Treating to Target in Type 2 Diabetes: The BEGIN® Trial Programme

Subhash K Wangnoo¹, Subhankar Chowdhury², PV Rao³

Abstract

Insulin degludec is a new-generation basal insulin with an ultra-long duration of action. The insulin degludec and insulin degludec/insulin aspart clinical trial programme was truly global, involving 40 different countries and encompassing a multitude of ethnic populations. It is the largest insulin development clinical trial programme on record – with more than 11,000 patients included worldwide. It includes two main components: BEGIN® (insulin degludec studied across the spectrum of diabetes) and BOOST® (insulin degludec in a fixed-dose combination with insulin aspart). In clinical trials (phase 2 and phase 3a), insulin degludec achieved similar glycaemic control to that seen with insulin glargine in patients with type 1 or 2 diabetes, but with a lower risk of nocturnal hypoglycaemia. In addition, trials examining a flexible dosing regimen of insulin degludec in patients with type 1 or 2 diabetes show the potential for adjusting the injection time, without compromising glycaemic control or safety. A 200 U/mL formulation of insulin degludec is also available for use in patients who require large volumes of basal insulin. Subcutaneous insulin degludec is generally well tolerated in patients with type 1 or 2 diabetes and represents a useful advance in the treatment of type 1 or 2 diabetes.

Introduction

The clinical trial programme for insulin degludec (IDeg) is the largest reported insulin development clinical trial programme. It includes two main components: BEGIN® (IDeg studied across the spectrum of diabetes) and BOOST® (IDeg in a fixed-dose combination with insulin aspart (IAsp)). Details of the BEGIN® clinical trial programme are presented in this supplement. The BEGIN® clinical trial programme (comprising nine trials) involved subjects from 40 countries, encompassing a multitude of ethnic populations. The programme included patients from all over the world (North America, South America, Europe, Africa, Asia and Australia) and encompassed a number of different ethnic populations. The majority of exposed patients had T2D, reflecting the large and growing size of this diabetes population. A broad spectrum of insulin regimens for both T1D and T2D were spanned, including basal–bolus therapy, basal plus oral therapy, and basal versus oral therapy, and also investigated...
flexible dosing options. The extent and breadth of the BEGIN® clinical trial programme provides an excellent overview of the potential of IDeg in the treatment of patients with both T1D and T2D compared with other available insulin treatment regimens.3-12

Common Principles Applied Across Protocols

Conduct of the trials

All the trials were done in accordance with the Declaration of Helsinki13and Good Clinical Practice Guidelines.14 Signed informed consent was obtained from each participant. The protocol and the consent form for each trial were reviewed and approved by the local independent ethics committee or institutional review board before trial initiation.

Treat-to-target design

All of the trials in the phase 3a programme were conducted as treat-to-target studies, in accordance with guidance from regulatory authorities such as the Food and Drug Administration (FDA) in the USA. The FDA requirement states that the 'Test and comparator groups should be treated to similar goals. Similar degrees of glycaemic control (test non-inferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycaemia will be interpretable in ultimate risk-benefit assessments'.15 Using a treat-to-target design means that between-treatment comparisons of the frequency and severity of hypoglycaemia can be interpreted without being confounded by different levels of glycaemic control.

Trial outcome measures/endpoints3-12

In all the phase 3a trials, the primary endpoint was the difference between treatment groups in the change in HbA1c from baseline to study end. The difference between groups in change in HbA1c was analysed for non-inferiority or superiority. A non-inferiority limit of 0.4%-points was set for the treatment difference in the phase 3a trials. Key secondary endpoints included hypoglycaemia rate, fasting plasma glucose (FPG), self-monitored plasma glucose (SMPG) profiles, insulin dose, body weight and adverse events (AEs). Some trials also included patient-reported outcomes such as health-related quality of life (HRQoL), using the validated Short Form 36 Health Survey, version 2.

Definitions of hypoglycaemia3-12

All the phase 2 and 3a trials used a standardised algorithm for reporting confirmed hypoglycaemia. Hypoglycaemia was classified as confirmed if a plasma glucose measurement of < 3.1 mmol/L (56 mg/dL) was obtained, irrespective of any symptoms, or if the hypoglycaemia was severe (i.e. assistance from another person was required). Nocturnal hypoglycaemic episodes were defined as those with time of onset between 00h01 and 05h59 inclusively.

Insulin dosing

Trials in T1D3-5

If patients had previously used a basal insulin OD, the same number of units OD were prescribed. If prior basal therapy was twice daily, the total basal dose was calculated and administered OD. For IDeg, this involved a 1:1 transfer to the full calculated dose (although dose reductions could be considered at the investigator’s discretion), while the IGlar dose was reduced by 20–30%, according to the approved labelling.

Trials in T2D6-12

Insulin-naïve patients and patients who had not previously used basal insulin were given a starting dose of 10 U of IDeg or IGlar. For patients already using a basal insulin OD, the same number of units OD was prescribed. If the prior basal insulin was taken more than OD, total daily basal dose was calculated. If the subject was randomised to IGlar, it was recommended to reduce the administered dose by 20–30%, according to the approved labelling. For subjects randomised to IDeg, a dose reduction was to be considered, according to the investigator’s discretion.

Titrination of basal and bolus insulin1-12

In the phase 2 studies of IDeg, the titration target was an FPG value of 4–6 mmol/L (72–108 mg/dL). FPG at the end of these trials did not indicate normoglycaemia, and hypoglycaemia rates were not increased compared with previous treat-to-target
studies; therefore, a more ambitious target of 3.9–4.9 mmol/L (70–89 mg/dL) was set for phase 3a. It was considered that, because of the ultra-long duration of action and flat profile of IDeg, it should be possible to administer it at any time of the day. Various administration schedules were used for IDeg OD in the phase 3a programme: morning, evening, mealtime, and at any time during the day. Some studies used a ‘forced flexible’ regimen, in which IDeg was injected at alternating intervals of 8 hours and 40 hours, or ‘Free-Flex’ regimens, in which patients were free to choose the time of administration, as long as the interval between injections was 8–40 hours. In all the trials that used IGlar, it was administered at the same time every day, according to its approved product label. Physicians and patients were free to choose the optimal administration time for IGlar for each individual.

Pre-specified titration algorithms were used for basal and bolus insulin. Physicians increased or reduced doses, or left it unchanged, according to measured blood glucose values and other relevant information (e.g. hypoglycaemic episodes, known lifestyle changes). In most of the trials, the basal insulin dose was titrated once weekly based on the mean pre-prandial plasma glucose level from the preceding 3 days. For the majority of trials that included bolus insulin supplementation, bolus doses were adjusted based on the mean pre-prandial plasma glucose level measured prior to the next meal or before bedtime. Basal insulin was titrated before bolus insulin doses were adjusted.

**Inclusion and exclusion criteria**

Inclusion criteria were set to ensure that a representative population was included, and to include only patients with T1D/T2D (as relevant). Exclusion criteria aimed to exclude patients with conditions or using other treatments that could confound the results, or whose safety could be compromised by participating in the trial due to existing co-morbidities, or who were unlikely to be able to follow the injection regimen adequately.

**Key inclusion criteria for the phase 3a trials:**

- Adults aged >18 years.
- The trials in T1D required patients to have been diagnosed with it for at least 1 year, and to have been using basal-bolus therapy for at least 1 year before screening.
- The trials in T2D required patients to have been diagnosed with it for at least 6 months.
- The trials in T2D included insulin-naïve or insulin-experienced users. For each trial, criteria were set to specify which medications patients had been using, and the duration of previous use.
- HbA1c < 10% in T1D and in the range of 7.0–10.0% in T2D. The upper limit was imposed to ensure that patients could control their disease to a certain extent. For T2D, it was considered that patients with HbA1c < 7.0% were already achieving good glycaemic control.
- BMI < 35 (T1D) or 40 kg/m² (T2D). An upper limit of BMI was imposed to exclude individuals with severe insulin resistance.

**Phase 2 Trials – Efficacy and Safety**

There were 2 phase trials conducted – one in T1D and T2D each. Both were clinical exploratory, proof-of-concept, 16-week, randomised, controlled, open-label, three-arm, parallel-group treat-to-target study comparing two formulations of IDeg to IGlar. IDeg Group A was of the same molar concentration as IGlar (600 μmol/L, 1 unit = 6 nmol); IDeg Group B was a higher strength formulation (900 μmol/L; 1 unit = 9 nmol). The higher strength formulation was tested for its efficacy and safety and to assess whether any extra benefit can be obtained from it.

**Type 1 Diabetes**

There was one phase 2 trial conducted in T1D, using IDeg in a basal-bolus regimen with IAsp at mealtimes versus IGlar as comparator. It included patients with T1D for > 1 year, previously treated continuously with any insulin regimen. Participants were randomised 1:1:1 into three groups: IDeg Group A, IDeg Group B, or IGlar, all given in the evening. IAsp was administered at mealtimes.

At 16 weeks, mean A1C was comparable for IDeg (A) (7.8%), IDeg (B) (8.0%), and IGlar (7.6%), as was FPG (8.3, 8.3 and 8.9 mmol/L, respectively). Estimated mean rates of confirmed hypoglycaemia were 28% lower for IDeg (A) and 10% lower for IDeg (B) compared with IGlar; rates of nocturnal hypoglycaemia were 58% lower for IDeg(A) and 29% lower for IDeg(B). At study end, the plasma glucose levels in the nine-point SMPG profiles were reduced in all treatment groups and were similar between groups. Mean total daily insulin dose was similar to baseline (60 units, 49 units and 51 units vs. 60 units, 59 units and 52 units at baseline respectively).

The overall rates of adverse events (AEs) for IDeg(A), IDeg(B), and IGlar were 8.7, 6.5, and 9.1 events/patient year. There were no specific patterns or clustering of the AEs; most were mild or moderate in severity and judged to have an unlikely relation to the trial insulin products. No injection-site reactions were reported. Four serious AEs were reported: diabetic ketoacidosis (IGlar), abdominal distension (IDeg(A)), hypoglycaemic unconsciousness (IDeg(A)), and hypoglycaemia (IDeg(B)).
At the end of the trial, there were no obvious differences between groups in clinical laboratory tests, ECG, fundoscopy, vital signs, or physical examination.

The level of IDeg specific antibodies was close to, or below, the limit of detection at screening and remained at the same level at the end of the treatment period.

**Type 2 Diabetes**

There was one phase 2 trial conducted in T2D which included insulin-naïve patients, diagnosed with T2D for > 3 months and with HbA1c 7.0-11.0% and BMI 23-42 kg/m². Patients were randomised 1:1:1:1 as follows: IDeg (900 μmol/L) three times a week; IDeg Group A; IDeg Group B; IGlar OD. In all the arms, insulin was dosed in combination with metformin.

At study end, mean Hba1C levels were much the same across treatment groups, at 7.3%, 7.4%, 7.5%, and 7.2%, respectively. Estimated mean Hba1C treatment differences from IDeg by comparison with IGlar were 0.08% for the three dose per week schedule, 0.17% for group A, and 0.28% for group B. Few participants had hypoglycaemia; however, the proportion of participants who had hypoglycaemia in IDeg group A was lower than was the proportion in the IGlar group and the IDeg three times a week group. The number of adverse events was much the same across groups; most were mild-to-moderate in severity with no apparent treatment specific pattern.

Most AEs were mild or moderate in severity, and there was no apparent treatment-specific pattern. Only two serious adverse events were reported: aggravation of a pretrial coronary heart disease in the three times a week IDeg group and worsening of paroxysmal atrial fibrillation in IDeg group B; both events were judged to be unlikely to be related to trial product.

AEs judged to have possible or probable relation to insulin were reported for six participants in the IDeg three times a week group (headache, dermatitis, pruritic rash, diarrhoea, stomach discomfort, and peripheral oedema), two participants in IDeg group A (three events; dizziness, dysgeusia, and palpitations), five participants in IDeg group B (headache, increased blood cholesterol, increased weight, pruritus, and muscle spasms), and two participants in the IGlar group (headache and increased blood cholesterol). There were few injection-site reactions. Concentrations of antibodies specific to IDeg and those cross-reacting between IDeg and human insulin were negligible.

Based on both these phase two studies, the 900 μmol/L formulation was not developed further, since it showed no added advantage over the conventional formulation.

**Phase 3a – The BEGIN trials**

There were three phase 3a trials conducted in T1D, using IDeg in a basal-bolus regimen with IAsp at mealtimes versus IGlar as comparator in two, and IDet in one. Both trials versus IGlar had extension periods.

**BEGIN® BB T1 long**

This was a 52-week, open-label, treat-to-target, non-inferiority trial comparing IDeg with IGlar, which included adults with T1D, who were previously treated with basal-bolus insulin for at least 1 year. Patients were randomly assigned in a 3:1 ratio to IDeg OD or IGlar OD.

In the 52-week extension period, for the second year, patients maintained their prior randomisation (IDeg:IGlar 3:1). The total duration of the trial was 2 years for patients enrolled in both trial periods.

**BEGIN® flex T1**

This was a 26-week, open-label, treat-to-target trial comparing a forced-flexible dosing regimen of IDeg (‘IDeg Forced-Flex’) with IDeg OD and IGlar OD. It included adults with T1D for ≥12 months, previously treated with any basal–bolus regimen. Subjects were randomised 1:1:1 as follows: IDeg OD administered with the evening meal; IDeg Forced-Flex, where subjects alternated insulin administration timing between morning and evening to create intervals of 8 to 40 hours between insulin doses; and IGlar OD at the same time each day. IAsp was used as prandial insulin in all three treatment groups.

The 26-week extension period, investigated the long-term safety and efficacy of IDeg in a ‘free flex’ regimen (‘IDeg Free-Flex’) in combination with meal-time IAsp. For the extension period, patients in the IDeg Free-Flex arm were free to choose the time of administration, provided that the interval between consecutive doses was more than 8 hours and less than 40 hours. The comparator was IGlar OD. The total duration of the trial was 52 weeks for patients enrolled in both trial periods.

There were six phase 3a trials conducted in T2D; two of which also had extension periods. Duration of these trials was 26 or 52 weeks.

**BEGIN® once-long**

This was a 52-week randomised, controlled, open-label, multinational, treat-to-target trial, comparing IDeg with IGlar, used in combination with oral anti-diabetics (OADs). The study enrolled insulin-naïve adults diagnosed with T2D for ≥ 6 months, previously treated with metformin ± a sulphonylurea (SU), glinide, DPP-4 inhibitor (DPP4-I), or α-glucosidase inhibitors (AGI), with dosing unchanged for >3 months. Patients were randomised 3:1 to receive IDeg OD in the evening or IGlar OD at the same time each
day, in combination with metformin ± DPP4-I (other OADs were discontinued). The extension period was for 52 weeks more, making the total duration of the trial 104 weeks for patients enrolled in both trial periods.

BEGIN early

This was a 26-week randomised, controlled, open label, multinational, treat-to-target trial, comparing IDeg with the DPP4-I, sitagliptin as add-on to current OADs. Insulin-naïve patients with T2D for > 6 months and inadequately controlled with 1–2 OADs were eligible. Patients were randomised 1:1 to receive IDeg injected OD (participants could choose the timing as long as they maintained an interval between 8 and 40 hours between injections), or sitagliptin taken OD. All patients continued taking their current OADs.

BEGIN BB T2

This was a 52-week, randomised, open-label, multinational, treat-to-target trial, comparing IDeg with IGlar, both administered OD in a basal-bolus regimen with IAsp as mealtime insulin ± treatment with metformin, ± pioglitazone. T2D patients with HbA1c 7.0–10.0% after > 3 months of any insulin regimen (with or without OADs) were included and randomised 3:1 to receive IDeg OD at the main evening meal or IGlar OD at the same time each day, stratified by previous insulin regimen. IAsp was given at breakfast, lunch and dinner and could be given at a fourth meal.

BEGIN once asia

This was a 26-week, randomised, controlled, open-label, multinational, treat-to-target trial comparing IDeg OD and IGlar OD, both administered with metformin, SUs, AGIs or glinides. The study enrolled insulin-naïve patients in Asia with T2D for > 6 months who were randomised 2:1 to IDeg OD in the evening or IGlar OD, both as add-on therapy to stable treatment with >1 OAD(s).

BEGIN flex

This was a 26-week randomised, controlled, open-label, multinational, three-arm, treat to target trial comparing fixed-flexible dosing of IDeg with IDeg OD and IGlar OD, with or without OADs. The study enrolled patients with type 2 diabetes for > 6 months, and with HbA1c 7.0–11.0% if previously treated with OADs, or HbA1c 7.0–10.0% if previously treated with any basal insulin ± OADs. Patients were randomised 1:1:1 to receive either IDeg OD or IGlar OD at the same time each day, or IDeg in a fixed-flexible regimen (IDeg OD Flex), with fixed 8- and 40-hour intervals between injections.

BEGIN low volume

This was a 26-week, randomised, controlled, open-label, multinational, treat-to-target trial comparing IDeg in a more concentrated formulation (200 U/mL) with IGlar, both administered OD with metformin with or without a DPP4-I.

Insulin-naïve patients diagnosed with T2D for > 6 months were enrolled and randomised 1:1 to receive either IDeg 200 U/mL OD with the main evening meal or IGlar OD at the same time each day. Both insulins were given in prefilled pen devices and in combination with metformin ± DPP4-I treatment as prior to randomisation.

Further details on the phase 3a trials are presented in the next article in this supplement, by Mithal et al titled “Preserving glycaemic control – Insights from BEGIN trials”.

FlexTouch® - New Insulin Delivery Device for Insulin Degludec

IDeg is available in FlexTouch® (Novo Nordisk A/S, Bagsværd, Denmark), a new prefilled disposable insulin pen and the device used across all trials for the delivery of IDeg. It has a new injection mechanism with no push-button extension. Additional features include an end-of-dose click, a large dose display, dial-back mechanism, a maximum deliverable dose of 80 international units (IU), an ergonomic design, and compatibility with most screw-thread needles.

The unique injection mechanism means that a lower injection force is required when injecting with FlexTouch® compared with other prefilled insulin pens, at all injection speeds tested. FlexTouch® also showed consistency and accuracy of dose delivery at minimum, medium and maximum doses (i.e., 1, 40 and 80 U) which should help to minimise glycaemic variations by reducing under- or over-dosing.

More than 95% of health care providers (HCPs) and patients with diabetes rated FlexTouch® as easy to use and hold stable, and responded that it was easy to depress the push-button/plunger and to read the dose scale.

In two preference studies among patients with diabetes and HCPs, over 80% of respondents preferred FlexTouch® and found it easier to use than comparator pens.

Dosing and Titration Guidelines

Timing

IDeg should be injected subcutaneously at any time of the day, preferably at the same time every day. When administration at the same time of the day is not possible, IDeg can be dosed flexibly with a minimum of 8 hours between injections.

Initial dosing and adjustments

For insulin naïve patients with T2D, recommended
initial dose is 10 U which should be adjusted individually thereafter. In T1D, if switching from a previous basal insulin used OD, the initial dose of IDeg can be transferred in a 1:1 ratio for most patients, followed by individual dose adjustment. If the previous basal insulin was used twice daily, or HbA1c < 8.0% at the time of switching, the dose must be determined individually for each patient. In T2D, whether using basal-bolus, premix, or self-mix regimens, IDeg can be transferred in a 1:1 ratio based upon the previous insulin dose, followed by individual dose adjustment.

Adjustments made weekly, using the mean of the preceding 3 days’ SMPG, take into account the fact that it takes IDeg 2–3 days to reach steady state.24

References


