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SYSTEMATIC REVIEWS AND META-ANALYSES

Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials☆

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Abstract *Background and aims:* Basal insulin analogues have a reduced risk of hypoglycaemia compared with NPH insulin, but hypoglycaemia still remains a major impediment to achieving recommended fasting plasma glucose (FPG) targets in patients with diabetes. Insulin degludec (IDeg) is a new basal insulin that forms soluble multihexamers after subcutaneous injection resulting in an ultra-long duration of action and stable glucose-lowering effect. The aim of this analysis was to compare the effect of IDeg on FPG and nocturnal confirmed hypoglycaemia as compared to insulin glargine (IGlar).

Methods and results: Data were included from seven phase 3a, randomised, open-label, treat-to-target clinical trials in which once-daily IDeg was compared with once-daily IGlar. Two trials included a total of 957 patients with type 1 diabetes (T1D) and five trials included a total of 3360 patients with type 2 diabetes (T2D); all trials were 26 or 52 weeks in duration. Confirmed hypoglycaemia was defined as plasma glucose <3.1 mmol/L or severe episodes requiring assistance, and nocturnal hypoglycaemia occurred between 00:01 and 05:59. In all trials, the mean end-of-trial FPG was lower for IDeg than IGlar, reaching statistical significance in three trials. Similarly, IDeg was associated with a lower rate of nocturnal confirmed hypoglycaemia vs. IGlar, which was statistically significant in three trials, regardless of type of diabetes or background therapy.

Conclusion: This analysis shows that the lower rate of nocturnal confirmed hypoglycaemia seen with IDeg relative to IGlar is accompanied by a reduced mean FPG, in particular in patients with T2D.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FPG, fasting plasma glucose; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; LOCF, last observation carried forward; NPH, neutral protamine Hagedorn; OD, once daily; PPG, postprandial glucose; PYE, patient year of exposure; RR, rate ratio; T1D, type 1 diabetes; T2D, type 2 diabetes.

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Introduction

Despite the well-established efficacy of insulin, the burden and fear of hypoglycaemia associated with insulin treatment remains a major barrier to patients achieving the recommended glycaemic targets [1]. This can result in suboptimal glycaemic control and, in patients with type 2 diabetes (T2D), in delayed initiation of insulin [2,3] and increased risk of developing diabetic complications. The basal insulin analogues insulin glargine (IGlar) and insulin detemir (IDet) have helped patients with type 1 diabetes (T1D) and T2D to achieve improved glycaemic control due to a reduced risk of hypoglycaemia compared to neutral protamine Hagedorn (NPH) insulin [4,5]. The pharmacokinetic and pharmacodynamic properties of IGlar and IDet, however, may be suboptimal due to within-patient variability, and periods of hyper- and hypoglycaemia [6]. Furthermore, the duration of action may not be sufficient for once-daily dosing in all patients [7,8].

Insulin degludec (IDeg) is a new basal insulin with a novel mechanism of protraction, resulting in an ultra-long duration of action (>42 h) and a half-life of ~25 h [9–11]. Following subcutaneous injection, IDeg hexamers associate to form a depot of soluble multihexamers, from which monomers slowly and continuously enter the circulation [10,12]. This creates a flatter, more stable pharmacokinetic and pharmacodynamic profile, resulting in four-times less within-patient variability compared with IGlar [13]. The BEGIN clinical trial programme investigated the efficacy and tolerability of IDeg across the spectrum of diabetes care, including patients with T1D, patients with insulin-treated T2D and insulin-naïve patients with T2D, with reduction in HbA_{1c} at end-of-trial as the primary endpoint. Results of these trials have been published previously, showing that IDeg is non-inferior to IGlar with respect to HbA_{1c} lowering, across patient populations [14–20]. Moreover, in a pre-planned meta-analysis (discussed with the regulatory authorities) individual patient-level data from the trials were pooled, so that they could be analysed as insulin-naïve T2D, all T2D, all T1D, and T1D and T2D combined. Results showed that the rates of confirmed and nocturnal confirmed hypoglycaemia were significantly lower in insulin-naïve and all T2D populations, and nocturnal confirmed hypoglycaemia was significantly lower in T1D [21]. Despite the treat-to-target design of the trials, a lower rate of nocturnal confirmed hypoglycaemia may represent an opportunity for achieving better fasting plasma glucose (FPG) levels.

HbA_{1c} is a composite endpoint dependent upon both post-prandial glucose (PPG) and FPG levels. Since the treat-to-target design of the trials resulted in similar HbA_{1c} reductions, the question could arise as to whether the lower rates of hypoglycaemia seen with IDeg were accompanied by higher FPG and/or PPG values, or whether aiming for lower PG targets might diminish the hypoglycaemia benefit observed with IDeg. We therefore performed this exploratory *post hoc* meta-analysis of nocturnal confirmed hypoglycaemia and FPG levels in patients treated with IDeg or IGlar, in order to address the clinical dilemma of aiming for better glycaemic control vs. increasing the risk of hypoglycaemia.

Methods

This *post hoc* meta-analysis included seven phase 3a, randomised, open-label, parallel, treat-to-target clinical trials in which once-daily (OD) IDeg was compared with OD IGlar (two in T1D and five in T2D) over 26 or 52 weeks. Data from the 'forced flexible' dosing arms in two trials were not included in this analysis as these extreme dosing interval regimens do not represent the recommended use of IDeg in clinical practice and may confound the results [17,18]. In all trials, insulin doses were titrated to achieve pre-breakfast self-measured plasma glucose levels of 3.9–4.9 mmol/L (70–90 mg/dL), using the same titration guideline for both IDeg and IGlar [14–20].

Mean FPG and the estimated treatment difference in FPG reduction at the end of the titration period, during the maintenance period and at end-of-trial were analysed. Similarly, the rate (in episodes per patient year of exposure [PYE]) and rate ratio of nocturnal confirmed hypoglycaemia at the end of the titration period, during the maintenance period and end-of-trial were analysed. The titration period was defined as the first 15 weeks of each trial, when active insulin dose titration took place. The maintenance period was defined as week 16 until the end of treatment, when stable glycaemic control and insulin dose had usually been achieved. Results for the titration and maintenance periods were analysed separately. Confirmed hypoglycaemia was defined as plasma glucose <3.1 mmol/L (56 mg/dL) or severe episodes requiring third-party assistance. Confirmed or severe hypoglycaemic episodes occurring between 00:01 and 05:59 inclusive were classified as nocturnal. The proportion of patients reaching FPG target and those doing so without nocturnal confirmed hypoglycaemia were also analysed for the four basal-oral therapy trials (patients were insulin-naïve in three out of four trials) [22].

Statistics

Post-baseline missing values were imputed using last observation carried forward (LOCF). Change in FPG was analysed using analysis of covariance (ANCOVA) with fixed factors for treatment, sex, region, and anti-diabetic therapy at screening, and with age and baseline value as covariates. In the FPG meta-analyses, the model also included trial as a fixed factor. Treatment differences were reported with 95% confidence interval (CI), for each trial and for the following patient populations: all T2D, all T1D and T1D + T2D combined. The patient-level meta-analysis of rate of nocturnal confirmed hypoglycaemia was performed as described in Ratner et al. [21]. Rates of hypoglycaemia were analysed using a negative binomial regression model using a log-link and with trial, treatment, sex, region and antidiabetic therapy at screening as fixed effects, age as covariate and logarithm of the exposure time as an offset. Treatment differences were reported as estimated rate

ratios (RRs) of IDeg/IGlar, with 95% CI, for each trial and for the following patient populations: all T2D, all T1D and T1D and T2D combined. The composite endpoint of patients achieving FPG target without nocturnal confirmed hypoglycaemia was analysed *post hoc* using a logistic regression model with logit link, which included treatment, sex, trial, antidiabetic treatment at screening, and region as fixed factors, and age and baseline FPG as covariates. Statistical significance was defined as $p < 0.05$.

Results

An overview of the patients randomised and the design of the seven BEGIN phase 3a clinical trials included in this analysis is presented in Table 1. These trials illustrated that IDeg is non-inferior to IGlar with respect to HbA_{1c} lowering [14–20]. Due to the treat-to-target design of the trials, it was expected that there would be no difference in end-of-trial HbA_{1c} with IDeg and IGlar. For each of the seven trials, mean FPG levels were significantly or numerically lower with IDeg than with IGlar at end-of-trial, at the end of the titration period and during the maintenance period, with the difference reaching statistical significance in three trials at end-of-trial, four trials at the end of the titration period and one trial during the maintenance period (Table 2). All pooled patient populations (all T1D, all T2D, and T1D and T2D combined) also had lower mean FPG with IDeg compared with IGlar that reached statistical significance during the three periods, with the exception of the T1D pooled population during the maintenance period, which was numerically but not significantly lower.

At end-of-trial, treatment with IDeg resulted in rates of nocturnal confirmed hypoglycaemia that were numerically or significantly lower than those with IGlar, in all trials (significant in three trials). During the titration period, rates of nocturnal hypoglycaemia with IDeg were similar to or numerically lower than those with IGlar, and in one trial (3668) rates were significantly lower. During the maintenance period, rates were numerically or significantly lower with IDeg than with IGlar (significantly lower in three trials) (Table 3). The end-of-trial rates of nocturnal confirmed hypoglycaemia were significantly lower for the pooled T2D and pooled T1D + T2D, and numerically lower for the pooled T1D population. They were significantly lower for all pooled populations during the maintenance period and for the pooled T1D + T2D group during the titration period.

A separate analysis of the four basal insulin-oral therapy trials in patients with T2D showed that more patients achieved the FPG target of <5 mmol/L (90 mg/dL) with IDeg (40.9%) vs. IGlar (29.4%). Additionally, the probability of patients reaching the FPG target without experiencing nocturnal confirmed hypoglycaemia was significantly higher with IDeg (34.9% of patients) compared with IGlar (23.8% of patients): estimated odds ratio IDeg/IGlar: 1.82 $[1.49; 2.22]_{95\%\ CI}$, corresponding to an 82% increase in the odds (Fig. 1) [22].

Discussion

This analysis shows that the lower rate of nocturnal confirmed hypoglycaemia seen in patients treated with IDeg compared with IGlar was accompanied by greater reductions in FPG across the IDeg phase 3a clinical trials, as summarised in Fig. 2. The reduction in FPG with IDeg was statistically significantly or numerically lower compared with IGlar in all the individual trials, over different timescales (entire trial, titration period, maintenance period), and in the pooled populations (pooled T2D, pooled T1D, and pooled T1D + T2D). Therefore, it is conceivable that a lower risk of nocturnal hypoglycaemia may provide an opportunity to achieve a more physiological FPG level. In keeping with this hypothesis, the chance of achieving FPG target for patients with T2D on basal-oral therapy without nocturnal confirmed hypoglycaemia has been found to be significantly higher with IDeg vs. IGlar [22]. This is specifically relevant for the large number of patients with T2D initiating insulin therapy in primary care in order to intensify their previous treatment and achieve better glycaemic control.

Table 1 Overview of the seven clinical trials included in the meta-analysis.

Study ID	Patients	Trial duration (weeks)	Randomisation (IDeg:IGlar)	Number of patients randomised		Age (years, mean ± SD)	Gender (F/M, %)	Baseline FPG (mmol/L, mean ± SD)	
				IDeg	IGlar			IDeg	IGlar
BEGIN Once Long (3579)	T2D (insulin-naïve)	52	3:1	773	257	59.1 ± 9.8	38/62	9.6 ± 2.6	9.7 ± 2.6
BEGIN Low Volume (3672)	T2D (insulin-naïve)	26	1:1	230	230	57.5 ± 9.2	47/53	9.6 ± 2.9	9.7 ± 2.6
BEGIN Once Asia (3586)	T2D (insulin-naïve)	26	2:1	289	146	58.6 ± 9.9	46/54	9.6 ± 2.1	9.7 ± 1.9
BEGIN Flex (3668)	T2D	26	1:1	226	229	56.4 ± 9.6	50/50	8.8 ± 2.8	9.0 ± 2.8
BEGIN Basal-bolus Type 2 (3582)	T2D	52	3:1	755	251	58.9 ± 9.3	46/54	9.2 ± 3.0	9.2 ± 3.2
BEGIN Basal-bolus Type 1 (3583)	T1D	52	3:1	472	157	43.0 ± 13.6	41/59	9.1 ± 4.0	9.7 ± 4.4
BEGIN Flex T1 (3770)	T1D	26	1:1	165	164	43.7 ± 13.1	45/55	10.0 ± 4.0	9.7 ± 4.2

IDeg, insulin degludec; IGlar, insulin glargine; SD, standard deviation; T1D, type 1 diabetes; T2D type 2 diabetes.

Table 2 Mean fasting plasma glucose at the end of the trials and during the titration and maintenance periods.

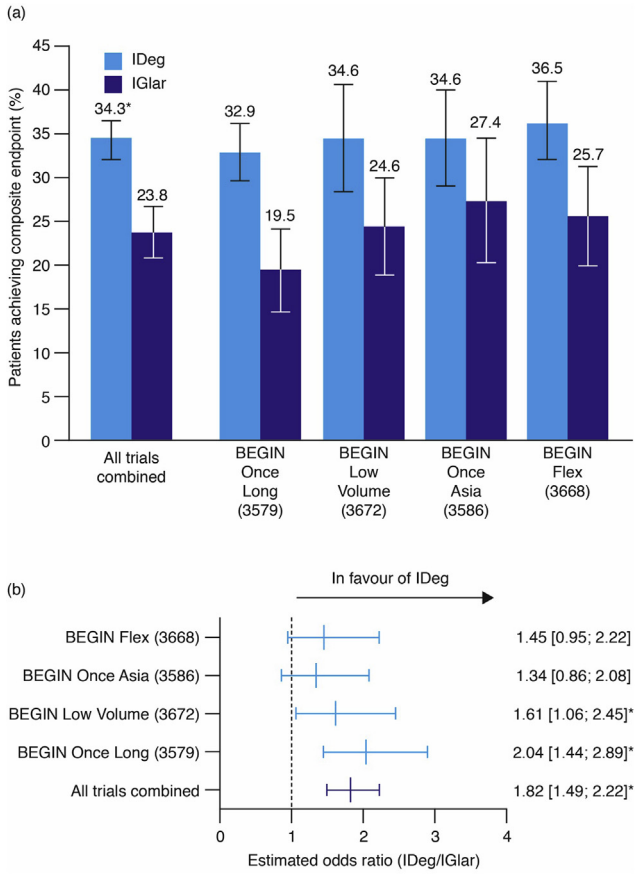
Study ID	Patients	End of trial			Titration period			Maintenance period		
		FPG (mmol/L, mean ± SEM)		Estimated treatment difference, IDeg − IGlar (mmol/L [95% CI])	FPG (mmol/L, mean ± SEM)		Estimated treatment difference, IDeg − IGlar (mmol/L [95% CI])	FPG (mmol/L, mean ± SEM)		Estimated treatment difference, IDeg − IGlar (mmol/L [95% CI])
		IDeg	IGlar		IDeg	IGlar		IDeg	IGlar	
BEGIN Once Long (3579)	T2D (insulin-naïve) $n = 1030$	5.9 ± 0.08 ($n = 769$)	6.4 ± 0.14 ($n = 257$)	−0.43 [−0.74; −0.13]*	6.2 ± 0.07 ($n = 773$)	6.6 ± 0.13 ($n = 257$)	−0.40 [−0.67; −0.13]*	5.6 ± 0.07 ($n = 685$)	6.1 ± 0.14 ($n = 226$)	−0.26 [−0.54; 0.02]
BEGIN Low Volume (3672)	T2D (insulin-naïve) $n = 460$	5.9 ± 0.20 ($n = 228$)	6.3 ± 0.20 ($n = 229$)	−0.42 [−0.78; −0.06]*	6.0 ± 0.13 ($n = 228$)	6.1 ± 0.12 ($n = 229$)	−0.15 [−0.49; 0.20]	5.7 ± 0.12 ($n = 206$)	6.1 ± 0.14 ($n = 210$)	−0.38 [−0.72; −0.04]*
BEGIN Once Asia (3586)	T2D (insulin-naïve) $n = 435$	5.5 ± 0.09 ($n = 289$)	5.7 ± 0.12 ($n = 146$)	−0.09 [−0.41; 0.23]	5.5 ± 0.09 ($n = 289$)	5.7 ± 0.13 ($n = 146$)	−0.21 [−0.51; 0.09]	5.4 ± 0.09 ($n = 261$)	5.6 ± 0.13 ($n = 139$)	−0.04 [−0.33; 0.25]
BEGIN Flex (3668)	T2D $n = 455$	5.8 ± 0.16 ($n = 228$)	6.2 ± 0.16 ($n = 228$)	−0.38 [−0.79; 0.04]	6.0 ± 0.14 ($n = 228$)	6.5 ± 0.16 ($n = 230$)	−0.45 [−0.84; −0.06]*	5.6 ± 0.14 ($n = 206$)	5.9 ± 0.13 ($n = 208$)	−0.10 [−0.42; 0.23]
BEGIN Basal-bolus Type 2 (3582)	T2D $n = 1006$	6.8 ± 0.09 ($n = 743$)	7.1 ± 0.17 ($n = 248$)	−0.29 [−0.65; 0.06]	6.9 ± 0.09 ($n = 744$)	7.3 ± 0.18 ($n = 248$)	−0.34 [−0.70; 0.02]	6.7 ± 0.09 ($n = 677$)	7.0 ± 0.17 ($n = 233$)	−0.19 [−0.54; 0.15]
BEGIN Basal-bolus Type 1 (3583)	T1D $n = 629$	7.8 ± 0.17 ($n = 472$)	8.3 ± 0.34 ($n = 155$)	−0.33 [−1.03; 0.36]	7.6 ± 0.16 ($n = 472$)	8.7 ± 0.29 ($n = 157$)	−1.01 [−1.63; −0.39]*	7.8 ± 0.18 ($n = 448$)	8.3 ± 0.34 ($n = 148$)	−0.30 [−1.02; 0.41]
BEGIN Flex T1 (3770)	T1D $n = 329$	7.4 ± 0.27 ($n = 165$)	8.4 ± 0.28 ($n = 163$)	−0.97 [−1.74; −0.20]*	7.2 ± 0.30 ($n = 165$)	8.4 ± 0.30 ($n = 164$)	−1.17 [−2.01; −0.33]*	7.3 ± 0.26 ($n = 148$)	8.3 ± 0.29 ($n = 155$)	−0.72 [−1.48; 0.03]
Overall	T2D pooled	–	–	−0.33 [−0.49; −0.17]*	–	–	−0.32 [−0.48; −0.17]*	–	–	−0.21 [−0.36; −0.06]*
Overall	T1D pooled	–	–	−0.61 [−1.13; −0.10]*	–	–	−1.10 [−1.60; −0.60]*	–	–	−0.48 [−1.00; 0.05]
Overall	T1D + T2D pooled	–	–	−0.40 [−0.57; −0.23]*	–	–	−0.50 [−0.66; −0.34]*	–	–	−0.27 [−0.43; −0.10]*

*$p < 0.05$. Missing values are imputed using last observation carried forward (LOCF). IDeg, insulin degludec; IGlar, insulin glargine; SEM, standard error of the mean; T1D, type 1 diabetes; T2D type 2 diabetes.

Table 3 Nocturnal confirmed hypoglycaemia risk at the end of trial and during the titration and maintenance periods.

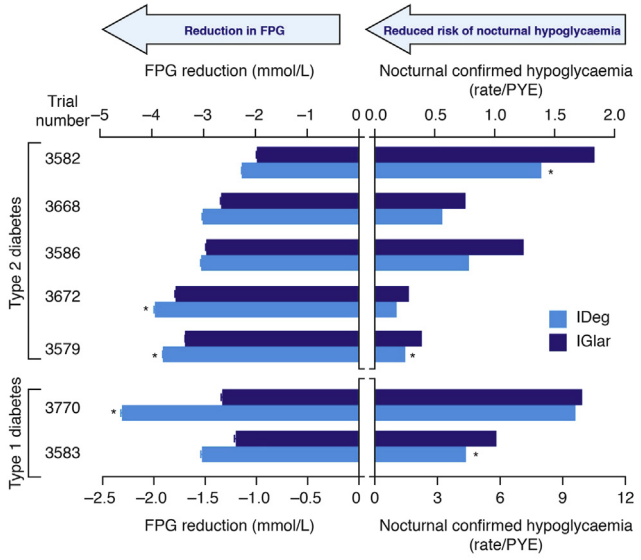
Study ID	Patients	End of trial						Titration period						Maintenance period					
		Exposure weeks	Episodes (% patients)		Rate per PYE		Rate ratio, IDeg vs. IGlar [95% CI]	Exposure weeks	Episodes (% patients)		Rate per PYE		Rate ratio, IDeg vs. IGlar [95% CI]	Exposure weeks	Episodes (% patients)		Rate per PYE		Rate ratio, IDeg vs. IGlar [95% CI]
			IDeg	IGlar	IDeg	IGlar			IDeg	IGlar	IDeg	IGlar			IDeg	IGlar	IDeg	IGlar	
BEGIN Once Long (3579)	T2D	52	169 (13.8)	84 (15.2)	0.25	0.39	0.64 [0.42; 0.98]*	16	362 (24.7)	136 (27.9)	0.23	0.16	1.26 [0.57; 2.78]	36	118 (12.3)	72 (14.2)	0.27	0.50	0.51 [0.32; 0.81]*
BEGIN Low Volume (3672)	T2D	26	19 (6.1)	30 (8.8)	0.18	0.28	0.64 [0.30; 1.37]	16	11 (4.4)	12 (3.9)	0.17	0.18	0.97 [0.37; 2.50]	10	8 (2.9)	18 (7.1)	0.21	0.45	0.45 [0.17; 1.19]
BEGIN Once Asia (3586)	T2D	26	104 (20.4)	87 (24.0)	0.78	1.24	0.62 [0.38; 1.04]	16	71 (15.5)	54 (19.2)	0.85	1.23	0.68 [0.39; 1.19]	10	33 (10.7)	33 (12.2)	0.66	1.25	0.52 [0.27; 1.01]
BEGIN Flex (3668)	T2D	26	67 (13.5)	58 (10.6)	0.56	0.75	0.64 [0.37; 1.11]	16	24 (6.6)	44 (14.8)	0.37	0.66	0.51 [0.27; 0.95]*	10	34 (7.8)	35 (11.5)	0.88	0.89	0.82 [0.39; 1.74]
BEGIN Basal-bolus Type 2 (3582)	T2D	52	930 (39.6)	422 (47.4)	1.39	1.84	0.75 [0.58; 0.99]*	16	362 (24.7)	136 (27.9)	1.63	1.81	0.86 [0.62; 1.18]	36	568 (29.7)	286 (37.0)	1.27	1.86	0.72 [0.51; 1.00]*
BEGIN Basal-bolus Type 1 (3583)	T1D	52	1905 (72.2)	845 (74.0)	4.41	5.86	0.75 [0.59; 0.96]*	16	769 (54.4)	333 (59.1)	5.43	7.20	0.78 [0.60; 1.02]	36	1136 (60.3)	512 (64.2)	3.91	5.22	0.73 [0.56; 0.96]*
BEGIN Flex T1 (3770)	T1D	26	453 (67.7)	732 (73.3)	9.61	9.96	0.99 [0.72; 1.34]	16	517 (68.5)	497 (65.2)	10.69	10.23	1.05 [0.77; 1.44]	10	215 (48.6)	285 (49.7)	7.72	9.51	0.83 [0.55; 1.25]
Overall	T2D pooled						0.68 [0.57; 0.82]*						0.81 [0.64; 1.02]						0.62 [0.49; 0.78]*
Overall	T1D pooled						0.83 [0.69; 1.00]						0.88 [0.72; 1.08]						0.75 [0.60; 0.94]*
Overall	T1D + T2D pooled						0.75 [0.65; 0.85]*						0.86 [0.74; 1.00]*						0.68 [0.58; 0.80]*

*Significantly lower risk based on the 95% confidence intervals.
IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient years of exposure; T1D, type 1 diabetes; T2D type 2 diabetes. The number of nocturnal confirmed hypoglycaemic episodes within trial are analysed using a Negative Binomial Regression Model using a log-link and with trial, treatment, sex, region and anti-diabetic therapy at screening as fixed effects, age as covariate and logarithm the exposure time as offset.



Analysed using a logistic regression model with logit link. *p<0.05 in favour if IDeg. The model included treatment, sex, trial, antidiabetic treatment at screening, and region as fixed factors, and age and baseline FPG as covariates. IDeg, insulin degludec; IGlar, insulin glargine. Error bars are 95% confidence intervals.

Figure 1 Patients on basal-oral therapy achieving FPG target without nocturnal confirmed hypoglycaemia [22]. a. Percent of patients; b. Estimated odds ratio.



FPG, fasting plasma glucose; IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient years of exposure
*p<0.05 for IDeg versus IGlar. Error bars are SEM.

Figure 2 Change from baseline in FPG and rate of nocturnal confirmed hypoglycaemia at the end of the trials.

The pre-specified hypoglycaemia meta-analysis showed that the rate ratio for overall confirmed hypoglycaemia was lower with IDeg vs. IGlar [21]. However, as the difference was not significant in all the individual trials, one could argue that the rate of nocturnal confirmed hypoglycaemia was offset by increased day-time hypoglycaemia. This was directly investigated in two studies showing no significant difference in the rate of diurnal confirmed hypoglycaemia in patients with T1D or T2D [14,16]. Further meta-analyses confirmed that the reduction in nocturnal confirmed hypoglycaemia was not accompanied by increased rates of daytime confirmed hypoglycaemia in pooled T1D, pooled T2D and pooled insulin-naïve T2D [23]. The trial protocol for insulin-experienced patients required that those who were switching from twice-daily to once-daily insulin dosing administer their total pre-trial basal insulin dose in the IDeg arm, but reduce the dose by 20–30% in the IGlar arm (as per the prescribing information). This could have biased the hypoglycaemia rates in favour of IGlar during the first weeks of the trials as the dose was lower [16]. However, the IGlar dose subsequently increased as patients titrated to target and end-of-trial doses for pooled T1D patients were higher with IGlar compared with IDeg [23].

Despite clinical guidelines recommending the attainment of glycaemic targets of HbA_{1c} < 7.0% and FPG < 7.2 mmol/L [24] many patients are unable to reach these targets. This may in part be due to the fear of hypoglycaemia. Traditionally, it has been thought that although lower FPG results in improved glycaemic control, this could be achieved at the expense of an unacceptably high risk of nocturnal confirmed hypoglycaemia [1,25]. The BEGIN trial programme, which had an ambitious treatment target (FPG 3.9–4.9 mmol/L), suggests that the flat and stable profile of IDeg, coupled with low within patient variability, may offer a better opportunity to achieve such a goal [9,13]. This could encourage healthcare professionals to attempt to achieve normoglycaemia in their patients with T1D and T2D, with a reduced risk of nocturnal hypoglycaemia.

The lack of a significant difference in HbA_{1c} may appear at variance with attainment of a lower FPG. However, because of the treat-to-target nature of the study and the primary endpoint of non-inferiority, a difference in HbA_{1c} was not expected. It is for this very reason that demonstrating a moderate but significant reduction in FPG while using a treat-to-target treatment strategy becomes of particular interest. Moreover, physicians should be aware that the benefit of a greater FPG reduction could be offset by changes in diurnal/post-prandial plasma glucose profiles, which are largely dependent on oral agents or pre-prandial short-acting insulin administration.

Finally, these data should be placed in the context of clinical practice, where additional barriers (such as fear of injections, difficulty in adhering to strict treatment regimens) hamper insulin therapy optimisation [2,26]. It will be of interest to observe to what extent the potential of IDeg observed in randomised, controlled clinical trials will translate into clinical practice. This is of particular interest because a limitation of this study is the rates of

hypoglycaemia recorded in the trials appear to be lower than those seen in clinical practice, as patients with recurrent severe hypoglycaemia were excluded. Conversely, the reporting of hypoglycaemic events is likely to be more accurate in controlled clinical trials than clinical practice where hypoglycaemia is less commonly reported and discussed with the doctor [27]. It is acknowledged that some hypoglycaemic episodes are asymptomatic, as continuous glucose monitoring was not conducted during this trial programme asymptomatic episodes of nocturnal hypoglycaemia would not be identified. An additional limitation is the open-label nature of all the trials (due to the use of different injection devices), however, the inclusion of only hypoglycaemia that was accompanied by a PG reading or requiring assistance should make any bias negligible.

The reduced risk of nocturnal hypoglycaemia and better FPG observed with IDeg may result in additional positive features of this long-acting insulin analogue, including greater flexibility as supported by the 'forced flexible' dosing regimen showing that glycaemic control and safety were not compromised when IDeg was dosed at extreme intervals [17,18]. The ability to dose IDeg with some flexibility has been reflected in the prescribing information [28] and may enable patients some respite from the strict regimens requiring dosing at the same time each day. Furthermore the results from a previous meta-analysis of data from patients on basal-oral therapy showed an improvement in health-related quality of life was seen in patients taking IDeg compared with IGlar, assessed using the Short-form 36 v2 questionnaire and EQ-5D health utility scale [29,30]. It has also been shown that frequency of hypoglycaemia and perceived poor metabolic control are negatively associated with quality of life [31].

In conclusion, this exploratory *post hoc* meta-analysis shows that the lower rate of nocturnal confirmed hypoglycaemia seen with IDeg relative to IGlar is accompanied by reduced FPG, in particular in patients with T2D. This analysis suggests that IDeg may help patients to reach FPG target with a reduced risk of nocturnal confirmed hypoglycaemia.

Disclosures

DRJ serves on an advisory board and is a consultant for Eli Lilly and Novo Nordisk, has received research support from Eli Lilly, Novo Nordisk, Boehringer Ingelheim and Serono, and has participated in speakers bureaus for Eli Lilly, Novo Nordisk and Sanofi. M-AG and MN are employees of Novo Nordisk. SDP serves on an advisory board for Sanofi, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Merck, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, Takeda and Intarcia. He is a consultant for Roche and has participated in speakers bureaus for Novartis, Merck and Sanofi. All authors (including the authors from Novo Nordisk) were involved in the design, interpretation, writing and approval of this manuscript. Novo Nordisk was responsible for the data analysis.

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