of choice for future diabetes therapy.

**7. Expert opinion**

With the increasing burden of diabetes and its concomitant complications, the issue of proper diabetes management to control the effects of the disease is a major question for ensuring public health. However, many patients on current therapies fail to achieve recommended glycemic targets. ADA/EASD consensus statement recommends sequential addition of drugs (including insulin) in diabetes therapy resulting in the escalation of monotherapy to double or triple drug therapy. Expectedly, different combinations of drugs and the sequence of addition have a major impact on the outcomes achievable by them. Increasing the number of drugs as a part of diabetes therapy also results in greater burden of the therapy on patients leading to lower adherence to therapy and worse outcomes. Different drugs also have varying clinical profiles in terms of their safety and efficacy due to which certain drug combinations can be expected to be more beneficial than others due to the synergistic effects of their individual components and their action. Due to these factors, intensification of therapy by progressing to combinations with more drugs cannot always be expected to show similar improvements in patients and the need arises for standardized combinations, which ideally harness the complementarity of actions in the constituent drugs to maximize efficacy while remaining well tolerated.

Insulin is widely acknowledged to be the agent with most potent glucose control action; however, insulin initiation is delayed in clinical practice due to concerns of hypoglycemia and weight gain. The wide variety of insulins that differentially alleviate FPG (basal insulins) or postprandial plasma glucose (PPG; bolus insulins) are available for clinical use. This means that in the course of intensification, multiple-daily injections of insulin will be required, which is complex, inconvenient and adversely affects patients’ quality of life. Availability of basal insulins analogs has ensured that they can be administered once daily to provide sufficient FPG control. Their combination with drugs alleviating PPG, while reducing concerns of hypoglycemia and weight gain is a rational approach. Thus, the combination of basal insulin analogs with GLP-1 RAs represents an option that addresses many of the concerns associated with other drug-insulin combinations. GLP-1 RAs are associated with weight loss (as opposed to weight gain seen with insulins) and very low/no risk of hypoglycemia. They additionally provide potent PPG control to complement the FPG control of basal insulins. This combination has been focused upon in the recent past and several RCTs have investigated its efficacy and safety. Currently published evidence unequivocally confirms the expected superiority of this combination in providing safe and potent glycemic control.

Among currently available basal insulins, ultra-long-acting IDeg that has a peakless, truly basal mode of action has been shown to have a better safety profile as compared to other long-acting analogs. It provides comparable glycemic control and needs to be administered once-daily irrespective of the time of previous administration due to its ultra-long-acting nature, making it an ideal choice for combining with GLP-1 RAs. Liraglutide, a long-acting once-daily GLP-1 RA has been shown in the LEAD series of trials to be associated with a best-in-class efficacy and safety profile. IDegLira is a fixed-dose combination of ultra-long-acting insulin and a GLP-1 RA (IDeg and liraglutide) with synergistic effects that combine the ultra-long-acting basal action of IDeg with the weight loss and hypoglycemic advantage of liraglutide. As it has been formulated as a fixed-dose combination, it avoids the need for separate injection for administering the constituents. Also, the long duration of action of both the constituents enables it to be used once daily without the need for increasing the number of doses per day. The impact of multiple doses in the therapy, especially injectable, has been previously noted. This single, fixed-dose combination can be expected to enhance patient convenience and the simplicity of the therapy. Preliminary clinical data from the DUAL-I trial was recently presented at the ADA annual conference and confirm the expected trends of safety and efficacy associated with IDegLira [16]. IDegLira showed a greater magnitude of decrease in HbA1c when compared to previously published reports investigating other combinations of basal insulins and GLP-1 RAs. This was also true for the number of patients achieving the recommended glycemic targets, which was greater than that previously reported for other combination of basal insulins and GLP-1 RAs.

In contemporary practice, a host of oral agents are used sequentially contributing to the worsening of the disease due to the lack of sufficient glycemic control. Hypoglycemia and weight gain are primary concerns, which delay the initiation.
and intensification of insulin therapy. The constituents of IDegLira cover both basal and bolus glucose excursions. While fixed-dose combinations of premixed insulins also perform a similar function, the weight loss and low rate of hypoglycemia associated with IDegLira is expected to enhance its acceptance both with health care providers and patients. The favorable safety profile of this combination should be a crucial consideration in encouraging early initiation of insulin without fears of the accompanying side effects in terms of weight gain and hypoglycemia. The ability to initiate insulin earlier in the course of the disease can greatly impact the overall treatment approach to diabetes. Further clinical studies evaluating the current combination against currently available therapeutic options will clarify the possible role of IDegLira in the diabetes treatment algorithm. From the preclinical studies, liraglutide is known to be associated with beneficial effects on the preservation of β-cell function (through promotion of β-cell proliferation and reduction of β-cell apoptosis) leading to the suggestion that it could possibly halt the worsening of the disease (48,49). Thus, one possible approach might be to use IDegLira similar to basal insulins (due to IDEg) in current treatment algorithms and initiation of IDegLira might be considered favorably over intensification of therapy with two or more OADs.

With the incidence of diabetes increasing rapidly in developing countries, there is a need for simple and flexible once-daily combinations that can be easily prescribed in resource-limited settings. IDegLira can be expected to fulfill this role due to its flexibility and once-daily dosing, which can help achieve a lifestyle as close that of a non-diabetic person as possible. Long-term clinical studies are crucial to evaluate its exact role in therapy and its relative benefits.

**Declaration of interest**

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