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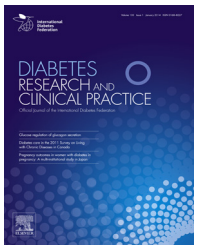

Review

Clinical use of insulin degludec

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ABSTRACT

The limitations of current basal insulin preparations include concerns related to their pharmacokinetic and pharmacodynamic properties, hypoglycaemia, weight gain, and perception of management complexity, including rigid dosing schedules. Insulin degludec (IDeg) is a novel basal insulin with improved pharmacokinetic and pharmacodynamic properties compared to insulin glargine (IGlar) including a long half-life of ~25 h and a duration of action >42 h at steady state, providing a flat and stable blood glucose-lowering effect when injected once daily. Evidence from phase 3a clinical trials with a treat-to-target design in patients with type 1 and type 2 diabetes has shown that IDeg has similar efficacy to IGlar, with a 9% and 26% reduction in risk of overall and nocturnal hypoglycaemia, respectively (in the pooled population) during the entire treatment period, and a 16% and 32% reduction during the maintenance period, respectively. Given its pharmacodynamic properties, IDeg offers a broad dosing window, allowing for flexible dose administration, if required. Two different formulations of IDeg are available (100 units/mL [U100] and 200 units/mL), the latter providing the same IDeg dose as the U100 formulation in half the injection volume. The unique pharmacokinetic profile of IDeg facilitates glycaemic control while minimising the risk of nocturnal hypoglycaemia.

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Contents

1. Introduction

The beneficial effect of improved glycaemic control, especially early in a patient's disease journey, has been demonstrated to reduce the risk of long-term complications in patients with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus [1,2].

Whilst current recommendations call for individualised glycaemic targets for patients with T1DM and T2DM [3,4], evidence indicates there is inertia in escalation of therapy at all stages of the disease process despite prolonged periods of poor glycaemic control [5,6]. Although insulin therapy has robust glucose-lowering efficacy, insulin treatment is often underutilised in T2DM, or the dose titration remains inadequate [7]. This is primarily due to the fear of hypoglycaemia, coupled with the restrictions on patients' lifestyle that can result from complex or inflexible dosing regimens [8,9]. New basal insulin products with an improved pharmacodynamic profile, including prolonged and consistent biological action, lower risk of hypoglycaemia and more flexible dosing schedules, are being developed to address these issues with the ultimate objective of improving long-term glycaemic control and the patient's experience with basal insulin therapy.

Typically, basal insulin is used to maintain stable blood glucose levels in the fasting or post-absorptive state, with mealtime supplementation using a rapid-acting insulin administered to control the postprandial rise in glucose levels. The basal insulins, insulin glargine (IGlar) and insulin detemir (IDet) both have advantages over neutral protamine Hagedorn (NPH) insulin due to their longer half-lives, comparatively reduced within-subject variability and fewer hypoglycaemic episodes [10–12]. IGlar is recommended for once-daily dosing and IDet for once- or twice-daily dosing; however, in clinical practice, more frequent than once-daily dosing of either of these basal insulin preparations may offer improved glycaemic control of blood glucose in some cases [13–17].

However, IDet and IGlar exhibit significant residual within-patient variability in their pharmacokinetic and pharmacodynamic profiles that can lead to less predictable glucose-lowering effects, which in turn contributes to the increased risk of hypoglycaemia and can undermine dose titration [11,18,19]. Improvements in the pharmacokinetic properties of basal insulin analogues would entail a prolonged duration of action combined with a less variable pharmacodynamic effect, which might lead to more predictable glycaemic control, less hypoglycaemia and greater dosing flexibility.

2. Insulin degludec: Structure, mechanism of action and pharmacokinetic properties

Insulin degludec (IDeg) is a new-generation basal insulin analogue that is available in formulations of 100 units/mL (U100) and 200 units/mL (U200), where the latter delivers the same amount of insulin as U100 in half the injection volume. Similar to IDeg U100, IDeg U200 is approved as a once-daily dose regimen, thereby offering an additional and effective option for patients with higher daily insulin requirements.

IDeg is derived by removal of the B30 threonine amino acid residue, and acylating the now DesB30 human insulin at the

ε-amino group of LysB29 with hexadecandioic acid via a γ-L-glutamic acid spacer [20,21]. IDeg is formulated in the presence of phenol and zinc to create a solution of di-hexamers. Following subcutaneous (SC) injection and the dispersion of phenol, the di-hexamers self-associate to form a stable depot of multi-hexamer chains at the injection site (Fig. 1). The subsequent diffusion of zinc from the multi-hexamers results in gradual dissociation of these chains into readily-absorbed IDeg monomers, providing a slow and continuous delivery of IDeg into the circulation [20]. In addition, IDeg can bind strongly but reversibly to albumin via its fatty di-acid side chain, resulting in plasma protein binding of more than 99% [22]. As the concentration of IDeg is very low compared to albumin (>10,000-fold), IDeg will occupy less than 0.01% of the albumin molecules [22]. Therefore, the pharmacokinetic properties of IDeg would not be affected in vivo by other albumin-bound drugs or by even very large changes in albumin concentration. The mode of protraction of IDeg contrasts with other basal insulin preparations, which achieve their prolonged action through different mechanisms, such as pH-dependent crystallisation (IGlar) [23] and local albumin binding (IDet) [20].

2.1. *Pharmacokinetic and pharmacodynamic properties of insulin degludec*

At steady state, IDeg has a half-life after SC administration of approximately 25 h [24,25]. As a result, the duration of action of IDeg at steady state exceeds 42 h [22,24,26] compared with the mean duration of action of IGlar of 20.5 h [27]. Pharmacodynamic analyses have further shown that the glucose-lowering effect of IDeg is evenly distributed across the entire 24-h dosing interval [24,28]. With IDeg, steady state is reached within three days of once-daily administration [24], therefore dose titrations can be safely carried out once-weekly to avoid overshooting the glycaemic target.

Due to the prolonged pharmacodynamics of IDeg, under steady-state conditions the overlapping effect of daily injections results in less variability in glucose-lowering effect [29]. In patients with T1DM, it has been shown that the day-to-day within-subject variability in glucose lowering effect is four-times less with IDeg compared with IGlar, theoretically translating into more predictable glycaemic control [26]. A flat and stable glucose-lowering effect with IDeg that is evenly distributed across the 24-h dosing interval has also been shown in patients with T2DM [24].

Importantly, the ultra-long pharmacokinetic and pharmacodynamic properties of IDeg observed in patients with T1DM and T2DM are maintained in various subpopulations, such as the elderly and those with hepatic or renal impairment (including those with end-stage renal disease) [30–32]. The pharmacokinetic and pharmacodynamic properties of IDeg are maintained in both of its formulations, U100 and U200 [33].

As of January 2015, IDeg has regulatory approval in Argentina, Aruba, Azerbaijan, Bangladesh, Bosnia & Herzegovina, Brazil, Chile, Colombia, Costa Rica, El Salvador, the EU [34], Honduras, Hong Kong, Iceland, India, Israel, Japan, Kazakhstan, Lebanon, Lichtenstein, Macedonia, Mexico, Nepal, Norway, Russia, South Korea, Switzerland and the UAE. Approval in the USA is pending further cardiovascular data in the form of a dedicated cardiovascular outcomes trial (CVOT), which is currently ongoing (NCT01959529).

2.2. *Co-formulation with insulin aspart*

Another pharmacological property of IDeg is that it can be combined with the rapid-acting insulin analogue IAsp without

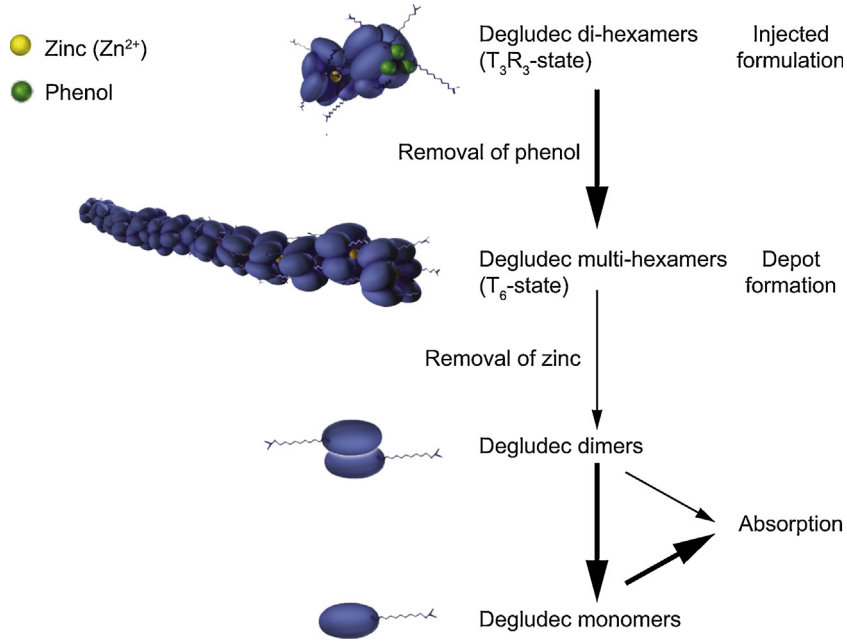

Fig. 1 – Schematic representation of the hypothesis for the mode of retarded absorption of insulin degludec (IDeg). IDeg is injected subcutaneously as a zinc phenol formulation containing the IDeg di-hexamer in the T_3R_3 conformation. Rapid loss of phenol changes the IDeg hexamers to a T_6 configuration and multi-hexamer chains form. With slow diffusion of zinc, these chains break down into dimers, which quickly dissociate into readily absorbed monomers.

altering the properties of either of the components. Insulin degludec/insulin aspart (IDegAsp), comprised of 70% IDeg and 30% IAsp, is the first soluble insulin combination product that provides a pharmacodynamic profile that reflects the prandial insulin profile of IAsp superimposed on the long and stable profile of IDeg in a single injection [35]. IDegAsp can be administered once- or twice-daily with the main meal(s) [36]. Twice-daily IDegAsp is associated with reduced risk of hypoglycaemia compared to premixed insulins and reduced treatment burden compared with basal-bolus therapy when dosed once-daily, in subjects with T2DM [37–39]. The administration of IDegAsp with a single meal, with additional bolus rapid-acting analogue injections at the remaining mealtimes, can further simplify the treatment regimen in T1DM by reducing the number of daily injections compared with standard basal-bolus therapy (IDet + IAsp) [40].

2.3. *Combination with liraglutide*

IDeg can also be combined with liraglutide, a once-daily GLP-1 analogue, in IDegLira, a novel, once-daily, fixed-ratio combination therapy (one dose step of IDegLira comprises 1 U of IDeg and 0.036 mg of liraglutide). IDegLira combines and preserves two complementary modes of action addressing the multiple underlying pathophysiological defects in T2DM [41,42]. In patients with T2DM, IDegLira leads to effective glycaemic control via reductions in FPG and postprandial glucose throughout the day and after all meals [43,44]. It is also associated with a significant reduction in body weight vs IDeg, comparable or lower risk of confirmed hypoglycaemia vs IDeg and an improved gastrointestinal side effect profile, particularly nausea, compared with liraglutide [43,44]. Therefore, IDegLira in a single pen and for once-daily injection offers patients a simple therapy intensification option. IDegLira was recently approved by the European Medicines Agency (EMA) for the treatment of patients with T2DM [45].

3. Clinical evidence

The implications of the promising pharmacokinetic and pharmacodynamic characteristics of IDeg have been investigated in a large clinical trial programme (BEGIN®) involving more than 11,000 patients with T1DM and T2DM (Table 1). IGlar was generally used as the comparator basal insulin, in the phase 3 studies, and overall, the randomisation of patients treated with IDeg vs IGlar was between 2:1 and 3:1. Nine phase 3a randomised, controlled, open-label, multicentre trials with a 'treat-to-target' design (in order to meet FDA recommendations for non-inferiority of new insulins) have been carried out. In all of the studies, insulin dose titration included adjustment of insulin doses to achieve pre-breakfast self-measured blood glucose (SMBG) values of 4–5 mmol/L (70–90 mg/dL). In addition, the same definition of confirmed hypoglycaemia (plasma glucose <3.1 mmol/L [<56 mg/dL] or severe hypoglycaemia) was used throughout the programme (see Appendix A). This definition of hypoglycaemia (that is, a low hypoglycaemia cut-off level due to the low target plasma glucose level) was chosen to avoid false positives and to discriminate hypoglycaemia with neuroglycopenic symptoms. Similarly, nocturnal hypoglycaemia was defined as confirmed episodes of hypoglycaemia occurring between 00.01 h and 05.59 h, in order to minimise confounding by any hypoglycaemia related to the prandial insulin component in the basal-bolus studies.

3.1. *Efficacy of insulin degludec in subjects with type 1 diabetes*

Data from the studies in subjects with T1DM have shown that when titrated to the same glycaemic targets, IDeg is non-inferior to IGlar in terms of the mean reduction in HbA_{1c} concentrations [46,47]. Subjects on a twice-daily regimen converted their total daily insulin dose 1:1 with IDeg, but reduced IGlar by 20%. The dose was converted on a 1:1 basis in subjects switching from a once-daily schedule [46,47]. In the basal-bolus trial in T1DM (IDeg vs IGlar), mean daily basal, daily bolus and total daily doses of insulin were significantly reduced by 14% ($p < 0.0001$), 10% ($p = 0.016$) and 11% ($p < 0.0001$), respectively, in the IDeg group compared with the IGlar group at end of trial [46]. These findings support the recommendation for reducing the dose of IDeg when switching patients from IGlar and are further reflected in a slightly higher rate of daytime hypoglycaemia being observed with IDeg [46] upon initiation compared to IGlar, as discussed below (Sections 3.3.1 and 4.1). Mean reductions in FPG levels were similar in subjects receiving IDeg and IGlar, with no statistically significant between-treatment differences reported in subjects with T1DM [46,47].

3.2. *Efficacy of insulin degludec in subjects with type 2 diabetes*

Studies in subjects with T2DM confirmed that IDeg is non-inferior to IGlar in terms of reducing HbA_{1c} concentrations in both insulin-naive [48,49] and previously insulin-exposed patients [50]. Clinical data from insulin-naive patients with T2DM [48,51] also indicate that, as seen in T1DM studies, the total daily insulin dose at the end of the trial was lower in subjects who received IDeg compared with those who received IGlar. There was also a trend towards lower FPG levels with IDeg compared with IGlar in five trials with T2DM [39,49–52], which reached statistical significance in three of them [49,51,52].

3.3. *Effects of insulin degludec on hypoglycaemia*

Based on prior discussions with, and subsequent review by the regulatory authorities, a pre-planned meta-analysis was conducted of pooled and analysed subject-level data from seven phase 3a trials (see Table 1) [53].

The primary endpoint in the meta-analysis was overall confirmed hypoglycaemia; although, episodes of nocturnal confirmed hypoglycaemia and severe hypoglycaemia were also evaluated (see Appendix A). In all of the analysed trials, 'confirmed hypoglycaemia' was defined as either a plasma glucose concentration of <3.1 mmol/L (56 mg/dL) or an episode of severe hypoglycaemia (requiring assistance).

Table 1 – Summary of the phase 3a clinical trials in the BEGIN® clinical programme with insulin degludec (IDeg).

Author (study name)	Population	Trial treatments (n)	Duration	Reduction in HbA_{1c}	Reduction in FPG	Confirmed hypoglycaemic episodes
Heller et al. (BEGIN™: T1) [46]	T1DM insulin-treated	IDeg OD (472) vs IGlar OD (157) plus IAsp TID	52 w	IDeg 0.40%; IGlar 0.39% (ETD IDeg vs IGlar -0.01%; non-inferior)	IDeg 1.3 mmol/L; IGlar 1.4 mmol/L (ETD IDeg vs IGlar -0.33 mmol/L; p = 0.35)	IDeg 43 vs IGlar 40 episodes per PYE; ERR 1.07, p = 0.48
Mathieu et al. (BEGIN™: Flex T1) [47]	T1DM insulin-treated	IDeg Forced-Flex OD (164) vs IDeg OD (165) and IGlar OD, (164) Extension: IDeg Free-Flex OD vs IGlar OD. All arms + IAsp TID	26 w (+ 26-w extension)	IDeg Forced-Flex 0.40%, IDeg 0.41%, IGlar 0.58% (ETD IDeg Forced-Flex vs IGlar 0.17%; non-inferior)	IDeg Forced-Flex 1.28 mmol/L; IDeg 2.54 mmol/L; IGlar 1.33 mmol/L (ETD IDeg Forced-Flex vs IGlar -0.05 mmol/L; p = ns)	IDeg (including both Forced-Flex and Free-Flex) 68.1 vs IGlar 63.4 episodes per PYE; ERR 1.09, p = ns
Garber et al. (BEGIN™: BB) [50]	T2DM insulin-treated	IDeg OD (744) vs IGlar OD (248)	52 w	IDeg 1.1%; IGlar: 1.2% (ETD IDeg vs IGlar 0.08%; non-inferior)	IDeg 2.3 mmol/L; IGlar 2.0 mmol/L (ETD IDeg vs IGlar -0.29 mmol/L; p = 0.1075)	IDeg 11.1 vs IGlar: 13.6 episodes per PYE; ERR 0.82, p = 0.0359
Meneghini et al. (BEGIN™: FLEX) [52]	T2DM (insulin naive or insulin-treated)	IDeg Flex OD (229), IDeg OD (228), IGlar OD (230)	26 w	IDeg Flex 1.28%; IDeg 1.07%; IGlar 1.26% (ETD IDeg Flex vs IGlar 0.04%; non-inferior)	IDeg Flex 3.2 mmol/L; IDeg 3.0 mmol/L; IGlar 2.8 mmol/L (ETD IDeg Flex vs IGlar -0.42 mmol/L; p = 0.04)	IDeg Flex 3.6 vs IDeg 3.6 vs IGlar 3.5 episodes per PYE; ERR 1.03, p = ns
Zinman et al. (BEGIN™: Once Long) [49]	T2DM insulin-naive	IDeg OD vs IGlar OD (+ metformin)	52 w	IDeg 1.06%; IGlar 1.19% (ETD IDeg vs IGlar 0.09%; non-inferior)	IDeg 3.8 mmol/L; IGlar 3.3 mmol/L (ETD IDeg vs IGlar -0.43 mmol/L; p = 0.005)	IDeg 1.52 vs IGlar 1.85 episodes per PYE; ERR 0.82, p = 0.103
Gough et al. (BEGIN™: LOW VOLUME) [51]	T2DM insulin-naive	IDeg 200 U/mL OD vs IGlar OD (+ metformin ± dipetidyl peptidase)	26 w	IDeg 1.3%; IGlar 1.3% (ETD IDeg vs IGlar 0.04%; non-inferior)	IDeg 3.7 mmol/L; IGlar 3.4 mmol/L (ETD IDeg vs IGlar -0.42 mmol/L; p < 0.05)	IDeg 1.22 vs IGlar 1.42 episodes per PYE; ERR 0.86, p = 0.46
Onishi et al. (BEGIN™: ONCE ASIA) [48]	T2DM insulin-naive	IDeg OD vs Glar OD (+ oral antidiabetic drugs)	26 w	IDeg 1.24%; IGlar 1.35% (ETD IDeg vs IGlar 0.11%; non-inferior)	IDeg 2.88 mmol/L; IGlar 2.97 mmol/L (ETD IDeg vs IGlar -0.09 mmol/L; p = 0.59)	IDeg 3.0 vs IGlar 3.7 episodes per PYE; ERR 0.82, p = 0.20
Philis-Tsimikas et al. (BEGIN™: EARLY) [73]	T2DM	IDeg OD vs sitagliptin (+ oral antidiabetic drugs)	26 w	IDeg 1.52%; sitagliptin 1.09% (ETD IDeg vs sitagliptin 0.43%; superior)	IDeg 3.41 mmol/L; sitagliptin 1.24 mmol/L (ETD IDeg vs sitagliptin -2.17 mmol/L; superior)	IDeg 3.1 vs sitagliptin 1.3 episodes per PYE; ERR 3.81, p = nr

ERR, estimated rate ratio; ETD, estimated treatment difference; FPG, fasting plasma glucose; IAsp, insulin aspart; IDeg, insulin degludec; IGlar, insulin glargine; nr, not reported; ns, not significant; PYE, patient-year of exposure; OD, once daily; TID, three times daily; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; w, weeks. Trials shaded in blue were included in the meta-analysis of hypoglycaemia rates, published by Ratner et al. [53], except the extension of the BEGIN Flex T1 trial, which was not included in the meta-analysis.

3.3.1. *Hypoglycaemia in subjects with type 1 diabetes*

In the T1DM trials included in the meta-analysis [46,47] there was no significant difference between IDeg and IGlar in the rate of overall confirmed hypoglycaemic episodes across the overall treatment period, although it was slightly higher with IDeg compared to IGlar (Fig. 2a) [53]. Absolute rates of confirmed hypoglycaemic episodes ranged from 53 to 93 per patient-year of exposure (PYE) with IDeg and from 49 to 83 per PYE with IGlar [53]. The higher rate of hypoglycaemic episodes seen with IDeg compared to IGlar appears to be mostly concentrated in the first four weeks of the trials, and during daytime, when the dose of IGlar was reduced initially while that of IDeg was not (as discussed in Section 4.1). In the maintenance period (defined as the period following active dose titration from 16 weeks to the end of treatment when typically only minor adjustments to insulin dose are required) there was no increase in hypoglycaemia with IDeg compared to IGlar. Overall, a lower rate of nocturnal hypoglycaemia with IDeg compared with IGlar was observed in subjects with T1DM (Fig. 2b). The reduction in estimated rate ratio (ERR) in nocturnal hypoglycaemic episodes reached statistical significance in the maintenance period (ERR 0.75; 95% CI 0.60, 0.94) (Fig. 2b) [53].

In a recent randomised, two-period, crossover study in 28 subjects with T1DM and normal hypoglycaemia awareness, hypoglycaemia was induced by administering three-times the usual daily insulin dose (IDeg or IGlar). The study showed that, despite moderate increases in counter-regulatory hormone responses with IDeg compared with IGlar, the rates of recovery from hypoglycaemia were similar with IDeg and IGlar, and the two basal insulins elicited comparable symptomatic and cognitive responses to induced hypoglycaemia [54].

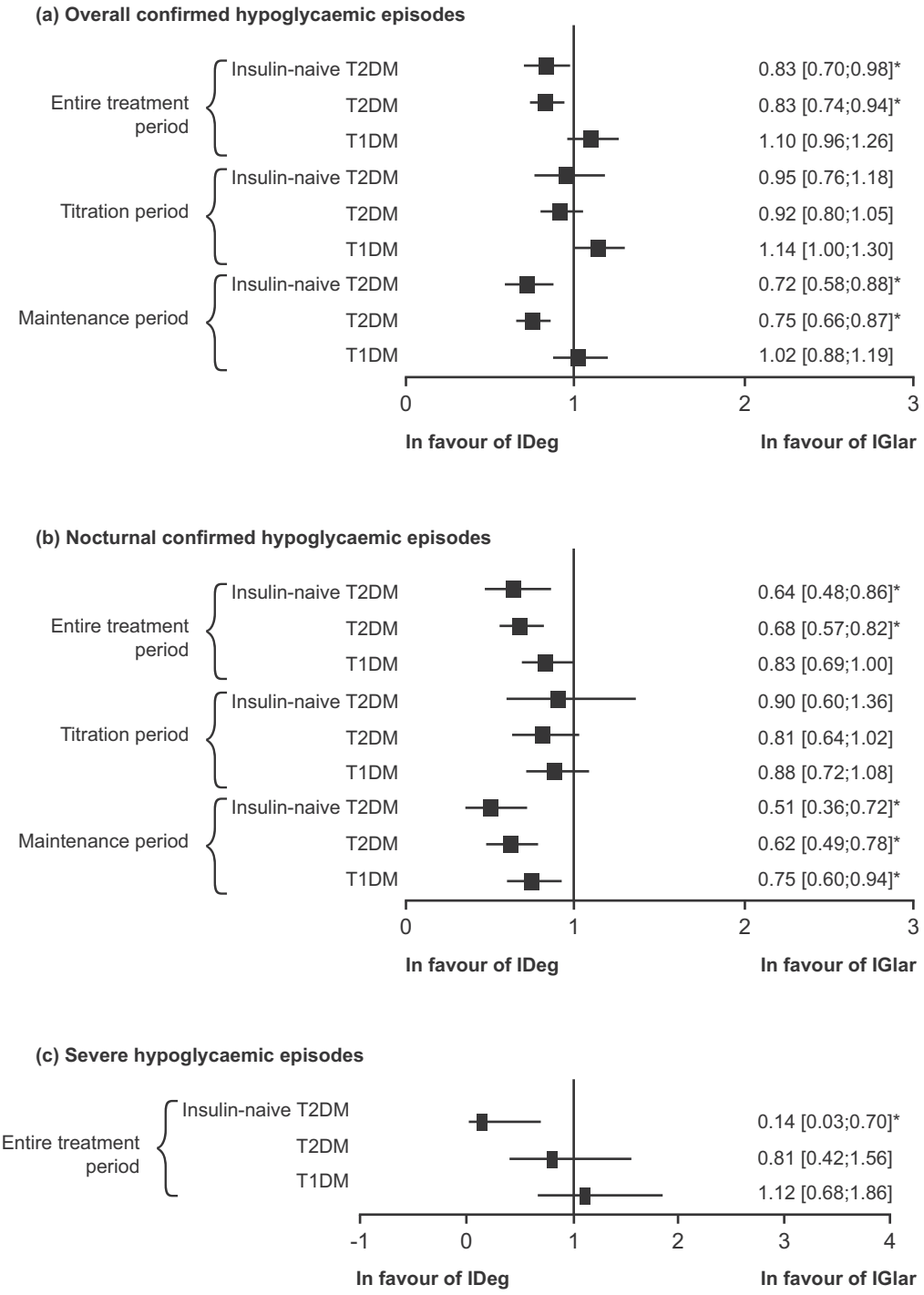

Fig. 2 – Hypoglycaemia rate ratio in subjects with type 1 (T1DM) and type 2 (T2DM) diabetes receiving insulin degludec (IDeg) or insulin glargine (IGlar). Data presented are estimated rate ratios (IDeg/IGlar) with 95% confidence intervals of (a) overall confirmed hypoglycaemic episodes, (b) nocturnal confirmed hypoglycaemic episodes and (c) severe hypoglycaemic episodes. Asterisks indicate significantly lower estimated rate ratio with IDeg compared with IGlar based on 95% confidence intervals (figures based on data from Ratner et al. [53]).

3.3.2. *Hypoglycaemia in subjects with type 2 diabetes*

In subjects with T2DM, the episodes of hypoglycaemia ranged from 1 (basal only) to 13 (basal-bolus) per PYE with IDeg, and from 1 (basal only) to 15 (basal-bolus) per PYE with IGlar [53]. The meta-analysis found that the rates of overall and nocturnal confirmed hypoglycaemia were significantly reduced with IDeg in insulin-naive subjects with T2DM compared with IGlar (ERR 0.83; 95% CI 0.70, 0.98 and ERR 0.64; 95% CI 0.48, 0.86, respectively) (Fig. 2). In the overall population of insulin-naive and insulin-experienced subjects

with T2DM, the rates of overall and nocturnal confirmed hypoglycaemia were 17% and 32% lower, respectively (Fig. 2b). The reduction in the ERR of overall (Fig. 2a) and nocturnal hypoglycaemia (IDeg/IGlar) (Fig. 2b) was even more pronounced in the maintenance period. A reduction in the relative risk of severe hypoglycaemia rates in favour of IDeg was observed in insulin-naive subjects with T2DM (ERR 0.14; 95% CI 0.03, 0.70) (Fig. 2c) [53]. However, the incidence of such severe episodes remains very low in both groups as would be expected due to the exclusion of patients with a history of severe hypoglycaemia in clinical trials. In addition, no statistically significant differences in hypoglycaemia were observed in subjects receiving U200 IDeg compared with IGlar (1.22 per PYE versus 1.42 per PYE; ERR 0.86; 95% CI 0.58, 1.28; $p = 0.46$) [51].

The meta-analysis therefore confirmed that there is a statistically significant 9% reduction in risk of overall hypoglycaemia and a 26% reduction in the risk of nocturnal hypoglycaemia with IDeg compared to IGlar at equivalent HbA_{1c} levels in the pooled population of patients with T2DM and T1DM [53]. It has been reported that higher rates of confirmed hypoglycaemia are associated with greater within-subject variability in FPG levels in subjects with T1DM and T2DM [55]. The reduction in hypoglycaemia associated with IDeg use might be partly attributed to the reduced pharmacodynamic variability in glucose-lowering effect compared to IGlar [53] that has been reported in subjects with T1DM [26] and in those with T2DM [56]. Further studies are required to confirm this hypothesis and to validate the benefit of IDeg in real-life studies.

3.3.3. *Treatment satisfaction with insulin degludec in patients with type 1 or 2 diabetes and recurrent hypoglycaemia*

The clinical trials discussed above, comparing IDeg and IGlar, excluded patients with severe recurrent hypoglycaemia [53], a population who might benefit most from a basal insulin with more stable glucose-lowering effects and a reduced risk of hypoglycaemia. However, this aspect has been addressed in early, real-world observational studies in patients with T1DM or T2DM and recurrent hypoglycaemia. Switching patients with frequent hypoglycaemia to IDeg has been shown to be associated with a reduction in the frequency of hypoglycaemic events and improved glycaemic control [57,58]. In these patients, switching to IDeg improved patients' treatment satisfaction [57].

3.3.4. *Exercise-related hypoglycaemia*

Exercise-related hypoglycaemia is a concern for patients with diabetes since the higher glucose requirement and insulin sensitivity during exercise can increase the risk of hypoglycaemia [59]. To investigate this further, a randomised, single-centre, open-label, two-period, multiple-dose, crossover trial was conducted to compare the effect of exercise (30 min bicycle exercise at 65% VO_{2peak}) on blood glucose between IDeg and IGlar, both in combination with mealtime IAsp, in 40 subjects with T1DM [60]. The study found that the risk of exercise-related hypoglycaemia was low and similar with IDeg compared to IGlar. Moreover, no episodes of hypoglycaemia were reported during the exercise phase with either IDeg or IGlar and the incidence of hypoglycaemia in the 24 h after exercising was also similar with both basal insulins [60]. Furthermore, a recent analysis of exercise-related hypoglycaemia events from seven randomised, open-label, treat-to-target, clinical trials in subjects with T1DM and T2DM comparing IDeg with IGlar (both given once-daily) reported that IDeg did not lead to an increased risk of self-reported exercise-related hypoglycaemia compared with IGlar [61].

3.4. *Cardiovascular safety*

In accordance with the FDA 2008 CV Risk Guidance recommendations, a pre-specified meta-analysis of major adverse cardiovascular events (MACE) in the IDeg phase 3 trials was carried out. In total, 80 patients in 16 clinical trials involving 8918 patients [34] experienced treatment-emergent MACE (53 in patients receiving IDeg or IDegAsp and 27 on comparator insulins). The incidence rates were 1.48 events per 100 PYE in patients treated with IDeg or IDegAsp and 1.44 events per 100 PYE in patients treated with comparator basal insulins. Subsequent post-hoc analyses of MACE data in clinical trials up to May 2012 were conducted. As these data neither confirmed nor excluded the possibility for an increased cardiovascular risk with IDeg in comparison with IGlar, the DEVOTE clinical trial was subsequently initiated to define better the cardiovascular profile of IDeg (and IDegAsp) in patients at high risk of cardiovascular events (NCT01959529). In addition, IDeg has been shown not to alter classical cardiovascular risk factors such as low density lipoprotein, high density lipoprotein and blood pressure compared with the comparator [62].

3.5. *Quality of life*

QoL assessment using the Short-Form 36 (SF-36) Health Survey version 2 questionnaire demonstrated significant improvements in both the physical (specifically bodily pain domain score) and mental (specifically vitality) components of the SF-36 with IDeg compared with IGlar ($p < 0.05$ or Cohen's effect size ~0.4–0.5) [50,63–65]. Similar findings in QoL have been reported with the U200 formulation of IDeg [51].

3.6. *Cost-effectiveness of degludec*

Several recent papers have demonstrated the cost–effectiveness of IDeg compared to IGlar [66–68]. A cost–utility model based on both data from a meta-analysis of phase 3 trials [53] and a questionnaire-based study conducted in Sweden, reported that IDeg was associated with greater quality-adjusted life year (QALY) gains in patients with T1DM (0.31 vs 0.26 QALYs gained for IGlar), patients with T2DM requiring basal insulin (0.76 vs 0.69 QALYs gained) and patients with T2DM requiring basal-bolus treatment (0.56 vs 0.47 QALYs gained) after one year of treatment [66]. While pharmacy costs for IDeg were higher, these were partially offset by cost savings due to reduced insulin doses, reduced direct costs of hypoglycaemia, reduced productivity losses and reduced costs of blood glucose monitoring [66]. Depending on the diabetic population (T1DM, T2DM basal-only insulin or T2DM basal-bolus insulin), IDeg was associated with incremental cost–effectiveness ratios of SEK 19,766, SEK 10, 082 and SEK 36,

074, respectively, per QALY gained [66]. These ratios were all within the previously reported willingness-to-pay threshold of SEK 500,000 per QALY gained.

Similarly, two UK-based studies examined cost–utility of IDeg compared to IGlar in the context of the UK national health service, in patients with T1DM [68] and T2DM [67], using hypoglycaemia rates for IDeg and IGlar from a pre-planned meta-analysis of phase III clinical trials [53]. In both studies, IDeg was within the previously reported willingness-to-pay threshold of £20,000 to £30,000 per QALY. Of note, sensitivity analyses demonstrated that using higher baseline non-severe hypoglycaemic events resulted in greater cost–effectiveness for IDeg compared to IGlar [67,68]. This is of particular importance as clinical trials, due to their controlled nature and exclusion criteria, are likely to report lower hypoglycaemia rates than those found in clinical practice.

In the developing world there is limited available evidence concerning cost–effectiveness. Hypoglycaemia and blood glucose monitoring contribute to the cost burden of diabetes, both for healthcare systems and for the individual patient. Results from the multinational, non-Western A1chieve study previously showed that, for insulin-experienced patients, switching to modern insulin analogues was associated with a reduction in hypoglycaemia rates [69]. More recently, the large-scale, observational Hypoglycaemia Assessment Tool (HAT) study, conducted across North America, Latin America, Europe and South East Asia and involving over 27000 patients, has reported higher hypoglycaemia rates than in previous studies limited to Europe and North America [70], highlighting the global burden of hypoglycaemia, particularly for countries with limited healthcare resources. Since lower rates of hypoglycaemia have been demonstrated for IDeg and less frequent blood glucose monitoring is needed compared to IGlar, use of IDeg could potentially reduce these costs. However, no cost–utility analysis for IDeg has yet been published for countries outside of Europe, and hence the cost–effectiveness of IDeg in developing countries has yet to be demonstrated.

4. Use of insulin degludec in clinical practice

IDeg is licensed for the treatment of adult patients (≥18 years) with T1DM and T2DM [34]. Simulated pharmacokinetic and pharmacodynamic profiles at steady state indicate a similar exposure and glucose-lowering effect of IDeg over a 24-h period regardless of the site of injection [25].

In patients with T1DM, IDeg should be administered once-daily in combination with a prandial fast-acting insulin to provide insulin coverage during mealtimes [34]. In patients with T2DM, IDeg can be administered alone, in combination with oral hypoglycaemic agents, GLP-1 analogues or with bolus insulin, as supported by clinical evidence [47–50]. Based on the phase 3 trials, the recommended starting dose of IDeg in insulin-naive patients with T2DM is 10 unit once-daily with subsequent adjustments and individualisation [34], although it is important to apply clinical judgement (considering the body mass index and the levels of insulin resistance of each subject) when determining the starting dose.

4.1. *Switching to insulin degludec*

Patients with either T1DM or T2DM can switch from other insulin-based regimens to IDeg, as supported by evidence from clinical trials [46,50]. However, switching between insulin products should be done under medical supervision and patients should be aware that dose adjustment may be required [34]. Before, during and in the weeks following a switch to IDeg, FBG levels should be monitored closely [34]. When switching patients from other basal insulins to IDeg, providers will need to manage the brief period between the loss of the previous basal insulin's effect and attainment of steady state with IDeg. During this period, patients may observe higher blood glucose values for 3–5 days following the switch to IDeg, and this possibility should be discussed with the patient prior to the switch. In addition, adjustments to dose and timing of concurrent short- or rapid-acting insulin analogues or other glucose-lowering treatment may also be required [34]. The authors have also noticed that as the effect of IDeg stabilises, some patients may experience a progressive (and in some cases marked) reduction in prandial insulin doses.

Switching to IDeg from other once-daily basal insulins, doses can usually be done on a 1:1 basis [34]. Based on their clinical experience, the authors suggest that the dose be reduced by 20% if transitioning from a twice-daily basal schedule (and depending upon individual glycaemic response), as recommended for IGlar [17]; if switching from a once-daily basal insulin schedule, a dose reduction can be considered also, if the patient has a low HbA_{1c} value. In addition, prandial insulin doses might also need to be adjusted to reduce the risk of hypoglycaemia during the day when switching to IDeg–specifically, the pre-breakfast prandial dose, especially when aiming for a strict FPG target as defined in the phase 3 trials (4.0–5.0 mmol/L). Further dose adjustment guidance when switching from other insulin products is provided in Fig. 3.

4.2. *Titration of insulin degludec in patients with type 1 or type 2 diabetes*

Dose adjustment with IDeg can be carried out once-weekly to achieve individual patient targets (Fig. 4). The treat-to-target goal and insulin dose adjustment are based around an individual's pre-breakfast FPG (or SMBG) level. A calculated mean FPG from the preceding 2 days can be compared to desired glycaemic goals and basal insulin doses can be adjusted up or down by 2 units, as shown in Fig. 4, to achieve target.

4.3. *Flexibility in dosing of insulin degludec in patients with type 1 or type 2 diabetes*

Anticipating or delaying a scheduled daily dose of basal insulin will affect its concentration in the circulation; however, this effect will be less for insulin preparations, such as IDeg, with a longer half-life and duration of action.

Similar to IGlar, IDeg should be administered once-daily, preferably at the same time every day; however, on occasions when administration at the same time of the day is not possible, IDeg allows for flexibility in the timing of dose administration provided a minimum of 8 h between injections

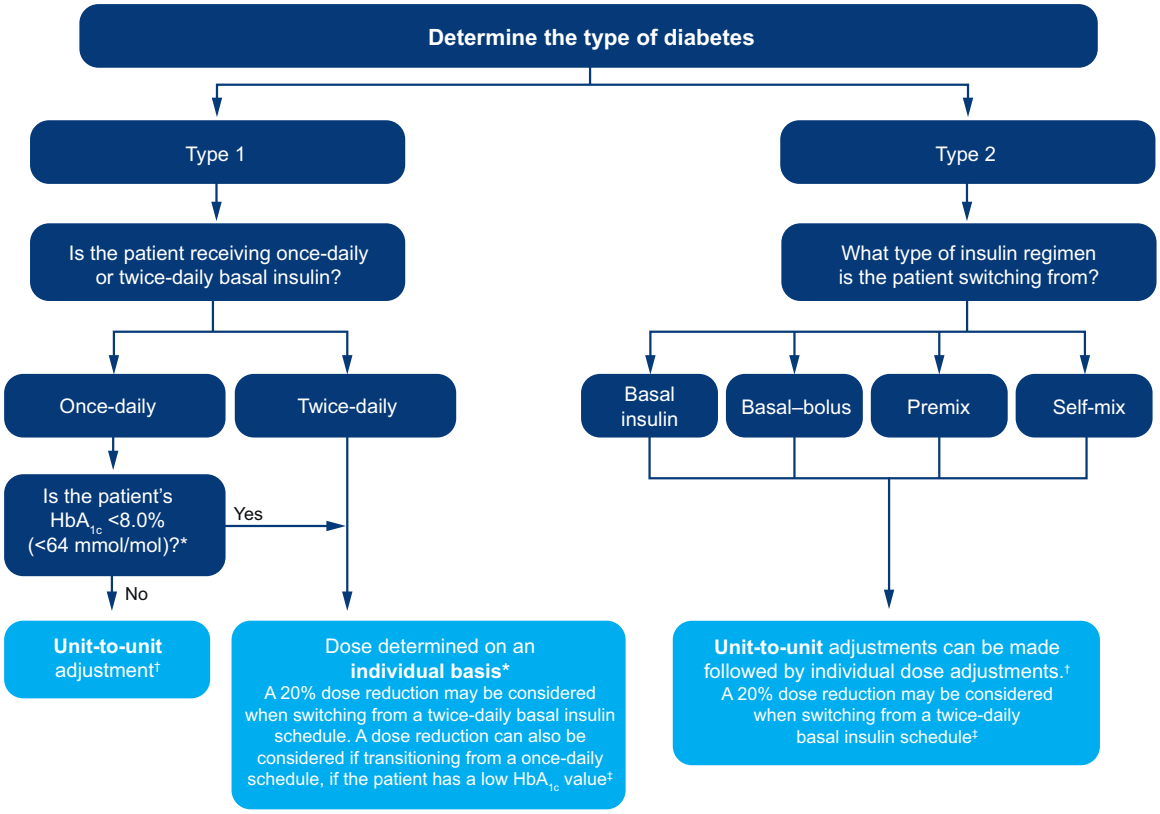

Fig. 3 – Dose adjustment algorithm providing guidance when switching to insulin degludec (IDeg) from other insulin-based products. * With further guidance from the patient's physician. † Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid- or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted. ‡ Based on individual glycaemic response and guidance from the patient's physician.

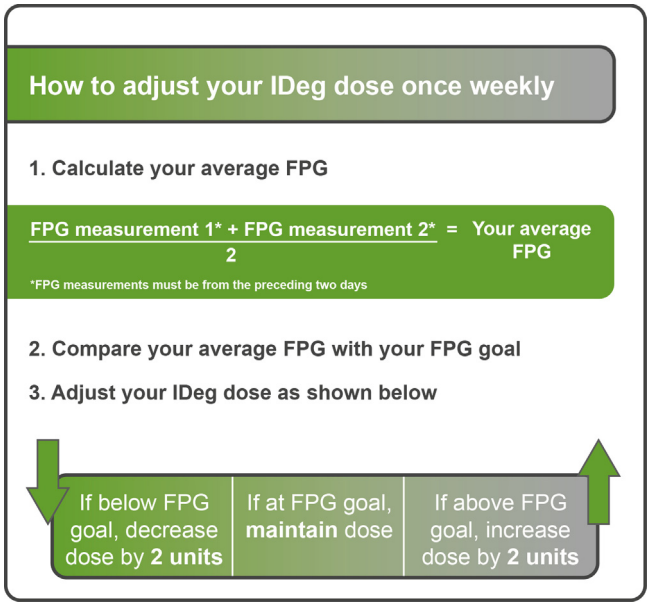

Fig. 4 – Dose titration recommendations for insulin degludec (IDeg). * FPG measurements must be from the preceding 2 days.

is ensured [34]. This concept was tested in patients with T1DM and T2DM, who were instructed to inject IDeg at forced intervals varying between 8 and 40 h, compared to IGlar, which was consistently injected at the same time every day [47,52]. The large variation in the injection time of IDeg did not compromise its efficacy or safety when compared to IGlar taken at the same time each day. The broader dosing window for IDeg can allow more flexibility in the timing of insulin administration. The daily IDeg dose can be either advanced or postponed in order to accommodate different patient lifestyles, with no negative impact on glycaemic control, provided a minimum interval of 8 h is maintained between IDeg injections [34]. It needs to be noted that back-to-back administrations of IDeg every 8 h will increase the risk of excess insulin and subsequent hypoglycaemia. A broader dosing window for insulin administration may allow patients to use a more convenient injection schedule without compromising either control of blood glucose levels or safety [52]. In the event of a missed dose, patients are advised to administer IDeg as soon as this is realised (unless this would result in a difference of less than 8 h between injections) and resume their usual once-daily dosing schedule [34].

4.4. *Administration of high insulin doses at lower volumes*

Many patients with T2DM may require larger insulin doses to overcome insulin resistance. The delivery of large insulin doses often requires the administration of an increased number of injections or high injection volumes which can cause substantial pain at the injection site [71]. As discussed, there are two different formulations of IDeg: 100 units/mL (U100) and 200 units/mL (U200), which have been shown to be bioequivalent [33]. The latter (IDeg U200) delivers half the volume of the U100 formulation and allows for administration of up to 160 units in one dose.

4.5. *Administration of insulin degludec in special populations*

IDeg is licensed for use in elderly patients (≥65 years of age) and is also suitable for use in patients with renal or hepatic impairment [34] as supported by clinical evidence, indicating that the pharmacokinetic characteristics of IDeg are preserved in these patient populations [30–32]. However, as recommended for other basal insulins [16,17], glucose-monitoring should be performed more frequently in these specific patient populations [34]. The safety and efficacy of IDeg in children and adolescents <18 years of age are currently being established [72]; in addition, there is currently no clinical experience with the use of IDeg in pregnant women [34].

5. Conclusions

IDeg is a new basal insulin with an ultra-long duration of action that exceeds 42 h, with a flat and stable glucose-lowering effect and reduced within-subject variability, resulting in consistent 24-h basal insulin coverage from a once-daily injection. Clinical evidence from a large phase 3a clinical trial programme in patients with T1DM and T2DM with a treat-to-target design have demonstrated that IDeg provides effective glycaemic control, similar to that observed with IGlar, but with lower rates of hypoglycaemia, in particular nocturnal hypoglycaemia, although the rates of symptomatic hypoglycaemia were low with both basal insulins due to the exclusion of subjects with recurrent hypoglycaemia. The consistent 24-h glucose-lowering effect and the reduction in hypoglycaemia that may be a result of low within-subject variability in FPG levels with IDeg, allow a broader, more flexible dosing window compared to other basal insulins, without compromising glycaemic control or safety. This flexibility in dose timing combined with an effective once-daily administration makes IDeg a less restrictive and more convenient basal insulin treatment option for both patients with T1DM and T2DM. IDeg is available in a U200 formulation (in addition to U100), which provides an option for large insulin doses to be administered at lower volumes. In addition, the availability of IDeg in combination with IAsp or liraglutide offer further potential for improved glycaemic control and a reduced number of daily injections for patients.

Overall, the clinical benefits of tight glycaemic control, reduced nocturnal hypoglycaemia and a more flexible treatment regimen associated with IDeg may help to overcome the barriers associated with initiation of basal insulin therapy and address the current unmet needs. By offering a basal insulin with a more flexible treatment schedule, as desired by the patient, IDeg may improve treatment adherence leading to better long-term clinical outcomes in patients with T1DM and T2DM.

Conflict of interest statement

JV has served on advisory boards and received support for research and attendance for national and international educational meetings and honoraria for lecturing from Novo Nordisk, Lilly, Sanofi, MSD, Takeda, Novartis and Abbott. AM has served on advisory boards and received speaker fees from Novo Nordisk, Sanofi, Novartis, Lilly, MSD, Boehringer Ingelheim, Bristol Myers Squibb and AstraZeneca. He has conducted clinical trials for Novo Nordisk, Sanofi, MSD and Boehringer Ingelheim. LM has performed research, served on advisory boards or provided consultation for Novo Nordisk, Sanofi, Halozyme Therapeutics, Boehringer Ingelheim, Pfizer and MannKind. ME has served as an advisory panel member for Novo Nordisk, Novartis, MSD and Sanofi, and received research support from Novo Nordisk. LLH has served on advisory boards and provided consultation for Novo Nordisk, and received lecture fees from Novo Nordisk, Sanofi, Bayer, MSD and Lilly. SH has received funding for research from Sanofi, Novo Nordisk, Janssen and AstraZeneca. He has served on advisory boards and provided consultation for Novo Nordisk, BI/Lilly, AstraZeneca-BMS, Sanofi, Merck, and Janssen. JLG has received grants and/or research support from Boehringer Ingelheim, Eli Lilly, GSK, Mannkind Corporation and Novo Nordisk. He has also provided consultation or served as a member of scientific advisory panels and speaker bureaux for Boehringer Ingelheim, Eli Lilly and Novo Nordisk. BC has served on advisory panels for Eli Lilly, Genfit, Novo Nordisk

and Sanofi and received grants/research support from Novo Nordisk and Sanofi. MR has served as a speaker for Novo Nordisk, Sanofi, Novartis, AstraZeneca, Bristol Myers Squibb and Eli Lilly. He has also served as an advisory board member for Novo Nordisk, AstraZeneca-BMS and Sanofi.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2015.04.002.

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