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Understanding the Safety of the New Ultra Long Acting Basal Insulin

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Abstract

Hypoglycaemia is a key safety concern in diabetes management. It is potentially dangerous and the fear of

may generate adverse effects and disease complications, will compromise the quality of life and will substantially increase the economic burden of treatment budged. Today, treat to target clinical trial designs are mandate for clinical development of any newer anti-diabetic medication. While similar glycaemic targets are expected to be achieved by test and comparator, the newer molecules are definitely expected to show advantage over standard comparator in terms of reduction in frequency and severity of hypoglycaemia. An ultra-long acting basal analogue insulin degludec (IDeg), has been recently approved for the treatment of type 2 and type 1 diabetes mellitus (T2DM and T1DM). The pooled patient-level data for self-reported hypoglycaemia from seven phase 3a trials with IDeg has shown significantly lower episodes of nocturnal confirmed and numerical low overall confirmed hypoglycaemia with IDeg, compared to Insulin glargine (IGlar), which was more pronounced during maintenance phase of treatment in all populations. The most plausible explanation being that, the flat peakless profile of IDeg with least glycaemic variability leads to less hypoglycaemia and adds to the safety profile of this ultra-long acting insulin. The real life practice will further validate the findings of clinical trials.

Introduction

Hypoglycaemia can cause recurrent morbidity for patients with diabetes. The cumulative effects and clinical consequences of multiple severe episodes over a lifetime of insulin therapy may be substantial. The short and long term complications induced by hypoglycaemia include neurologic damage, trauma, cardiovascular events and sudden death.1 It is highly desirable that newer modes of treatment of diabetes offer advantage in terms of reducing episodes of hypoglycaemia to a minimum. This article will focus on the incidence of hypoglycaemia in T2DM and T1DM patients, its clinical symptoms and consequences, impact on health-related quality of life, economic burden and results of phase 3a trials of IDeg in terms of overall confirmed and nocturnal confirmed hypoglycaemia along with implications of this data on clinical diabetology practice.

Incidence of Hypoglycaemia in Type 2 and Type 1 Diabetes

The risk of hypoglycaemia is almost always present in diabetology practice. This may be due to excessive exogenous

Between 7 and 25% of patients with T2DM using insulin, experience at least one severe episode annually2 while the reported annual prevalence of severe hypoglycaemia in unselected populations of patients with T1DM is 30 40%. A metanalysis of randomised controlled clinical trials on efficacy of insulin analogues in achieving the haemoglobin A1c target of < 7%in type 2 diabetes has shown that compared with basal insulin, biphasic insulin is found to be associated with a significant increase in hypoglycaemic events (0.34 mean events/patient/30 days), no mean difference in the incidence of hypoglycaemia events/patient/30 days between biphasic and prandial, a non-significant increase in the incidence of hypoglycaemia with prandial compared to basal insulin and no difference in incidence of hypoglycaemia between biphasic and basal bolus.3 Another meta-analysis has reported, incidence of 47.9 % and 44.2 % of overall hypoglycaemia and 11% and 17% of nocturnal hypoglycaemia with BiAsp 30 and biphasic human insulin respectively.4 Nocturnal hypoglycaemia is reported to be 50% lower with detemir at bedtime than with NPH at bedtime, and 87% lower with detemir in the morning than with bedtime NPH.5 The risk of hypoglycaemia at any time of day is 47% lower and nocturnal hypoglycaemia 55% lower with insulin detemir than with NPH.6 Timing of administration of glargine in the morning or evening does not result in any significant difference in rates of nocturnal hypoglycaemia.7 Patients with type 2 diabetes using insulin for > 5 years have reported a prevalence of mild and severe hypoglycaemia similar to that for patients with type 1 diabetes of short duration, supporting the notion that risk of hypoglycaemia rises with increasing duration of therapy.8 Though there are reports from India on overcoming the barrier of hypoglycaemia in routine diabetes practice by integrating telemedicine and decision support system, it requires enormous resources to maintain the system.9

Clinical Symptoms and Consequences

Symptoms of hypoglycaemia can be divided into three broad groups: autonomic (sweating, pounding heart, shaking, hunger, nausea, headache, dizziness, feeling unwell, apprehension, dry mouth, and weakness), neuroglycopenic (confusion, odd behaviour, speech difficulty, incoordination, tingling around lips, and difficulty concentrating, and general perhaps due to glucagon release.10 In patients with diabetes of long duration and having underlying vascular disease, release of potent vasoactive substances in response to hypoglycaemia could aggravate existing vascular problems and increase risk of acute macrovascular events.11 Evidence suggests that 4 10% of deaths of patients with

characterised by symptoms such as disturbed sleep, nightmares and headaches on waking up.

Effect of Hypoglycaemia on Adherence of Insulin Therapy

Fear of hypoglycaemia may predispose patients to undesirable behaviours (such as decreasing insulin dose) that compromise glycaemic control and increase the risk of other complications of diabetes.13 Study by Leiter et al has reported that 43%of patients modify their insulin dose after mild or moderate hypoglycaemic episodes.14 GAPP study also has shown higher insulin omission/non-adherence among patients with frequent hypoglycaemia.15

Impact of Hypoglycaemia on Health Related Quality of Life

Hypoglycaemia has a large impact on patient lives, and quality-of-life decreases with increasing frequency and severity of hypoglycaemic events13. In patients with type 2 diabetes, those who have had at least one hypoglycaemic episode during the previous year, have lower scores for physical health and mental health compared to people not reporting hypoglycaemia.16 Patients report that both singular severe and non-severe events affect their health-related quality of life,17 although severe events have an incrementally larger impact.18 This effect also increases with the frequency of non-severe events.19 On an average, it takes half a day to recover from a non-severe hypoglycaemic event.20 Hypoglycaemia impacts not only persons with diabetes, but their family members as well.21

Economic Impact of Hypoglycaemia

Though there is lack of pharmaco economic data from India on this aspect, studies in other parts of the world suggest that non-severe hypoglycaemic events are found to be associated with substantial economic consequences for employers and patients due to lost productivity.22 Patients with type 2 diabetes and hypoglycaemia have significantly higher diabetes-related health care costs than those without hypoglycaemia,23 the mean attributable total cost of a hypoglycaemic event for patients newly initiated on an intermediate- or long-acting insulin has been reported as $1087.24 In case of severe hypoglycaemia, hospitalisation cost and in case of non-severe hypoglycaemia economic

strips, lancets, and use of bus, taxi other transports etc.

Data on Hypoglycaemia from Phase 3a Begin Programme of IDEG

The BEGIN® programme was a comprehensive series of phase 3a trials using IDeg once daily (OD) in type 1 and type 2 diabetes. There were a total of nine trials, three in type 1 diabetes and six in type 2 diabetes, of which six trials included subjects with type 2 diabetes, insulin naive or on insulin at baseline to evaluate several regimens - basal oral therapy, basal bolus therapy, basal versus oral (sitagliptin) therapy and flexible dosing. All trials were randomised, controlled, open-label, treat-to-target, multi-centre, multinational in nature. As mentioned by Shah et al earlier that these trials were designed to prove non inferiority with efficacy as primary outcome measure and hypoglycaemia as secondary outcome measure. BEGIN programme used a standardised algorithm for reporting hypoglycaemia (Figure 1) classified as confirmed if a plasma glucose measurement of 56 mg/dL (< 3.1 mmol/L) irrespective of any symptoms, or severe (i.e. assistance from another person is required) and nocturnal hypoglycaemia as episodes between 00h01 and 05h59 inclusively. Overall confirmed hypoglycaemia included both minor and severe hypoglycaemia.25 The cut-off level of 3.1mmol/l(56 mg/dL) was used and accepted as it gives fair balance between the glucose range where counter regulatory mechanisms step in, and the range where patients report symptoms, compared to higher cut-off values. A lower cut-off level also limits the number of false positive recordings, considering the FPG target of 4-5 mmol/l(72 90 mg/dl). This cut off level has been suggested by international regulatory authorities as well.

All descriptive statistics on hypoglycaemia and dose, used the safety analysis set (all patients receiving at least one dose of the IDeg or its comparator) while the analysis for significance used the full analysis set (all randomised patients). The treatment-emergent period was defined as on or after the first day of trial drug administration and up to and including 7 days after last trial drug administration. The regression model was adjusted for the trial, type of diabetes, anti-diabetes therapy, sex, geographical region and age. Significance was assessed for the 95% confidence interval (CI) values.20 The number of treatment-emergent hypoglycaemic episodes were analysed by using a negative binomial regression model. For each of the regimens (and type of diabetes) descriptive statistics (safety

numbers meeting an endpoint, results of statistical analysis were shown.

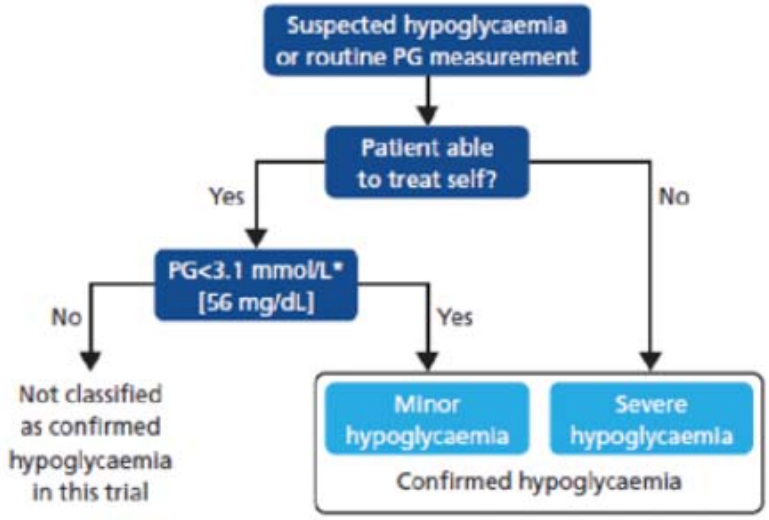


Fig. 1 : Hypoglycaemia algorithm in the BEGIN^Δ Programme

Table 1 : Hypoglycaemia with IDeg Therapy-

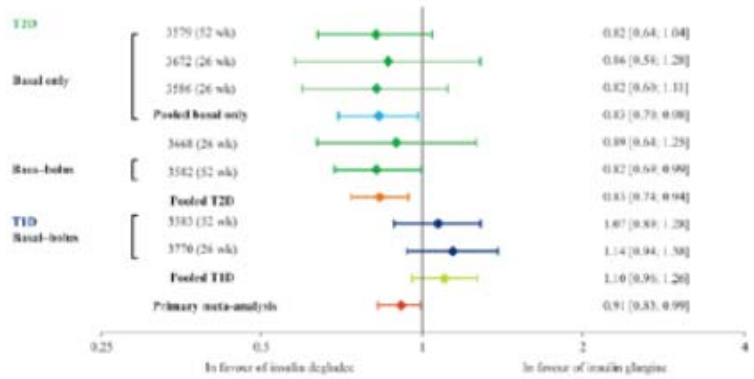
Study Name	No. of Patients	Study Duration	Mean end-of-study dose	Hypoglycaemia (no. of episodes per patient-year of exposure)		
				Overall	Severe	Nocturnal
Type 2						
BEGIN	IDeg (773)	52 weeks	0.59 U/kg	1.52	0.003**	0.25**
Once Long	IGlar (257)		0.60 U/kg	1.85	0.023 (-86%)	0.39 (-36%)
BEGIN	IDeg (744)	52 weeks	0.75 U/kg**	11.09**	0.06	1.39**
Basal Bolus T2	IGlar (248)		0.69 U/kg	13.63 (-18%)	0.05	1.84 (-25%)
BEGIN	IDeg Flex (230)	26 weeks	0.60 U/kg	3.6	No data	0.6
Flex T2	IDeg (226)		0.60 U/kg	3.6		0.6
	IGlar (229)		0.60 U/kg	3.5		0.8

Low Volume	IGlar (229)		0.60 U/kg	1.42		0.28
Type 1						
BEGIN	IDeg (472)	52 weeks	0.35 U/kg*	42.5	0.21	4.4**
Basal Bolus T1	IGlar (157)		0.39 U/kg	40.5	0.16	5.9 (-25%)
BEGIN	IDeg Flex (164)	26 weeks	0.77 U/kg#	82.4	0.3	6.2***
Flex T1	IDeg (165)		0.70 U/kg	88.3	0.4	9.6
	IGlar (161)		0.84 U/kg	79.7	0.5	10.0 (-37%)

*p < 0.0001, **p < 0.05, ***p < 0.01, # Basal + Bolus dose (Bolus: Insulin aspart); ^For the maintenance period of the trial (week 16 to end-of-trial, when insulin doses and glycaemic indicators appeared to have stabilised for most subjects),

Table 2 : Percentage reduction of overall and nocturnal confirmed hypoglycaemia with IDeg

Total treatment period		Maintenance period	
Overall		Overall	
Insulin-naïve T2D	-17%*	Insulin-naïve T2D	-28%*
Pooled T2D	-17%*	Pooled T2D	-25%*
Pooled T1D	+10%	Pooled T1D	+2%
T1D and T2D	-9%*	T1D and T2D	-16%*
Nocturnal		Nocturnal	
Insulin-naïve T2D	-36%*	Insulin-naïve T2D	-49%*
Pooled T2D	-32%*	Pooled T2D	-38%*
Pooled T1D	-17%	Pooled T1D	-25%*
T1D and T2D	-26%*	T1D and T2D	-32%*



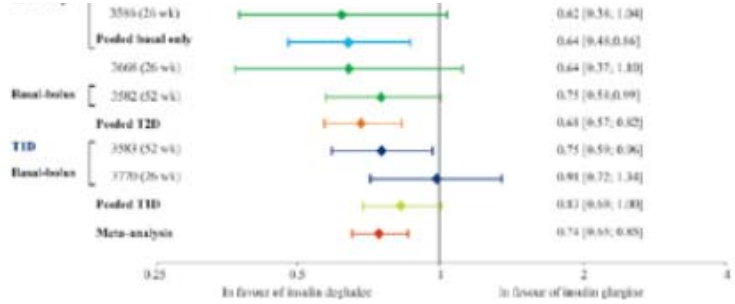


Fig. 2 : Pre-specified meta-analyses: overall confirmed hypoglycaemia (A) and nocturnal confirmed hypoglycaemia (B)

Hypoglycaemia with IDeg Therapy

BEGIN programme with IDeg included; Once Long, Basal Bolus T2, Flex T2, Once Asia and Low Volume studies with type 2 or type 1 diabetes subjects of age > 18 years (Table 1). In these trials,26 patients with history of more than one severe hypoglycaemic episode in last 12 months were excluded from both the groups as per the ADA clinical trials guidance. The reason for this exclusion criterion has been to ensure the safety of the patients. It is a general recommendation to individualise glycaemic targets for selected patient populations and less stringent goals should be set for patients with a history of severe hypoglycaemia. These patients are therefore not appropriate for a treat-to-target study with ambitious glycaemic targets of fasting blood glucose of > 70 to < 90 mg/dl. The details of inclusion and exclusion criteria's have been mentioned by Wangnoo et al earlier. Frequency of hypoglycaemic episodes has also been analysed in the maintenance phase (defined as period after stable glycaemic control and stable insulin dose has been achieved following active titration, i.e., 16 weeks onwards).

In Type 2 diabetes

BEGIN Once Long study with insulin naive patients {IDeg (N=773),IGlar (N=257)}reported statistically significant reduction of 86% in severe hypoglycaemia and 36% in nocturnal confirmed hypoglycaemia with same trend in

hypoglycaemia. There was numerical reduction of 18% in overall confirmed hypoglycaemia which was similar in two groups during the maintenance phase.27

BEGIN Basal Bolus type 2 study with patients previously exposed to insulin therapy {IDeg (N=744),IGlar (N=248)}showed that overall confirmed hypoglycaemia was 18% lower and confirmed nocturnal hypoglycaemia was 25% lower with IDeg compared to IGlar and both these values were statistically significant.28

BEGIN Flex T2 study included either insulin-naà¯ve patients receiving oral antidiabetic drugs (OADs) or patients previously on basal insulin ±OAD, {IDeg Flex (N=230), IDeg (N=226), IGlar (N=229)}. There was no statistically significant difference in overall hypoglycaemia, while numerical reduction of 23% in nocturnal hypoglycaemia was observed between IDeg OD Flex and IGlar OD arms.29

Another two studies with Insulin naive patients, BEGIN Once Asia30 {IDeg (N=289), IGlar (N=248)}and BEGIN Low volume31 {IDeg (N=228), IGlar (N=229)}with U200 preparation showed similar rates of overall confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia for both IDeg and IGlar during full trial period.

In Type 1 Diabetes

BEGIN Basal Bolus T1 study included adult subjects {(aged ≥18 years) IDeg (N=472), IGlar (N=157)} who had been diagnosed with type 1 diabetes mellitus for at least 1 year and had received any basal-bolus insulin therapy for at least 1 year before screening, Rates of overall confirmed hypoglycaemia were similar in the IDeg and IGlar groups and rate of nocturnal confirmed hypoglycaemia was 25% lower with IDeg than with Iglar which was statistically significant.32

BEGIN Flex T1 study was conducted with type 1 diabetes patients with same eligibility where confirmed hypoglycaemia rates were similar at weeks 26 and 52. There was statistically significant reduction in nocturnal confirmed hypoglycaemia with IDeg Forced-Flex vs IDeg by 37% and Vs IGlar by 40% at week 26 and 25% lower with IDeg Free Flex vs IGlar at week 52.33 Table 1 summarises number of episodes per patient-year of exposure for BEGIN trials mentioned above

Hypoglycaemia Meta-analysis25

Outcome rates in individual trials can fail to reach statistical significance due to limited statistical power. Meta-analysis makes it possible to compare outcomes across a number of trials. A prospectively planned meta-analysis of hypoglycaemic events was conducted with primary endpoint of overall confirmed hypoglycaemia that used patient-level data from all seven phase 3a studies in which IDeg OD was compared with IGlar OD. The meta-analysis showed that, for equal reductions in HbA1c, confirmed hypoglycaemia, and in particular nocturnal confirmed hypoglycaemia, occurred less frequently with IDeg OD than with IGlar OD. This finding was seen consistently in patients with T2DM, insulin-naà¯ve patients with T2DM and the pooled population of T2DM plus T1DM. This metaanalysis included 4330 subjects: 3372 with type 2 diabetes and 958 with T1DM. Hypoglycaemia occurred less frequently in patients with T2DM compared with T1DM. Differences in rates of confirmed hypoglycaemia with IDeg versus IGlar were as follows (Table 2).

In insulin-naà¯ve T2DM, pooled T2DM, Pooled T2DM and T1DM patients, reductions were consistently seen with IDeg versus IGlar in the rates of overall confirmed hypoglycaemia which was most pronounced during the maintenance phase after glycaemic control and stabilised dosing and in nocturnal confirmed hypoglycaemia as shown in Figure 2.

This meta-analysis confirms that similar improvements in HbA1c can be achieved, with fewer hypoglycaemic episodes, with IDeg compared with IGlar. Three major strengths of this meta-analysis are the inclusion of all phase 3a studies comparing IDeg OD with IGlar OD, the use of patient-level data, and its prospective design.

Sub-analysis in elderly patients34

The elderly are a subgroup of patients who are more prone to hypoglycaemia; Multiple factors contribute to this predisposition.35 As diabetes population continues to age, hypoglycaemia becomes a major determinant in choice of therapy. A pre-planned sub-analysis of the hypoglycaemia meta-analysis was performed for patients ≥ 65 years, which showed numerical reduction of 18% in confirmed hypoglycaemia and significant reduction of 35% in nocturnal

Adverse Events, Insulin Dose and Body Weight in Type 2 Diabetes

Apart from hypoglycaemia other aspects of safety and tolerability were also studied in the BEGIN trials. There were no marked differences between-treatment in the rate or pattern of adverse events in any of the phase 2/3a trials in T2DM and most AEs were mild or moderate. Few injection-site reactions were reported with IDeg. Mean daily end-of-trial basal insulin doses were generally similar for IDeg and IGlar but in one trial in insulin-naà¯ve Asian patients, the mean dose of IDeg was significantly lower than that of IGlar at 26 weeks.24 In general, adverse events (AEs) were similar for IDeg and IGlar. Some of the commonly reported AEs were: headache, diarrhoea, upper respiratory tract infection, nasopharyngitis and oropharyngeal pain. Injection site reactions were few or absent in all treatment groups. IDeg concentrations of IDeg-specific antibodies were low at screening and remained low at end of trial in all the studies. Body weight change did not differ significantly in any of the trials comparing IDeg and IGlar. Mean increase in body weight with IDeg varied from 2.4 to 3.6 kg at 52 weeks, and from 1.3 to 2.3 kg at 26 weeks.

Quality of Life

IDeg has been associated with modest but statistically significant improvements measured by using SF-36 questionnaire, in HRQoL compared with IGlar, in patients with type 1 diabetes, patients with type 2 diabetes starting insulin, and patients with type 2 diabetes using basal-oral therapy.36-38 Improvement in HRQoL with IDeg has been driven primarily by improvements in the social functioning and mental health domains.

Significant difference in favour of IDeg versus IGlar for the SF-36 domain of bodily pain was noted in basal bolus type 2 trial.28 Pre-planned meta-analysis on patient-level data from three studies in patients with type 2 diabetes starting on insulin39 showed significantly greater improvement in the overall physical component score of the SF-36 and bodily pain with IDeg versus IGlar.

Nocturnal Hypoglycaemia and Fasting Plasma Glucose Analysis

comparators across the BEGINï£¨programme with different regimens. The results were statistically significant in BEGIN once long, low volume, flex T2 and flex T1 studies as shown in Table 3.

Nocturnal hypoglycaemia was consistently lower with IDeg across the individual trials further, a meta-analysis showed lower rates of nocturnal hypoglycaemia during the maintenance phase for IDeg compared to IGlar for both type 1 and type 2 diabetes.

Thus, across the seven phase 3a studies comparing IDeg with IGlar, IDeg revealed a beneficial effect on FPG profile while concurrently demonstrating lower rates of nocturnal hypoglycaemia.

Table 3 : Mean Change in fasting plasma glucose (FPG) from baseline

Trials	Treatment Arms (N)	Mean Change in FPG from baseline (mg/dl)
Type 2		
BEGIN	IDeg (773)	-68.4***
Once Long	IGlar (257)	-59.4
BEGIN	IDeg (744)	-41.4
Basal Bolus T 2	IGlar (248)	-36.0
BEGIN	IDeg Flex (230)	-57.6**
Flex T2	IDeg (226)	-54.0
	IGlar (229)	-49.4
BEGIN	IDeg (289)	-51.84
Once Asia	IGlar (248)	-53.46
BEGIN	IDeg (228)	-66.7**
Low Volume	IGlar (229)	-60.9
Type 1		
BEGIN	IDeg (472)	-23.4
Basal Bolus T 1	IGlar (157)	-25.2
BEGIN	IDeg Flex (164)	-23.04
Flex T1	IDeg (165)	-45.72**

Discussion

Hypoglycaemia is an important complication of glucose lowering therapies and achieving intensive glycaemic control without increasing the risk of hypoglycaemia is the key to success for newer molecules. Hypoglycaemia does not only impair the quality of life but also leads to other serious complications like unconsciousness or even death in rare cases.1 It has been reported that 74% of T1DM and 43% of T2DM patients "sometimes or always" modify their insulin doses following non-severe hypoglycaemia.14 Fear of hypoglycaemia leads to delaying of insulin treatment when it is

needed.40-41 Approximately eight out of 10 physicians are concerned that people with diabetes will experience a severe or nocturnal hypoglycaemic episode. This can limit insulin dosing, as physicians have been shown to prescribe insulin sub-optimally due to concern over hypoglycaemic episodes.42

Nocturnal hypoglycaemia presents a better reflection of the effect of basal insulin than daytime hypoglycaemia, where other influences such as bolus insulin (if used) can confound results and this is the principal point of differentiation of IDeg from other basal insulin. The lower rate of nocturnal hypoglycaemia has been a robust and consistent finding across the individual trials regardless of insulin regimen (basal-only or basal-bolus therapy), time of dosing (OD evening or flexible intervals), or patient population (T1DM, T2DM, insulin naà¯ve, insulin-treated and geriatric patients).The lower rate of hypoglycaemia, particularly nocturnal hypoglycaemia, observed with IDeg across trials, likely to be due to its ultra-long and stable pharmacokinetic profile, and lower day-to-day variability in glucose-lowering action that has provided more consistent and predictable response.20 As nocturnal hypoglycaemic episodes are typically unrelated to the use of bolus insulin; hence, the rate of nocturnal episodes provides the most relevant standard of comparison for basal insulin preparations. This finding is further supported by observed higher rates of overall confirmed hypoglycaemia with both IDeg and IGlar in both type 1 and type 2 basal-bolus trials. The slight increase in confirmed hypoglycaemia observed with IDeg in the first few weeks of the clinical trials may probably have

twice-daily pre-trial. There has been 1:1 switch for IDeg for total daily basal dose while there has been 20%-30% for IGlar(according to its prescribing information) thus resulting in slightly more risk of hypoglycaemia with IDeg in the initial weeks of treatment. In metaanalysis results of T1DM, majority of hypoglycaemic episodes are driven by the bolus insulin and reflected a consequence of the dose conversion from BID NPH when being assigned to either IDeg or IGlar as mentioned above. Based on the temporal pattern of hypoglycaemia, most episodes of confirmed hypoglycaemia have occurred during daytime hours and have been related to mealtime bolus insulin administration.

As recurrent severe hypoglycaemia has been an exclusion criterion for safety reasons, the total number of severe hypoglycaemic episodes is generally low in both the treatment arms. The low rate of severe hypoglycaemia in type 2 diabetes patients also reflects the relative disease state of these patients treated with basal-only insulin therapy, i.e., they do not require basal-bolus therapy, the bolus component of which would likely increase the occurrence of severe hypoglycaemia. Subcutaneous IDeg has been generally well tolerated in patients with type 1 or 2 diabetes.

BEGIN programme with IDeg has shown significantly greater improvement in the overall physical component score of the SF-36 and bodily pain versus IGlar.

Pharmacokinetic studies conducted on special patient population group have shown that no significant differences between subjects with normal renal function and those with mild, moderate or severe renal impairment or end-stage renal disease in terms of the IDeg Cmax, AUC120 and apparent clearance.43 Similarly, there has been no significant difference in IDeg Cmax, AUC120 and apparent clearance between subjects with normal hepatic function and those with mild, moderate or severe hepatic impairment.44

No differences have been observed between IDeg and IGlar recipients in physical examination findings, vital signs, ECG recordings, fundoscopy or laboratory parameters.43 In the phase 3a clinical trial programme IDeg was compared to IGlar in seven out of nine clinical trials. There were no observed differences in the overall risk of a cardiovascular event between IDeg and IGlar. It was pre-specified to combine exposure to IDeg and insulin

order to increase statistical power as MACE are usually rare. The pre-specified MACE definition included four components, viz CV death, stroke, ACS (which included MI + UAP leading to hospitalisation) In the pre-specified MACE analysis for the IDeg and IDegAsp phase 3 trial programme, incidence rates were similar for IDeg + IDegAsp (1.48 patients with MACE per 100 PYE [53 patients with MACE]) and comparator (1.44 patients with MACE per 100 PYE [27 patients with MACE. The overall estimated hazard ratio (IDeg + IDegAsp /comparator) was 1.097 [95% CI: 0.681; 1.768].(Note: Note that this was 2:1 randomisation hence degludec patients were twice the number of comparator).26,45-47 However, as requested by FDA a dedicated cardiovascular safety outcome trial with IDeg is also underway. A G Unnikrishnan et al have mentioned earlier in non-clinical pharmacology and toxicology that insulin receptor binding studies have indicated that IDeg has a low affinity for the human insulin-like growth factor-1 receptor "ratio of IGF1/insulin receptor binding" comparable with that of human insulin (1) and much less with IDeg (<<1), with a low mitogenic/metabolic potency ratio.47

Compared with currently available basal insulin analogues, IDeg has better tolerability with a longer and more stable action profile that translates into less risk of hypoglycaemia, particularly at night for patients with type 2 diabetes or type1 diabetes while achieving the targeted glycaemic control. The largest clinical development programme has shown the efficacy of IDeg in terms of lowering HbA1c and FPG with a lower risk of overall and nocturnal hypoglycaemia. This indicates that patients treated with IDeg can strive for more ambitious treatment goals, and health care providers have the opportunity for providing improved long-term glycaemic control in clinical practice.

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