**The role of incretin-based therapies and SGLT2 inhibitors as adjuncts to insulin therapy in type 2 diabetes with special reference to IDegLira Running head: Adjuncts to insulin therapy in T2DM with special reference to IDegLira**

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**Abstract**

The progressive nature of type 2 diabetes necessitates treatment intensification over time in order to maintain glycaemic control, with many patients ultimately requiring insulin therapy. While insulin has unlimited potential efficacy, its initiation is often delayed and improvements in glycaemic control are typically accompanied by weight gain and an increased risk of hypoglycaemia, particularly as HbA1c approaches and falls below target levels. This may account for the sub-optimal control often achieved following insulin initiation. Combining insulin with antihyperglycaemic therapies that have a low risk of hypoglycaemia and are weight neutral or result in weight loss is a therapeutic strategy with the potential to improve type 2 diabetes management. Although the effects differ with each individual class of therapy, clinical trials have demonstrated that adding a glucagon-like peptide-1 receptor agonist (GLP-1 RA), dipeptidyl peptidase-4 inhibitor or sodium-glucose co-transporter-2 inhibitor to insulin regimens can offer a significant reduction in HbA1c without substantially increasing hypoglycaemia risk, or weight. The evidence and merit of each approach is reviewed within. Once-daily co-formulations of a basal insulin and a GLP-1 RA have been developed (insulin degludec/liraglutide, IDegLira) or are under development (lixisenatide/insulin glargine, LixiLan). IDegLira phase 3 trials and a LixiLan phase 2 trial have demonstrated robust HbA1c reductions, with weight loss and a low risk of hypoglycaemia. With IDegLira now approved in Europe, an important consideration will be the types of patients who may benefit most from a fixed-ratio combination: this is discussed here, together with a look toward future developments in the field.

**1. Introduction**

The pathophysiology of type 2 diabetes is complex, typically characterized by insulin resistance, impaired insulin secretion and hyperglucagonaemia. Type 2 diabetes is also a progressive disease, necessitating intensification of treatment over time to achieve and maintain glycaemic control. When intensifying treatment regimens to reduce hyperglycaemia, an approach combining treatments with complementary effects that together combat a wider spectrum of the core defects of type 2 diabetes, would, theoretically at least, seem optimal.

Many patients ultimately require insulin therapy; insulin has unsurpassed potential efficacy but is often underutilized due to the risk or fear of hypoglycaemia and weight gain. Landmark studies have shown that intensive glycaemic control with insulin therapy is associated with weight gain and severe hypoglycaemia [1–3]. Additionally, initiation and intensification of insulin therapy are often substantially delayed. A large observational study (*n* = 17,374) involving 10 countries reported that mean HbA1c at insulin initiation ranged from 67 mmol/mol (8.3%; China) up to 84 mmol/mol (9.8%; UK), with a mean across the study of 74 mmol/mol (8.9%) [4].

The European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) position statement recommends an HbA1c target of <53 mmol/mol (<7.0%) with initiation of insulin therapy, typically with basal insulin, as dual or triple therapy if a patient does not achieve/maintain target after ~3 months of mono- or dual therapy, respectively [5]. In England and Wales, following dual therapy, the National Institute for Health and Care Excellence (NICE) recommends treatment intensification either with a third oral agent, a glucagon-like peptide-1 (GLP-1) agonist or basal insulin therapy in patients with an HbA1c of ≥58 mmol/mol (≥7.5%) [6]. However, a recent retrospective cohort study of >80,000 patients with type 2 diabetes in the UK reported that in patients with an HbA1c ≥58 mmol/mol (≥7.5%), the median time to insulin initiation was >6 years [7]. Considering insulin intensification, another retrospective UK primary care database analysis of patients receiving basal insulin reported that intensification of basal insulin treatment was uncommon (only occurred in 33% of patients), despite most patients having higher than recommended HbA1c levels [8].

There is a clear need for earlier insulin initiation and intensification. The prospect of using new therapies, or combination therapies, which can offer the efficacy of insulin but with an improved risk-to-benefit profile may help to overcome this inertia. Due to the complementary nature of their modes of action and clinical effects compared with basal insulin, GLP-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium–glucose co-transporter-2 (SGLT2) inhibitors are increasingly being used in combination with basal insulin therapy. GLP-1 RAs improve glycaemic control by stimulating insulin secretion and inhibiting glucagon secretion, both in a glucose-dependent manner. Although the magnitude of clinical effects varies between different formulations and depending on background therapy, glycaemic improvements with GLP-1 RAs are generally accompanied by clinically significant weight loss and a low risk of hypoglycaemia. DPP-4 inhibitors have a similar mode of action to GLP-1 RAs but only increase endogenous GLP-1 levels within the physiological range. As such, DPP-4 inhibitors offer significantly smaller HbA1c reduction versus GLP-1 RAs and are generally weight neutral [9]. SGLT2 inhibitors are competitive inhibitors of sodium–glucose co-transporter-2, a low-affinity, high-capacity transporter that mediates renal glucose reabsorption [10]. Glycaemic improvements with SGLT2 inhibitors are associated with weight loss and a low risk of hypoglycaemia [10].

The aim of this article is to review the effects of insulin initiation and intensification on glycaemic control, also considering the incidence of hypoglycaemia and changes in body weight. We then consider the alternative approaches to insulin intensification, such as adding a GLP-1 RA, a DPP-4 inhibitor or an SGLT2 inhibitor to basal insulin. Finally, we discuss the clinical potential of a new approach, fixed-ratio combinations of a GLP-1 RA and a basal insulin in a single, once-daily injection.

**2. Insulin initiation**

Retrospective analyses of UK primary care records indicate that initiation of insulin therapy in real-life clinical practice results in an HbA1c reduction of 1.3–1.4% (from a baseline of 78–81 mmol/mol [9.3–9.6%]), with less than 30% of patients achieving an HbA1c of <53 mmol/mol (<7%) [11–13].Insulin initiation is also associated with substantial weight gain, regardless of the type of insulin initiated (Table 1).The frequency of hypoglycaemia was not reported in these studies.

Despite the development of newer basal insulin analogues, which provide relatively peakless and more physiological insulin-replacement therapy, neutral protamine Hagedorn (NPH) insulin is still recommended as first-line insulin therapy in many countries, including the UK [6]. Clinical trials have demonstrated that basal insulin analogues provide similar glycaemic improvements to NPH insulin but with a lower incidence of hypoglycaemia and sometimes less weight gain [14–17]. Three basal insulin analogues are available: insulin glargine (IGlar), insulin detemir (IDet) and insulin degludec (IDeg).

Phase 3 head-to-head studies have compared basal insulin initiation in insulin-naïve patients with type 2 diabetes of IDeg versus IGlar and IGlar versus IDet [18,19]. A similar HbA1c reduction was reported with IDeg versus IGlar (−1.1 vs. −1.2%, respectively) and a greater HbA1c reduction with IGlar versus IDet (−0.7 vs. −0.5%, *P* < 0.05) [18,19]. The overall rate of confirmed hypoglycaemia (plasma glucose [PG] <3.1 mmol/l or severe episodes requiring assistance) was similar for IDeg versus IGlar (1.52 vs. 1.85 events per patient-year), but the incidence of nocturnal hypoglycaemia was significantly lower in the IDeg group versus IGlar (0.25 vs. 0.39 events per patient-year; *P* = 0.038) [18]. Treatment with IDet resulted in a significantly lower incidence of total hypoglycaemia (symptomatic, major [unable to self-treat] or minor [if the patient could self-treat and PG was confirmed *<*3.1 mmol/l with or without symptoms]) versus IGlar (3.29 vs. 4.41 events per patient-year, *P* = 0.034), but this should be considered in the context of the lower end-of-trial HbA1c in the IGlar group (54 mmol/mol vs. 58 mmol/mol [7.1 vs. 7.5%]) [19]. Treatment with IDeg and IGlar resulted in similar weight gain (2.4 vs. 2.1 kg), while IDet was weight neutral (−0.5 kg) compared again to weight gain with IGlar (+1.0 kg) [18,19].

While the incidence of hypoglycaemia with basal insulin analogues is relatively low (compared with more intensive insulin regimens), the risk increases substantially as HbA1c approaches and falls below target levels (Figure 1). Data also illustrate that basal insulin analogues have a lower risk of hypoglycaemia vs. NPH insulin at all levels of HbA1c [16,20].

It should be noted that while IDeg is approved for use in Europe, Japan and many other countries, the FDA issued a complete response letter to IDeg, requesting additional cardiovascular safety data from a dedicated trial [21]. As a result, the long-term safety of IDeg is being investigated in an ongoing, 5-year cardiovascular outcomes trial in ~7,500 patients at high risk of cardiovascular disease (DEVOTE; NCT01959529) which is expected to finish in 2016. The required number of major adverse cardiovascular events for the pre-specified interim analysis were accumulated by the end of January 2015 and, in April 2015, the FDA accepted for review the Class II Resubmissions for IDeg, which included these interim data [22,23].

In summary, glycaemic improvements associated with basal insulin initiation are commonly associated with weight gain and an increased risk of hypoglycaemia, particularly as HbA1c approaches target levels, and to a greater extent with NPH insulin.

**3. Insulin intensification**

Blak *et al*. identified patients treated with basal insulin ± oral antidiabetic drugs (OADs) in UK primary care (*n* = 3185) and evaluated treatment changes over a period of 3 years (2006–2009) [8]. Basal insulin ± OADs was maintained without therapy intensification in 60% of patients during follow-up, despite a mean HbA1c of 68 mmol/mol (8.4%) at baseline and 65 mmol/mol (8.1%) at end-of-trial. During follow-up, 19% of patients were intensified with prandial (*n* = 464) or premixed (*n* = 150) insulin and 14% (*n* = 435) switched to premixed insulin. Those who were intensified with prandial or premixed insulin had a mean baseline HbA1c of 77 mmol/mol (9.2%) and 78 mmol/mol (9.3%), respectively, and a mean HbA1c of 70 mmol/mol (8.6%) and 72 mmol/mol (8.7%) at end of follow-up. BMI increased by 0.3 kg/m2 with prandial intensification and by 1.1 kg/m2 with premixed intensification. Switching from basal insulin to premixed insulin reduced mean HbA1c from 80 mmol/mol (9.5%) at baseline to 69 mmol/mol (8.5%) and was accompanied by a BMI increase of 0.9 kg/m2. The incidence of hypoglycaemia was not reported.

Phase 3 clinical trial data demonstrate the variety of options available for insulin intensification to improve glycaemic control, but all are commonly associated with an increased risk of hypoglycaemia and increased regimen complexity (Table 2) [24–27]. In support of the real-life data, in the clinical trials insulin intensification was also associated with substantial weight gain.

**4. Combining insulin with other agents**

When insulin is initiated, metformin is usually continued as studies have shown that there is less weight gain when the two agents are used together [28]. However, the insulin secretagogues, sulphonylureas and glinides, may be discontinued due to an increased risk of hypoglycaemia without additional glycaemic benefit [5]. Similarly, it is generally recommended to discontinue or reduce the dose of thiazolidinediones (TZDs) to avoid oedema and excessive weight gain [5,29]. In contrast, more recently available non-insulin therapies, namely GLP-1 RAs, DPP-4 inhibitors and SGLT2 inhibitors, may be continued after insulin initiation, and are also added to existing insulin therapy as an alternative approach to insulin intensification.

*4.1 Use of SGLT2 inhibitors in combination with insulin*

The SGLT2 inhibitors are the newest class of oral antihyperglycaemic therapy for type 2 diabetes management. As such, their inclusion in existing treatment algorithms is limited; however, the three agents approved for use in Europe – dapagliflozin, canagliflozin and empagliflozin – all have broad licensed indications for use, including in combination with insulin [30–32]. Three phase 3 studies, one for each agent, have compared the efficacy and safety of adding an SGLT2 inhibitor or placebo to advanced insulin regimens (mean daily insulin doses 78–92 U) [33–35]. In all three trials, the addition of the SGLT2 inhibitor resulted in a significant improvement in HbA1c and weight loss, but was associated with a greater frequency of genital mycotic infections and hypoglycaemia compared with placebo (Table 3) [33–35]. It should also be noted that in May 2015, the FDA warned that SGLT2 inhibitors may lead to ketoacidosis [36]. Ketoacidosis does not appear to be commonly associated with SGLT2 inhibitors, except when there are other predisposing factors present; therefore, it is key to identify the patients most at risk and to reduce the risk to all patients [37].

Most recently, Rosenstock *et al*. investigated the efficacy and safety of adding the SGLT2 inhibitor empagliflozin (10 or 25 mg) or placebo to multiple daily injections of insulin [mean 92 U/day) in obese people (mean BMI 34.8 kg/m2) with inadequately controlled type 2 diabetes (mean HbA1c 66 mmol/mol [8.3%]) [33]. After the first 18 weeks of treatment (where total insulin dose was to remain within 10% of prescribed dose at randomisation), the reduction in HbA1c was significantly greater with empagliflozin 10/25 mg (−0.94/−1.02%) compared with placebo (−0.50) (*P* < 0.001 for both comparisons). Body weight increased with placebo (0.34 kg) but decreased with empagliflozin 10/25 mg (−0.97/−1.54 kg) (*P* < 0.001 for both comparisons). The proportion of patients with confirmed hypoglycaemia (PG ≤ 3.9 mmol/L or requiring assistance) was slightly higher in the empagliflozin groups (40/41%) compared with placebo (37%). Consistent with previous findings, over the full 52-week treatment period, more events consistent with genital infections were reported by patients treated with empagliflozin 10/25 mg (4.3/9.5%) compared with placebo (1.6%). All events were mild or moderate in intensity and only one led to discontinuation (on empagliflozin 25 mg) [33].

SGLT2 inhibitors act independently of insulin and therefore should be an effective treatment at most stages of diabetes, and also when used in combination with insulin. SGLT2 inhibitors may also result in a lower risk of hypoglycaemia and weight gain when added to insulin, compared with the addition of some other classes of drugs [5]. Based on their mechanism of action, the patients who may experience reduced efficacy with SGLT2 inhibitors are those with renal impairment – that may also explain the reduced efficacy with canagliflozin observed in elderly versus younger patients with type 2 diabetes [34].

*4.2 Use of DPP-4 inhibitors in combination with insulin*

DPP-4 inhibitors are recommended for use in combination with insulin therapy as part of the EASD/ADA position statement [5] and five phase 3 trials have investigated the use of five different DPP-4 inhibitors as add-on to insulin therapy. Similar to the SGLT2 inhibitor add-on studies, the DPP-4 inhibitor or placebo were added onto a variety of insulin regimens, except in one study, which was limited to basal insulin [38–42]. In all studies, a significantly greater reduction in HbA1c was observed versus placebo but the HbA1c reductions were modest (−0.6 to 0.8%) considering the baseline HbA1c (67–78 mmol/mol [8.3–9.3%]) and, as a result, mean HbA1c did not approach target levels at end-of-trial (61–70 mmol/mol [7.7–8.6%]) (Table 3). The addition of a DPP-4 inhibitor to existing insulin therapy was generally weight neutral (similar to addition of placebo) and hypoglycaemia was experienced by 8–27% of patients (vs. 7–24% in placebo arms).

The addition of a DPP-4 inhibitor to insulin therapy may be of particular interest when metformin is no longer a treatment option; for example, in patients with moderate to severe renal impairment. In this scenario, an SGLT2 inhibitor is also contraindicated, so a DPP-4 inhibitor may be the preferred option with a low level of treatment complexity.

*4.3 Use of GLP-1 RAs in combination with basal insulin*

Use of GLP-1 RAs in combination with basal insulin in triple therapy with metformin is recommended as part of the EASD/ADA position statement: both adding basal insulin to existing metformin and GLP-1 RA therapy or adding a GLP-1 RA to metformin and a basal insulin [5]. While this treatment combination has only recently been included in the product labels for some GLP-1 RAs , this is not a new concept in secondary care in the UK [43,44]. The ABCD audits for exenatide twice daily (2007–2009) and liraglutide (2009–2011) reported that over one third of GLP-1 RA use was in the (then) unlicensed combination with insulin therapy [43,44].

4.3.1 Insulin initiation as add-on to a GLP-1 RA: phase 3 data

Two studies have investigated the sequential addition of the GLP-1 analogue liraglutide to OAD therapy followed by basal insulin initiation in patients still not achieving HbA1c target (<53 mmol/mol [<7.0%]) [45,46]. The addition of either IDet, titrated up as required (end of trial (EOT) mean dose 40 U) or IDeg (EOT mean dose 51 U) resulted in improvements in glycaemic control, to a mean end-of-trial HbA1c of 54/48 mmol/mol (7.1/6.5%), with a very low risk of hypoglycaemia (Table 3). The addition of IDet resulted in maintenance of liraglutide-associated weight loss during the run-in period, while insulin initiation with IDeg resulted in weight gain of 2.0 kg.

These data suggest that continuing with existing GLP-1 RA therapy is beneficial when initiating insulin therapy, with the potential to lower HbA1c to below target levels with a very low risk of hypoglycaemia.

4.3.2 Insulin intensification with the addition of a GLP-1 RA: phase 3 data

The GLP-1 RAs as a class can broadly be divided into two categories: short- and long-acting. Short-acting GLP-1 RAs (exenatide twice daily and lixisenatide) target postprandial glucose at the meal immediately after dosing, an effect predominantly due to a delay in gastric emptying [47,48]. Long-acting GLP-1 RAs (liraglutide and weekly GLP-1 RAs) target both fasting plasma glucose (FPG) and postprandial glucose across all three daily meals, due to their 24-hour action profiles. However, their impact on postprandial glucose at the meal after dosing is significantly lower compared with short-acting GLP-1 RAs, but often greater with long-acting GLP-1 RAs at subsequent meals when the short-acting GLP-1 RA is not dosed again [48–50].

Seven phase 3 studies have investigated the addition of a GLP-1 RA in patients uncontrolled on basal insulin therapy (Table 3) [51–57]. In four studies, the addition of the GLP-1 RA was compared with placebo while three studies compared the addition of a GLP-1 RA to basal insulin intensification with one or three daily bolus insulin doses.

The addition of a GLP-1 RA to basal insulin resulted in a significantly greater reduction in HbA1c versus the addition of placebo, and a significant reduction from baseline in body weight in three of the four studies (Table 3). Although the patient populations and background insulin titration varied across the studies, a crude comparison suggests that the long-acting GLP-1 RA liraglutide (placebo-corrected change in HbA1c −1.2%) resulted in a greater reduction in HbA1c when added to basal insulin compared to short-acting GLP-1 RAs (placebo corrected change in HbA1c −0.4 to −0.7%).

Mathieu *et al*. compared the addition of liraglutide 1.8 mg versus IAsp (before the largest meal) in patients uncontrolled (HbA1c ≥53 mmol/mol [≥7.0%]) on IDeg and metformin [54]. After 26 weeks, the addition of liraglutide resulted in a significantly greater reduction in HbA1c versus IAsp (−0.74 vs. −0.39%; *P* = 0.0024). Liraglutide addition was associated with weight loss, while IAsp resulted in weight gain (−2.8 vs. +0.9 kg; *P* < 0.0001). The observed rate of confirmed hypoglycaemia was over 8-fold greater with IAsp versus liraglutide (8.15 vs. 1.00 episodes per patient-year; *P* < 0.0001), while gastrointestinal adverse events were more common with liraglutide, with 1.1% of patients in the liraglutide group withdrawing due to nausea or vomiting. Rosenstock *et al*. compared the addition of another long-acting GLP-1 RA, albiglutide 30 mg once weekly (OW), versus three-times daily (TID) insulin lispro (ILisp) to IGlar and metformin and/or pioglitazone [55]. After 26 weeks of treatment, there was a significantly greater reduction in HbA1c with albiglutide OW versus ILisp TID (−0.82 vs. −0.66%; *P* < 0.0001). Weight decreased with albiglutide but increased with ILisp (−0.73 vs. +0.81; *P* < 0.0001). More patients experienced documented hypoglycaemia with ILisp versus albiglutide (30% vs.16%) and gastrointestinal adverse events with albiglutide versus ILisp (nausea: 11% vs. 1%). Finally, Diamant *et al*. compared the addition of the twice-daily short-acting GLP-1 RA exenatide versus ILisp TID to patients uncontrolled on IGlar [57]. Unlike the long-acting GLP-1 RAs that provided a superior HbA1c reduction versus the additional of mealtime insulin, addition of exenatide twice daily (BID) resulted in a similar HbA1c reduction (−1.13% vs. −1.10%) to ILisp TID, while again weight decreased with the GLP-1 RA and increased with insulin intensification (exenatide BID: −2.5 kg; ILisp TID: +2.1 kg; *P* < 0.001). The incidence of minor hypoglycaemia was significantly greater with ILisp (41% vs. 30%; *P* = 0.004), while more patients experienced gastrointestinal adverse events with exenatide (47% vs. 13%), with 3.5% of patients in the exenatide group withdrawing due to nausea or vomiting.

In summary, several phase 3 clinical trials have now shown that combining a GLP-1 RA with basal insulin results in a significant HbA1c reduction, in some cases to well within target levels, while maintaining a low risk of hypoglycaemia and often with the added benefit of weight loss (Table 3) [45,46,51–56]. In general, long-acting GLP-1 RAs appear to be the most potent at lowering HbA1c and may be the best choice for patients who are not near their HbA1c target after basal optimisation. Short-acting GLP-1 RAs may be an alternative in patients already near target and experiencing significant postprandial glucose excursions [58–60]. The studies involving liraglutide, albiglutide and exenatide BID have shown that GLP-1 RAs are a particularly attractive alternative to intensification with mealtime insulin dose(s) [54,55,57].

As a result of the benefits of co-usage of a GLP-1 RA and basal insulin demonstrated in ‘loose combination’ studies, a product combining the complementary clinical effects of liraglutide and IDeg (IDegLira) in a single, once-daily injection has been developed. Additionally, a product combining lixisenatide and insulin glargine (LixiLan) in a single injection is under development.

**5. IDegLira, a novel once-daily combination of a basal insulin and GLP-1 RA**

IDegLira is the only fixed-ratio combination of a basal insulin (IDeg) and a GLP-1 RA (Lira), delivered once daily in one pen, currently approved for use in Europe [61]. The dose ratio is such that one dose step of IDegLira is the equivalent of 1 U of IDeg and 0.036 mg of Lira (maximum dose: 50 U IDeg/1.8 mg Lira). The starting dose of IDegLira in phase 3 trials has been 10 dose steps (10 U IDeg/0.36 mg liraglutide) in patients uncontrolled on OADs, ensuring insulin dose equivalent to a recommended 10 U initiation of basal insulin, and 16 dose steps (16 U IDeg/0.58 mg liraglutide) in patients previously uncontrolled on basal insulin or a GLP-1 RA, ensuring the highest possible insulin dose in those transferring from pre-trial basal insulin, while taking into consideration the recommended starting dose of liraglutide (0.6 mg). In clinical trials, titration was performed in a similar manner to basal insulin titration, twice weekly based on self-measured FPG target of 4.0–5.0 mmol/L with dose changes of +2/−2 dose steps if patients were above or below the FPG target, respectively. The two phase 3 trials, DUAL I and DUAL, II were included as part of the submission package for review by European Medicines Agency: DUAL I (IDegLira vs. IDeg or Lira in patients uncontrolled on OADs; 26 weeks with 26-week extension) and DUAL II (IDegLira vs. IDeg in patients uncontrolled on basal insulin + OADs; 26 weeks) [62,63].

*5.1 IDegLira compared with its individual components, IDeg or liraglutide alone, in patients uncontrolled on oral glucose-lowering therapy (DUAL I)*

In a randomized, open-label study in 1663 patients with T2D uncontrolled (HbA1c 53–86 mmol/mol [7.0–10.0%]) on metformin ± pioglitazone, IDegLira (n=834) was compared with IDeg (n=414) or liraglutide (n=415) alone. Liraglutide was titrated by 0.6 mg/week to a maintenance dose of 1.8 mg [62]. IDegLira could be titrated to a maximum of 50 dose steps (50 units IDeg/1.8 mg liraglutide); no maximum dose was specified for the IDeg arm. At screening, >80% of patients were receiving metformin monotherapy and at baseline, mean HbA1c was 67 mmol/mol (8.3%), mean BMI was 31.2–31.3 kg/m2 and mean duration of diabetes was ~7 years.

Treatment with IDegLira resulted in a significantly greater reduction in HbA1c and a greater proportion of subjects achieving HbA1c targets of <53 mmol/mol (<7.0%) (81% vs. 65%/60%) and ≤48 mmol/mol (≤6.5%) (70% vs. 47%/41%) versus IDeg or liraglutide alone (Table 4).

The liraglutide component of IDegLira appeared to mitigate insulin-associated weight gain and the rate of confirmed hypoglycaemia was 32% lower with IDegLira versus IDeg (*P* = 0.0023), but higher versus liraglutide (*P* < 0.0001), which had a very low rate of hypoglycaemia (Table 4). Compared with IDeg alone, IDegLira was associated with a significantly lower insulin dose (Table 4). Numerically fewer patients experienced gastrointestinal adverse events with IDegLira versus liraglutide, likely due to the slower up-titration of the liraglutide component in IDegLira and the lower mean end-of-trial dose (Table 4).

In a 26-week extension study, the 26-week HbA1c of 6.4% observed with IDegLira was maintained to week 52 with only a mean dose increase of one dose step (1 U IDeg/0.036 mg liraglutide) to 39 dose steps, demonstrating the durability of treatment effects (Table 4) [64].

* 1. *IDegLira versus IDeg in patients with type 2 diabetes poorly controlled on basal insulin (DUAL II)*

DUAL II was a 26-week trial designed to assess the relative contribution of the liraglutide component of IDegLira by comparing it with IDeg, with a dose cap of 50 U. Unlike DUAL I, which was an open-label study, DUAL II was double-blinded. The trial included patients with type 2 diabetes uncontrolled on basal insulin (20–40 units) and metformin ± sulphonylurea/glinides (SU/glinide discontinued at baseline) [63].

After 26 weeks of treatment, the mean insulin dose was equivalent for both IDegLira and IDeg, allowing evaluation of the contribution of the liraglutide component of IDegLira (Table 4). HbA1c reduction was1.1% greater with IDegLira compared with IDeg (*P* < 0.0001) (Table 4), with a greater proportion of patients achieving an HbA1c target of <53 mmol/mol (<7.0%) with IDegLira versus IDeg (60% vs. 23%; *P* < 0.0001). IDegLira resulted in weight loss of 2.7 kg compared with no weight change in the IDeg group (*P* < 0.0001). Rates of confirmed hypoglycaemia were similar with IDegLira and IDeg, despite the lower end-of-trial HbA1c in the IDegLira arm (Table 4). Overall, the frequency of adverse events was similar, with very low and comparable rates of nausea in this double-blinded trial.

These data illustrate that in patients with type 2 diabetes uncontrolled on basal insulin, the addition of the liraglutide component in IDegLira offers superior glycaemic control to IDeg at equivalent insulin doses, without a higher risk of hypoglycaemia and with the additional benefit of weight loss.

*5.3 IDegLira: which patients may benefit most?*

As a new treatment option for patients with type 2 diabetes, it is important to consider which patients may benefit most from a fixed-ratio combination of a GLP-1 RA and basal insulin such as IDegLira.

Based on the summary of product characteristics, IDegLira is licensed for use with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control [61]. Considering that GLP-1 RAs and basal insulin are already available for use in ‘free’ or ‘loose’ combination, IDegLira may be considered in patients who are very poorly controlled (HbA1c >8.5%) on oral therapy, where initiation of a GLP-1 RA or basal insulin alone may not be sufficient, and initiation of basal–bolus or premix insulin is not appropriate. Another group of patients who may be considered for IDegLira are those with significant weight problems who are already receiving modest doses of basal insulin and failing to achieve their glycaemic targets – the convenience of IDegLira compared with the addition of a second injection when adding a GLP-1 RA may appeal to some patients; other options might include insulin intensification, with known risks of weight gain and hypoglycaemia, or the addition of an SGLT2 inhibitor or DPP-4 inhibitor. Although not currently licensed or studied to date, given the improved gastrointestinal tolerability of IDegLira versus a GLP-1 RA, patients who have previously been unable to tolerate standard GLP-1 RA up-titration may find a fixed-ratio preparation more acceptable.

*5.4 Fixed-ratio combinations: what’s next?*

Additional clinical trial data for IDegLira are expected in 2015, which will describe the safety and efficacy of IDegLira when added to existing SU ± metformin therapy (DUAL IV), when switching from a GLP-1 RA (DUAL III) and in patients uncontrolled on basal insulin therapy versus up-titration of insulin glargine (DUAL V). In addition, there is another fixed-ratio combination of a GLP-1 RA and basal insulin under development. The LixiLan device combines lixisenatide and insulin glargine in one pen with a maximum dose of 60 U insulin glargine and 30 µg lixisenatide used in a phase 2 study [65]. The study compared the safety and efficacy of adding LixiLan or insulin glargine in patients uncontrolled on metformin. After 24 weeks, mean HbA1c had decreased from 8.0% at baseline to 6.3% and 6.5% with LixiLan and insulin glargine, respectively (treatment difference −0.17%, *P* = 0.01). LixiLan resulted in a weight reduction of 1 kg while weight increased by 0.5 kg with insulin glargine (treatment difference −1.4 kg, *P* < 0.0001), with a similar proportion of patients experiencing hypoglycaemia in both arms (22 vs. 23%). Two LixiLan phase 3 studies were initiated in 2014 and results are expected late in 2015.

**6. Summary**

Insulin initiation and intensification are often severely delayed. The initiation of insulin therapy is associated with weight gain and hypoglycaemia, particularly as patients approach target HbA1c levels. Intensification of insulin therapy to improve glycaemic control often results in further weight gain and an increased risk of hypoglycaemia. Use of an SGLT2 inhibitor, DPP-4 inhibitor or GLP-1 RA in combination with basal insulin can reduce these insulin-associated side effects. While GLP-1 RAs have largely been studied in combination with basal insulin, SGLT2 inhibitors (and to a lesser extent DPP-4 inhibitors) have been shown to be effective at reducing HbA1c and body weight when added to advanced insulin regimens.

Combining both a GLP-1 RA and basal insulin in a once-daily injection using a simple pen device may help overcome clinical inertia to treatment intensification caused by hypoglycaemia, weight gain, treatment complexity or the inability to use a GLP-1 RA due to gastrointestinal side effects. Additional data from the IDegLira and LixiLan clinical programmes are now awaited to further establish the safety and efficacy of fixed-ratio combinations in additional patient populations with type 2 diabetes.

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**Tables and figures**

**Table 1** Insulin initiation in UK clinical practice [11–13]

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Data source** | **N** | **Duration** | **Type of insulin initiated** | **Baseline HbA1c** | **Change in HbA1c** | **End-of-study HbA1c** | **Patients achieving HbA1c target(s)** | **Change in body weight** |
| Practice records [11] | 516 | 3 years | Basal | 78.1 mmol/mol (9.3%) | −15.3 mmol/mol(−1.4%) at 6 months, similar at 3 years\* | 63 mmol/mol (7.9%) at 6 months, similar at 3 years\* | HbA1c <53 mmol/mol (<7%): 29%\* | +3.6 kg\* |
| GPRD [12] | 3783 | 2 years | Basal (41%)  NPH (29%)  Premix (29%)  Short acting (5%) | 81.4 mmol/mol (9.6%) | −15.3 mmol/mol(−1.4%) | 66 mmol/mol (8.2%)† | HbA1c ≤58 mmol/mol (≤7.5%): 26–41%, depending on baseline BMI | After 1 year:  Basal, +3.4 kg  NPH, +3.7 kg  Premix, +4.4 kg  Short acting, +3.5 kg |
| THIN [13] | 4045 | 6 months | Basal (52%)  Premix (42%)  Basal–bolus (4%)  Prandial (2%) | 81.4 mmol/mol (9.6%) | −14.2 mmol/mol −1.3% | 67 mmol/mol (8.3%) | HbA1c <53 mmol/mol (<7%): 17% HbA1c <58 mmol/mol (<7.5%): 30% | +0.9 kg  (25% of patients gained >3.6 kg) |

\*At end-of-study, 43% of patients had intensified their basal insulin by incorporating short-acting insulins. †Not reported in publication, calculated by mean baseline value minus mean change.

BMI, body mass index; NPH, neutral protamine Hagedorn

**Table 2** Landmark clinical trials studying the effects of insulin intensification [24–27]

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Duration** | **Background  treatment** | **Randomized treatment added** | **Baseline HbA1c** | **Change in HbA1c** | **End-of-trial HbA1c** | **Hypoglycaemia(events/patient/year)** | **Weight change** |
| Holman *et al*. 2009  (4-T) [24] | 3 years | MET + SU | BIAsp 70/30 BID  (+ midday IAsp) | 70 mmol/mol (8.6%) | −1.3% | 54 mmol/mol (7.1%) | 3.0 | +5.7 kg |
| MET + SU | IDet OD (+ IAsp TID) | 68 mmol/mol (8.4%) | −1.2% | 52 mmol/mol (6.9%) | 1.7 | +3.6 kg |
| MET + SU | IAsp TID (+ IDet OD) | 70 mmol/mol (8.6%) | −1.4% | 51 mmol/mol (6.8%) | 5.7 | +6.4 kg |
| Lankisch *et al*. 2008 (OPAL) [25] | 24 weeks | IGlar + OADs | IGlu breakfast | 57 mmol/mol (7.4%) | −0.3% | 53 mmol/mol (7.0%) | Overall: 2.72 | +1.0 kg |
| IGlar + OADs | IGlu main meal | 56 mmol/mol (7.3%) | −0.4% | 52 mmol/mol (6.9%) | Overall: 3.69 | +0.9 kg |
| Meneghini *et al*. 2011 (STEPwise) [27] | 12 + 3x12 weeks | IDet + OADs | Stepwise addition of IAsp doses to largest perceived meal | 72 mmol/mol (8.7%) | −1.1% | 58 mmol/mol (7.5%) | Minor: 6.0  Major: 0.04 | +2.7 kg |
| IDet + OADs | Stepwise addition of IAsp dose to meal with largest PPG increment | 74 mmol/mol (8.9%) | −1.3% | 61 mmol/mol (7.7%) | Minor: 5.9  Major: 0.01 | +2.0 kg |
| Davidson *et al*. 2011[26] | 24 weeks | IGlar + OADs | 1 x IGlu | 63 mmol/mol (7.9%) | −0.4% | 57 mmol/mol (7.4%) | Severe: 0.28 | +3.8 kg |
| IGlar + OADs | 2 x IGlu | 62 mmol/mol (7.8%) | −0.4% | 57 mmol/mol (7.4%) | Severe: 0.89 | +4.1 kg |
| IGlar + OADs | 3 x IGlu | 62 mmol/mol (7.8%) | −0.4% | 56 mmol/mol (7.3%) | Severe: 0.64 | +3.9 kg |

BIAsp, biphasic insulin aspart; BID, twice daily; IAsp, insulin aspart; IDet, insulin detemir; IGlar, insulin glargine; IGlu, insulin glulisine; MET, metformin; OAD, oral antidiabetic drug; OD, once daily; PPG, postprandial glucose; SU, sulphonylurea; TID, three-times daily.

**Table 3** Phase 3 studies assessing the combination of SGLT2 inhibitors, DPP-4 inhibitor and GLP-1 RAs with insulin therapy [33–35,38–42,45,56,51–57]

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Reference** | **Treatment arm (not including background OADs or comparator arms)** | **Baseline insulin dose (U/day)** | **Permitted insulin dose changes/titration** | **Change in insulin dose (U/day)** | **Baseline HbA1c** | **Change in HbA1c** | **Placebo corrected HbA1c** | **End-of-trial HbA1c** | **Change in body weight** |
| Addition of an SGLT2 inhibitor to insulin | Neal *et al*. 2015≠ [34] | Insulin + canagliflozin 300 mg | 60 | Stable background insulin dose (maintained within 15% of randomisation dose) | NR | 67 mmol/mol (8.3%) | NR | −0.73 | NR | −2.4% |
| Wilding *et al*. 2012 [35] | Insulin + dapagliflozin 10 mg | 78 | Stable background insulin dose (maintained within 10% of randomisation dose) | −0.7 (+10.5 with placebo) | 70 mmol/mol (8.6%) | −0.96 | −0.57 | 60 mmol/mol (7.6%)\*\* | −1.61 kg |
| Rosenstock *et al*. 2014≠ [33] | MDI insulin + empagliflozin 25 mg | 92 | Stable background insulin dose (maintained within 10% of randomisation dose) | NR | 67 mmol/mol (8.3%) | −1.02 | −0.52 | 56 mmol/mol (7.3%) | −1.54 kg |
| Addition of a  DPP-4 inhibitor to insulin | Rosenstock *et al.* 2009 [38] | Insulin + alogliptin 25 mg | 55 | Continued pre-randomisation insulin dose | +0.4 (+0.6 with placebo) | 78 mmol/mol (9.3%) | −0.7 | −0.6 | 70 mmol/mol (8.6%)\*\* | +0.6 kg |
| Vilsbøll *et al.* 2010 [39] | Insulin + sitagliptin 100 mg | 67/44† | Stable background insulin dose | 0 (+1.6 with placebo) | 72 mmol/mol (8.7%) | −0.6 | −0.6 | 65 mmol/mol (8.1%) | +0.1 kg |
| Barnett *et al*. 2012 [40] | Insulin + saxagliptin 5 mg | 53 | Stable background insulin dose (maintained within 20% of randomisation dose) | +1.7 (+5.0 with placebo) | 72 mmol/mol (8.7%) | −0.7 | −0.4 | 64 mmol/mol (8.0%)\*\* | +0.4 kg |
| Yki-Järvinen *et al*. 2013 [41] | Basal insulin + linagliptin 5 mg | 42 | Stable background insulin dose (maintained within 10% of randomisation dose) | +0.1 (+0.4 with placebo) | 67 mmol/mol (8.3%) | −0.6 | −0.65 | 61 mmol/mol (7.7%) | −0.2 kg |
| [Kothny](http://www.ncbi.nlm.nih.gov/pubmed?term=Kothny%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23039321) *et al.* 2013 [42] | Insulin + vildagliptin 50 mg | 40 | Stable background insulin dose (maintained within 10% of randomisation dose) | −1.1 (−0.2 with placebo) | 73 mmol/mol (8.8%) | −0.8 | −0.7 | 64 mmol/mol (8.0%)\*\* | +0.1 kg |
| GLP-1 RA in combination with basal insulin | *Addition of basal insulin to a GLP-1RA* | | | | | | | | | |
| DeVries *et al*. 2012 [45] | Liraglutide 1.8 mg + IDet | 0 | IDet started at 10 U and then titrated weekly to FPG 4.1-6.0 mmol/L | +39.5 | 60 mmol/mol (7.6%) | −0.5 | N/A | 54 mmol/mol (7.1%) | −0.2 kg |
| Aroda *et al*. 2014 [46] | Liraglutide 1.8 mg + IDeg | 0 | IDeg started at 10 U and then titrated to FPG 4-5 mmol/L | +51 | 58 mmol/mol (7.5%) | −1.04 | −0.92 | 48 mmol/mol (6.5%) | +2.0 kg |
| *Addition of a GLP-1RA to basal insulin vs. placebo* | | | | | | | | | |
| Buse *et al*. 2011 [51] | IGlar + exenatide 10 µg BID | 50 | Background IGlar titrated to <5.6 mmol/L | +13 (+20 with placebo) | 67 mmol/mol (8.3%) | −1.74 | −0.69 | 49 mmol/mol (6.6%) | −1.8 kg |
| Riddle *et al*. 2013 [52] | IGlar + lixisenatide 20 µg | 43 | Background IGlar titrated to 4.4-5.6 mmol/L | +3.1 (+5.3 with placebo) | 60 mmol/mol (7.6%) | −0.71 | −0.32 | 53 mmol/mol (7.0%) | −1.8 kg |
| Riddle *et al*. 2013 [53] | Basal insulin + lixisenatide 20 µg | 54 | Basal insulin dose reduced 20% at baseline if HbA1c ≤7.5%. Insulin dose maintained within 20% of randomisation dose | −5.6 (−1.9 with placebo) | 68 mmol/mol (8.4%) | −0.7 | −0.4 | 62 mmol/mol (7.8%) | +1.2 kg |
| Ahmann *et al*. 2014 [56] | Basal insulin + liraglutide 1.8 mg | 48# | Basal insulin dose reduced 20% at baseline if HbA1c ≤8.0%. Insulin dose maintained at pre-trial level. | −5 (−1 with placebo) | 66 mmol/mol (8.2%) | −1.30 | −1.2 | 52 mmol/mol (6.9%) | −3.5 kg |
| *Addition of a GLP-1RA to basal insulin vs. meal-time insulin* | | | | | | | | | |
| Mathieu *et al*. 2014 [54] | IDeg + liraglutide 1.8 mg | 69# | IDeg dose decreased by 20% at baseline and up-titrated if FPG ≥5 mmol/L after week 6 | −7 | 61 mmol/mol (7.7%) | −0.74 | N/A | 53 mmol/mol (7.0%) | −2.8 kg |
| Rosenstock *et al.* 2014 [55] | IGlar + albiglutide 30 mg OW | 47 | IGlar titrated to <5.6 mmol/L | +6 | 69 mmol/mol (8.5%) | −0.82 | N/A | 60 mmol/mol (7.6%) | −0.73 kg |
| Diamant *et al.* 2014 [57] | IGlar + exenatide 10 µg BID | 61 | Background IGlar reduced by 10% at baseline and then titrated to ≤5.6 mmol/L | −4.5 | 67 mmol/mol (8.3%) | −1.13 | N/A | 55 mmol/mol (7.2%) | −2.5 kg |

≠18-week efficacy data are presented before insulin titration was permitted in the study. \*Placebo-corrected value; \*\*Not reported, calculated using baseline value and change in HbA1c value reported; † 67 U for those on premixed insulin (27%) and 44 U for those on long- or intermediate-acting insulin (73%); # Basal insulin dose reduced by 20% at randomization

BID, twice daily; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; MDI, multiple daily injections; NR, not reported; OAD, oral antidiabetic drug; OW, once weekly; SGLT2, sodium–glucose co-transporter-2

**Table 4** Summary of key data from the IDegLira phase 3a clinical trials [62–64]

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study duration** | **Treatment  arms** | **Mean EOT  dose** | **Mean ΔHbA1c (%)** | **Mean EOT HbA1c (%)** | **Hypoglycaemia (events/  patient-year)** | **Mean Δ body weight (kg)** |
| DUAL I (Gough *et al*. 2014) [62] | 26 weeks | IDegLira | 38 dose steps  (38 U; 1.4 mg) | −1.9\*,† | 6.4 | 1.8\*,† | −0.5\*,† |
| IDeg | 53 U | −1.4 | 6.9 | 2.6 | +1.6 |
| Lira 1.8 mg | 1.8 mg | −1.3 | 7.0 | 0.2 | −3.0 |
| DUAL I extension (Gough *et al*. 2014) [64] | 52 weeks | IDegLira | 39 dose steps  (39 U; 1.4 mg) | −1.8\*,† | 6.4 | 1.8\*,† | -0.4\*,† |
| IDeg | 62 U | −1.4 | 6.9 | 2.8 | +2.3 |
| Lira 1.8 mg | 1.8 mg | −1.2 | 7.1 | 0.2 | −3.0 |
| DUAL II (Buse *et al*. 2014) [63] | 26 weeks | IDegLira | 45 dose steps  (45 U; 1.6 mg) | ½1.9\* | 6.9 | 1.5 | −2.7\* |
| IDeg (max 50 U) | 45 U | −0.9 | 8.0 | 2.6 | 0.0 |

\**P* < 0.0001 vs. IDeg; †*P* < 0.0001 vs. liraglutide

EOT, end-of-trial; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide

**Figure 1** Relationship between incidence of hypoglycaemia (events per patient-year) and end-of-study HbA1c [16,20]

S:\Watermeadow\Projects\Hermes\NVO\IDL\GB-13481 Glycaemic control and side effects with insulin therapy review ms\Graphics\13481 Figure A.tif

S:\Watermeadow\Projects\Hermes\NVO\IDL\GB-13481 Glycaemic control and side effects with insulin therapy review ms\Graphics\13481 Figure B.tif

1. IDet vs. NPH as add-on to OAD therapy in insulin-naïve patients with T2D in a 26-week study [16]. (Adapted from Hermansen *et al. Diabetes Care* 2006, with permission from Elsevier.)
2. IGlar vs. NPH in combination with OAD therapy in patients with T2D in a 5-year study. Prandial insulin could be added at the investigator’s discretion [20]. (Adapted from Rosenstock *et al. J Diabetes Complications*, with permission from the American Diabetes Association.)

IDet, insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; T2D, type 2 diabetes