

Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial



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Summary

Background Insulin degludec is a new basal insulin that forms soluble multihexamer assemblies after subcutaneous injection, resulting in an ultra-long action profile. This study aimed to assess efficacy and safety of insulin degludec injected once a day or three times a week compared with insulin glargine once a day in insulin-naïve people with type 2 diabetes, who were inadequately controlled with oral antidiabetic drugs.

Methods In this 16-week, randomised, open-label, parallel-group phase 2 trial, participants aged 18–75 years with type 2 diabetes and glycosylated haemoglobin (HbA_{1c}) of 7·0–11·0% were enrolled and treated at 28 clinical sites in Canada, India, South Africa, and the USA. Participants were randomly allocated in a 1:1:1 ratio by computer-generated block randomisation to receive insulin degludec either once a day or three times a week or insulin glargine once a day, all in combination with metformin. Investigators were masked to data until database release. The primary outcome was HbA_{1c} after 16 weeks of treatment. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00611884.

Findings Of 367 patients screened, 245 were eligible for inclusion. 62 participants were randomly allocated to receive insulin degludec three times a week (starting dose 20 U per injection [1 U=9 nmol]), 60 to receive insulin degludec once a day (starting dose 10 U [1 U=6 nmol]; group A), 61 to receive insulin degludec once a day (starting dose 10 U [1 U=9 nmol]; group B), and 62 to receive insulin glargine (starting dose 10 U [1 U=6 nmol]) once a day. At study end, mean HbA_{1c} levels were much the same across treatment groups, at 7·3% (SD 1·1), 7·4% (1·0), 7·5% (1·1), and 7·2% (0·9), respectively. Estimated mean HbA_{1c} treatment differences from insulin degludec by comparison with insulin glargine were 0·08% (95% CI –0·23 to 0·40) for the three dose per week schedule, 0·17% (–0·15 to 0·48) for group A, and 0·28% (–0·04 to 0·59) for group B. Few participants had hypoglycaemia and the number of adverse events was much the same across groups, with no apparent treatment-specific pattern.

Interpretation Insulin degludec provides comparable glycaemic control to insulin glargine without additional adverse events and might reduce dosing frequency due to its ultra-long action profile.

Funding Novo Nordisk.

Introduction

Prevalence of type 2 diabetes and diabetes-related health complications and mortality continue to increase.^{1–3} Despite availability of many therapies, many people with diabetes are unable to reach guideline-recommended rates of glycosylated haemoglobin (HbA_{1c}).^{4–6}

Insulin degludec is an ultra-long-acting insulin in clinical development. The ultra-long action profile of this insulin is mainly attributable to formation of soluble multihexamers at the injection site, from which monomers gradually separate and are absorbed into the circulation, resulting in a flat and stable pharmacokinetic profile at steady state.⁷ These features suggest that the risk of hypoglycaemia might be reduced and clinical effectiveness might be achievable with dosing three-times a week in people with type 2 diabetes who were

previously insulin-naïve, which could help with early initiation of and adherence to insulin treatment.

This clinical proof-of-concept trial aimed to assess efficacy and safety of insulin degludec once a day or three times a week compared with insulin glargine once a day, in combination with metformin, in insulin-naïve people with type 2 diabetes who were inadequately controlled on oral antidiabetic drugs.

Methods

Study design and participants

This phase 2, 16-week, randomised, open-label, parallel-group trial was done at 28 clinics in four countries (Canada, India, South Africa, and the USA) between Jan 8, 2008, and Aug 20, 2008. Men and women diagnosed with type 2 diabetes for at least 3 months and who were

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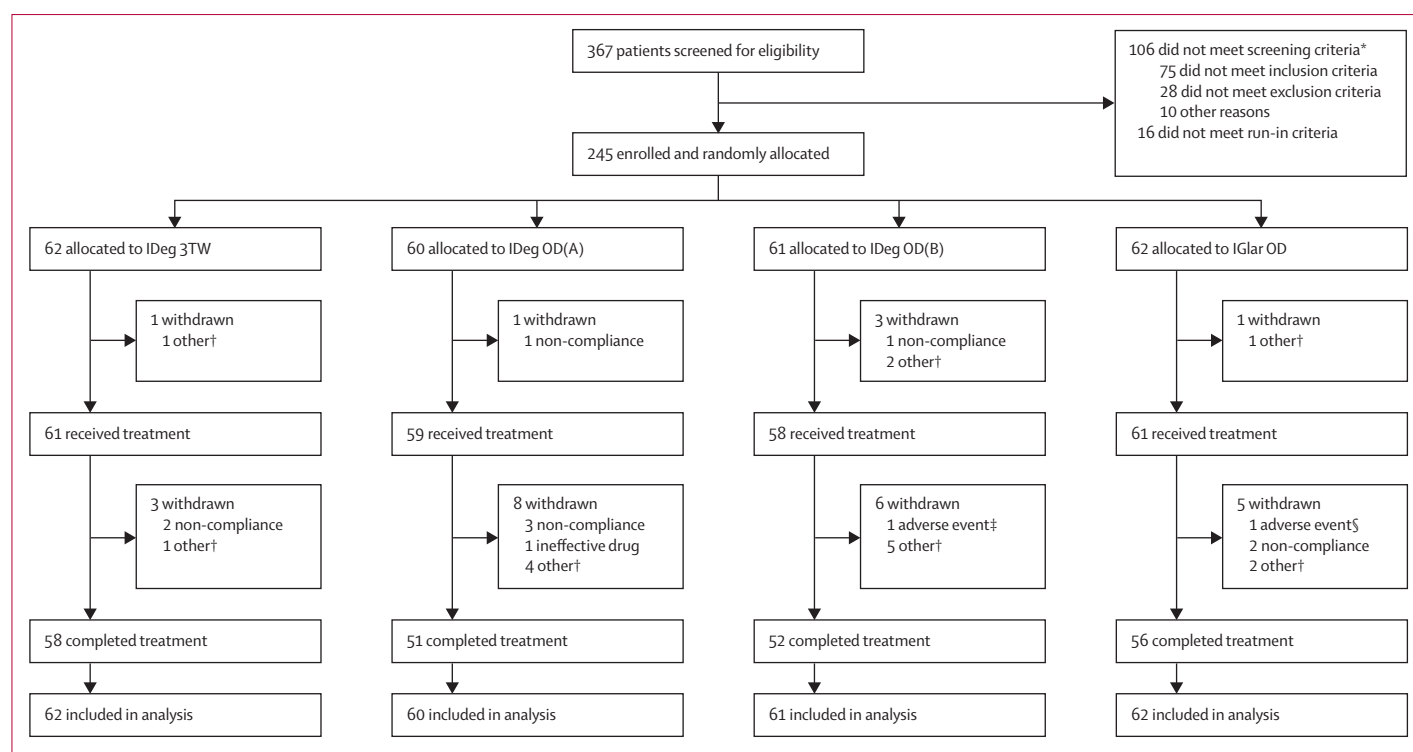


Figure 1: Trial profile

Insulin degludec group A received a starting dose of 10 U (1 U=6 nmol) per day and group B received a starting dose of 10 U (1 U=9 nmol). IDeg 3TW=insulin degludec three times a week. IDeg OD(A)=insulin degludec (group A) once a day. IDeg OD(B)=insulin degludec (group B) once a day. IGlar=insulin glargine once a day. *Seven participants met a combination of criteria.

†Withdrawal of consent, withdrawal because of personal reasons, withdrawal due to stress about giving injections on a regular basis, withdrawal for the safety of the participant, withdrawal due to meeting an exclusion criteria, withdrawal due to randomisation in error, or withdrawal because participant was lost to follow-up. ‡Weight gain (5.7 kg) was unacceptable to the participant.

§Moderate case of pulmonary tuberculosis.

aged 18–75 years with an HbA_{1c} of 7.0–11.0% and a body-mass index of 23–42 kg/m² were eligible for enrolment. Before trial entry, participants had to be insulin-naïve and have been treated with one or two oral antidiabetic drugs (metformin, α -glucosidase inhibitors, sulphonyl-urea, or meglitindes) for more than 2 months at stable half-maximum to maximum allowed doses. Patients were excluded if they were treated with thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or other interventions that could interfere with glucose metabolism within 3 months of the start of the trial. Patients were excluded if they had contraindications to metformin, substantial medical issues, a history of recurrent hypoglycaemia, or unawareness of hypoglycaemia. Women who were breastfeeding or pregnant were also excluded.

Before randomisation, eligible participants discontinued their pretrial oral antidiabetic drug treatment and underwent a 2-week forced metformin-titration period (dose increased to 2000 mg per day; 1000 mg at breakfast and evening meal), which was followed up by a 1-week metformin maintenance period. Patients were eligible for randomisation if the maximum metformin dose (2000 mg) or maximum-tolerated dose (1500 mg) per day remained unchanged in the maintenance period, and if the median before-breakfast self-monitored blood glucose

value (measured on 3 consecutive days immediately before randomisation) was 7.5 mmol/L or more. The trial was approved by independent ethics committees or institutional review boards before trial initiation, and written informed consent was obtained from every participant before trial entry. The trial was undertaken in accordance with the Declaration of Helsinki⁸ and good clinical practice guidelines.⁹

Randomisation and masking

Block randomisation was computer-generated and done by use of an interactive voice and web-based system. Participants were stratified according to previous oral antidiabetic drug treatment. Participants were randomly allocated in a 1:1:1:1 ratio to receive insulin degludec (Novo Nordisk, Bagsvaerd, Denmark) three times a week (900 nmol/mL formulation, dosed in the evening on Monday, Wednesday, and Friday), insulin degludec group A (600 nmol/mL formulation) once a day, insulin degludec group B (900 nmol/mL formulation) once a day, or insulin glargine (600 nmol/mL formulation; Sanofi-Aventis, Paris, France) once a day, all in combination with metformin. The study was open-label. Investigators were masked to data until database release from the statistician,

although a Novo Nordisk safety committee undertook ongoing safety surveillance.

Procedures

Insulin degludec and insulin glargine were injected subcutaneously (preferably into the thigh). Insulin degludec was injected with a 3 mL FlexPen (Novo Nordisk), and insulin glargine was injected with either a 3 mL Optiset pen (Sanofi-Aventis Deutschland, Frankfurt, Germany) or, in the USA and Canada, from 10 mL vials with a needle and syringe. Insulin glargine was injected before bedtime and insulin degludec was injected in the evening (no earlier than 1 h before last main meal and no later than before bedtime). The starting dose for all participants who were randomly allocated to once a day treatments was 10 U per injection (60 nmol for insulin degludec group A, 60 nmol for the insulin glargine group, and 90 nmol for insulin degludec group B). For the three doses a week group, the starting dose was double that of the once a day group B dose (ie, 20 U or 180 nmol). On the basis of concentrations of selfmonitored blood glucose before breakfast (lowest value from 3 consecutive days), insulin doses were individually titrated once a week throughout the trial (by clinic or telephone contacts), aiming at a fasting glucose concentration of 4.0–6.0 mmol/L. Webappendix p 1 describes the titration algorithm. Participants measured blood glucose with a plasma-calibrated blood glucose meter (Abbott Diabetes Care, Abbott Park, IL, USA).

The primary efficacy endpoint was HbA_{1c} after 16 weeks of treatment. Secondary efficacy endpoints were changes in laboratory measured fasting plasma glucose, required insulin dose, and nine-point profiles of selfmonitored blood glucose. Safety variables consisted of adverse events, hypoglycaemic episodes, injection-site reactions, and changes in bodyweight, or abnormal results on laboratory analyses (haematology, biochemistry, and antibodies), physical examination, vital signs, standard fundoscopy, and electrocardiogram (ECG). Laboratory analyses were done at the commercial central laboratories (Quintiles Central Laboratories in Mumbai, India, Gauteng, South Africa, and Marietta, GA, USA). The commercial laboratory Celerion (formerly MDS Pharma Services) in Fehraltorf, Switzerland, analysed antibodies that were specific to insulin degludec and crossreactive between insulin degludec and human insulin using a subtraction radio-immunoassay method¹⁰ that was validated according to standard procedures.¹¹ Four questionnaires were used to assess quality of life at randomisation and end of trial.^{12–15} Hypoglycaemia and adverse events were recorded by the trial participants on an ongoing basis. Hypoglycaemia was classified as severe if assistance from another person was required, confirmed if a plasma glucose measurement of less than 3.1 mmol/L was reported irrespective of symptoms or classification

	Insulin degludec three times a week	Insulin degludec (group A) once a day	Insulin degludec (group B) once a day	Insulin glargine once a day
Participants	62	60	61	62
Female	34 (55%)	27 (45%)	22 (36%)	25 (40%)
Race				
White	18 (29%)	16 (27%)	21 (34%)	23 (37%)
Black	8 (13%)	11 (18%)	10 (16%)	4 (6%)
Asian	34 (55%)	32 (53%)	30 (49%)	34 (55%)
Other	2 (3%)	1 (2%)	0	1 (2%)
Age (years)	54.4 (8.8)	55.3 (8.7)	53.9 (8.5)	53.1 (10.2)
Bodyweight (kg)	78.5 (20.8)	78.5 (16.9)	81.7 (20.5)	79.5 (18.5)
Body-mass index (kg/m ²)	29.7 (5.3)	29.5 (5.1)	29.5 (4.8)	29.4 (5.3)
Waist circumference (cm)	101.1 (14.8)	100.6 (11.3)	103.1 (13.3)	101.3 (13.1)
Duration of diabetes (years)	6.6 (5.4)	7.3 (5.2)	7.2 (4.4)	6.7 (5.0)
Prestudy treatment with oral antidiabetic drugs				
Metformin and/or α -glucosidase	25 (40%)	23 (38%)	25 (41%)	25 (40%)
SU $\pm$ α -glucosidase	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Metformin and SU	36 (58%)	35 (58%)	35 (57%)	35 (56%)
HbA _{1c} (%)	8.8 (1.1)	8.6 (1.2)	8.7 (1.1)	8.7 (1.1)
Fasting plasma glucose (mmol/L)	10.6 (3.4)	9.9 (3.2)	10.6 (3.6)	9.8 (3.1)

Data are number (%) or mean (SD) unless otherwise stated. Data are from screening visit. SU=sulphonylurea (including meglitinides).

Table 1: Baseline characteristics of the randomised population

as severe, or nocturnal if time of onset was between 2300 h and 0559 h (inclusive). See Online for webappendix

Statistical analysis

All randomly allocated participants were included in the statistical assessment of HbA_{1c}, fasting plasma glucose, bodyweight, and hypoglycaemic episodes, which was done on an intention-to-treat basis. Missing values for HbA_{1c}, fasting plasma glucose, and bodyweight were imputed with the method of last observation carried forward. Treatment differences in HbA_{1c}, fasting plasma glucose, and bodyweight after 16 weeks of treatment were estimated by analysis of variance (ANOVA), which was adjusted by country, sex, age, and HbA_{1c} (and fasting plasma glucose or bodyweight for these estimates) at randomisation and by oral antidiabetic drug treatment at screening. Estimates of rate ratio of hypoglycaemic episodes during the exposure to trial insulin were made by a negative binomial regression model, in which the number of episodes per patient-year of exposure (events per patient-year) was adjusted by country, sex, age, and HbA_{1c} at randomisation and by oral antidiabetic drug treatment at screening.¹⁶ The proportion of participants having at least one confirmed hypoglycaemic episode was estimated with a logistic-regression model (which was not prespecified in the protocol), expressing the difference between treatments in terms of odds ratios and adjusted for the characteristics as previously mentioned.

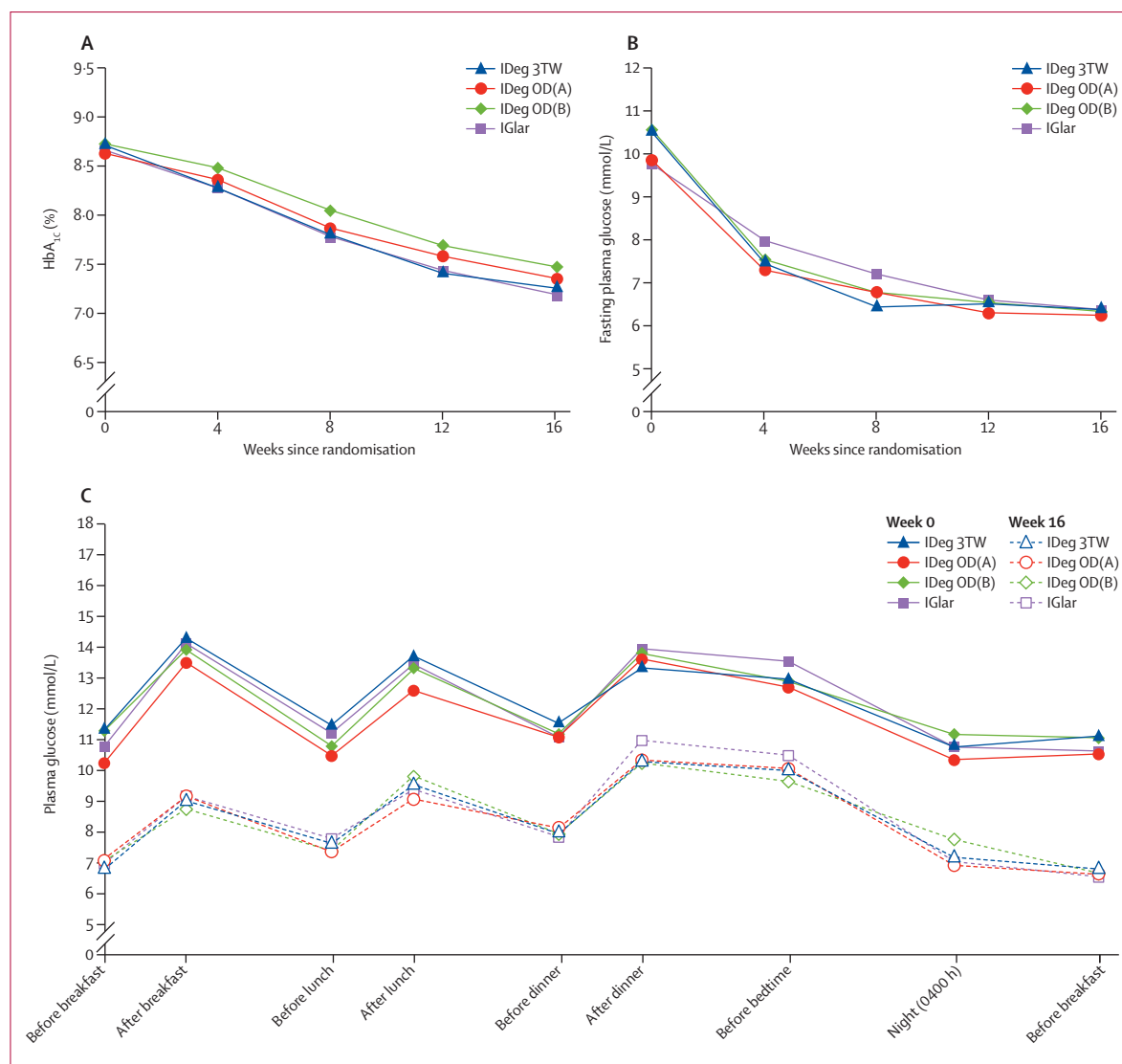


Figure 2: Mean HbA_{1c} and plasma glucose concentrations by trial intervention

(A) Mean HbA_{1c}. (B) Mean fasting plasma glucose. (C) Mean nine-point self-monitored blood glucose profiles. Data are reported mean values from all randomised participants. Last observation carried forward is used for each timepoint in A and B. Plasma-calibrated values are shown in C. IDeg 3TW=insulin degludec three times a week. IDeg OD(A)=insulin degludec (group A) once a day. IDeg OD(B)=insulin degludec (group B) once a day. IGlar=insulin glargine once a day.

Our phase 2 study did not aim to determine superiority or non-inferiority of treatment groups, but rather to estimate a treatment difference (in HbA_{1c}) with sufficient precision. A 95% CI for the treatment difference, with a total width of 0.8% (absolute), was regarded as sufficient for this exploratory trial and would be obtained with 50 completed participants per group. No confirmatory hypotheses were prespecified. On the basis of the chosen precision for HbA_{1c} and an expected dropout rate of 15%, 60 participants were to be randomised to every treatment group. Values are presented as mean (SD) for descriptive statistics and as estimated difference or ratio (95% CI) for inferential statistics from ANOVA and from regression models. SAS version 9.1 was used for all analyses.

This trial is registered with ClinicalTrials.gov, number NCT00611884.

Role of the funding source

The sponsor of the study participated in the study design, data collection, review, analysis, and interpretation, and preparation of the report. All authors had full access to the trial data and had final responsibility for the content of the report and the decision to submit for publication.

Results

Figure 1 shows the trial profile. Baseline characteristics at randomisation were much the same between treatment groups, apart from modest differences in

	n	HbA _{1c} (%)			Fasting plasma glucose (mmol/L)			Bodyweight (kg)			Insulin dose per week (U/kg)*		
		Baseline	Week 16†	Change from baseline	Baseline	Week 16†	Change from baseline	Baseline	Week 16†	Change from baseline	Baseline	Week 16†	Change from baseline
Insulin degludec three times a week	62	8.8 (1.1)	7.3 (1.1)	-1.5 (1.1)	10.7 (3.5)	6.5 (2.4)	-4.2 (3.5)	78.8 (20.8)	78.9 (20.9)	0.1 (2.6)	1.2 (0.3)	3.4 (1.7)	2.2 (1.7)
Insulin degludec (group A) once a day	60	8.6 (1.2)	7.4 (1.0)	-1.3 (1.1)	9.9 (3.2)	6.3 (2.1)	-3.6 (3.3)	78.6 (17.0)	78.6 (17.1)	0.0 (1.9)	0.9 (0.2)	3.1 (1.5)	2.2 (1.5)
Insulin degludec (group B) once a day	61	8.8 (1.1)	7.5 (1.1)	-1.3 (1.1)	10.6 (3.6)	6.4 (3.2)	-4.2 (4.3)	81.2 (21.0)	82.2 (21.7)	0.7 (2.5)	1.4 (0.4)	4.5 (1.9)	3.0 (2.0)
Insulin glargine once a day	62	8.7 (1.1)	7.2 (0.9)	-1.5 (1.1)	9.8 (3.1)	6.4 (2.6)	-3.4 (2.9)	79.3 (18.6)	79.1 (18.7)	-0.3 (2.4)	0.9 (0.2)	3.3 (1.6)	2.4 (1.6)

Data are reported means (SD) for all participants who were randomly allocated to treatment groups. Baseline values are at randomisation visit apart from for insulin dose per week, for which values are from first week. *1 U is 6 nmol insulin for all dose groups. †Last observation carried forward.

Table 2: Mean changes from baseline in HbA_{1c}, fasting plasma glucose concentration, bodyweight, and insulin dose

race, sex ratio, and concentration of fasting plasma glucose (table 1).

Mean HbA_{1c} and fasting plasma glucose concentrations were much the same between treatment groups (figure 2). Mean HbA_{1c} reductions from baseline were between -1.3% and -1.5% for all treatment groups (table 2), and reductions of HbA_{1c} did not differ between treatment groups (table 3). At study end, mean fasting plasma glucose concentrations were much the same across treatment groups (table 2), and no differences were noted in the ANOVA analysis (table 3).

After 16 weeks, mean nine-point selfmonitored blood glucose profiles were lower in all treatment groups than they were at baseline, and the overall shape of the mean profiles was nearly the same for the four treatment groups (figure 2).

Insulin doses were adjusted during the trial to achieve specified fasting plasma glucose targets. The weekly starting doses for insulin degludec three times a week and once a day (group B) were higher than they were for the other two groups because of formulation differences (table 2). After 16 weeks, mean weekly insulin dose was very similar for all treatment groups apart from for insulin degludec once a day group B (table 2). In terms of mean daily doses after 16 weeks of treatment, the three times a week dose was 1.14 U/kg per injection (corresponding to 90 U per injection and 0.49 U/kg per day), and the once a day doses were 0.45 U/kg per injection (35 U per injection) for insulin degludec group A, 0.64 U/kg per injection (53 U per injection) for insulin degludec group B, and 0.48 U/kg per injection (38 U per injection) for insulin glargine.

Overall reported rates of hypoglycaemia were low in all treatment groups; 77–92% of participants did not have a hypoglycaemic episode (table 4). Rates of hypoglycaemia did not differ between groups as seen from the 95% CI (table 5, left column). However, the proportion of participants who had hypoglycaemia in insulin degludec group A was lower than was the proportion in the insulin glargine group and the insulin degludec three times a week group (odds ratio; table 5, right column). The rate

	HbA _{1c} difference (%)	Fasting plasma glucose difference (mmol/L)	Bodyweight difference (kg)
IDeg 3TW vs IGlar	0.08 (-0.23 to 0.40)	0.04 (-0.84 to 0.92)	0.41 (-0.41 to 1.22)
IDeg OD(A) vs IGlar	0.17 (-0.15 to 0.48)	-0.09 (-0.97 to 0.79)	0.36 (-0.46 to 1.18)
IDeg OD(B) vs IGlar	0.28 (-0.04 to 0.59)	-0.20 (-1.08 to 0.68)	1.00 (0.17 to 1.83)*
IDeg OD(A) vs IDeg 3TW	0.08 (-0.23 to 0.40)	-0.13 (-1.01 to 0.76)	-0.05 (-0.86 to 0.77)
IDeg OD(B) vs IDeg 3TW	0.19 (-0.12 to 0.51)	-0.23 (-1.12 to 0.65)	0.60 (-0.23 to 1.43)
IDeg OD(B) vs IDeg OD(A)	0.11 (-0.21 to 0.43)	-0.11 (-1.01 to 0.79)	0.64 (-0.20 to 1.49)

Data are estimated treatment differences (95% CI) from an analysis of variance (ANOVA) model of all randomised participants. For analysis of HbA_{1c} and fasting plasma glucose concentrations, 62 participants in the IDeg 3TW group, 60 in the IDeg OD(A) group, 61 in the IDeg OD(B) group, and 62 in the IGlar group were assessed. For the bodyweight analysis, 62 participants in the IDeg 3TW group, 59 in the IDeg OD(A) group, 57 in the IDeg OD(B) group and 61 in the IGlar group were assessed. IDeg 3TW=insulin degludec three times a week. IGlar=insulin glargine once a day. IDeg OD(A)=insulin degludec (group A) once a day. IDeg OD(B)=insulin degludec (group B) once a day. *p<0.05.

Table 3: Estimated treatment differences in HbA_{1c}, fasting plasma glucose concentration, and bodyweight at trial end

of confirmed nocturnal hypoglycaemia was low in all treatment groups (table 4). Webappendix pp 2–3 lists hypoglycaemic episodes according to American Diabetes Association definitions.

Bodyweight was stable throughout the trial in every group (table 2). A significant difference in bodyweight was noted between the insulin degludec group B and insulin glargine groups (table 3). No obvious differences were noted between treatments in physical-examination findings, vital signs, standard laboratory analyses (haematology and biochemistry), funduscopy, or ECGs.

Most (>97%) adverse events 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 insulin degludec group and worsening of paroxysmal atrial fibrillation in the once a day insulin degludec group B; both events were deemed by the investigator to be unlikely to be related to trial product. Adverse events deemed by the investigators to have possible or probable relation to insulin were reported for six participants in the insulin degludec three times a week group (headache, dermatitis, pruritic

	n	Confirmed (plasma glucose <3.1 mmol/L or assistance required)			Severe (assistance required)			Confirmed nocturnal (2300 h–0559 h)			Confirmed with symptoms		
		Participants (%)	Episodes	Rate*	Participants (%)	Episodes	Rate*	Participants (%)	Episodes	Rate*	Participants (%)	Episodes	Rate*
Insulin degludec three times a week	62	14 (23%)	41	2.3	1 (2%)	1	0.1	3 (5%)	4	0.2	8 (13%)	13	0.7
Insulin degludec (group A) once a day	60	5 (8%)	10	0.6	0	0	..	1 (2%)	2	0.1	3 (5%)	3	0.2
Insulin degludec (group B) once a day	61	9 (15%)	15	0.9	0	0	..	1 (2%)	1	0.1	6 (10%)	7	0.4
Insulin glargine once a day	62	14 (23%)	20	1.1	0	0	..	0	0	..	8 (13%)	12	0.7

Data are number (%) of all patients who were randomly allocated to treatment groups, unless otherwise stated. *Unadjusted event rate (events per patient-year of exposure).

Table 4: Hypoglycaemic episodes

	Estimated rate ratio (95% CI)†	Estimated odds ratio (95% CI)‡
IDeg 3TW vs IGLar	1.17 (0.46–2.96)	0.84 (0.35–2.03)
IDeg OD(A) vs IGLar	0.44 (0.15–1.28)	0.26 (0.08–0.81)*
IDeg OD(B) vs IGLar	0.54 (0.19–1.51)	0.57 (0.22–1.49)
IDeg OD(A) vs IDeg 3TW	0.38 (0.14–1.04)	0.31 (0.10–0.95)*
IDeg OD(B) vs IDeg 3TW	0.46 (0.18–1.16)	0.68 (0.26–1.77)
IDeg OD(B) vs IDeg OD(A)	1.22 (0.40–3.73)	2.18 (0.66–7.21)

Confirmed hypoglycaemia was defined as plasma glucose of <3.1 mmol/L or assistance required. IDeg 3TW=insulin degludec three times a week. IGLar=insulin glargine once a day. IDeg OD(A)=insulin degludec (group A) once a day. IDeg OD(B)=insulin degludec (group B) once a day. *p<0.05. †Number of events per patient-year of exposure; rate ratios were estimated with a negative binomial regression model that used data for all participants who were randomly allocated to treatment. ‡Odds for reporting of at least one episode of confirmed hypoglycaemia during the trial; odds ratios were estimated with a logistic regression model that used data for all randomised participants. 62 participants were included in the IDeg 3TW group, 60 in the IDeg OD(A) group, 61 in the IDeg OD(B) group, and 62 in the IGLar group.

Table 5: Estimated rate ratios and odds ratios of confirmed hypoglycaemic episodes

rash, diarrhoea, stomach discomfort, and peripheral oedema), two participants in the insulin degludec group A (three events; dizziness, dysgeusia, and palpitations), five participants in the insulin degludec group B (headache, increased blood cholesterol, increased weight, pruritus, and muscle spasms), and two participants in the insulin glargine group (headache and increased blood cholesterol). There were few injection-site reactions. One participant in the insulin degludec group A had two itchy erythematous rashes on one observation day, but both were assessed by an independent dermatologist (Dermatolo-Venerology and Wound Healing Centre, Charlottenlund, Denmark) as being probably non-allergic on the basis of digital photographs and detailed history. One participant in the insulin degludec group B and two participants who were treated with insulin glargine had one non-allergic skin reaction each. One mild event of injection-site haematoma occurred in the once a day insulin degludec group B. No skin reactions occurred in the group injected with insulin degludec three times a week.

Concentrations of antibodies that were specific to insulin degludec and those cross-reacting between insulin degludec and human insulin remained close to zero during the trial (webappendix p 4). Most participants did not develop insulin degludec-specific or cross-reactive antibodies, and only eight participants had cross-reactive antibody concentrations of 10% B/T or more in the insulin degludec group A, three in group B, and two in the three times a week group. There was no apparent association between the development of cross-reacting antibodies and hypoglycaemia, HbA_{1c}, or insulin dose in any of the treatment groups (data not shown).

Overall, quality of life assessments suggested marginal changes in patient-reported outcome scores at the end of the trial (webappendix p 5).

Discussion

In this exploratory, clinical proof-of-concept trial in insulin-naïve people with type 2 diabetes, insulin degludec provided once a day or three times a week as add-on to metformin did not differ from insulin glargine in terms of glycaemic control, with no apparent treatment-specific patterns or clustering of adverse events.

Physiological replacement of basal insulin in patients with type 1 and type 2 diabetes is challenging and remains an elusive goal.¹⁷ Presently, there are two basal insulin analogues with improved subcutaneous absorption pharmacokinetics in clinical practice (insulin glargine and insulin detemir).¹⁸ Although both drugs provide very similar glycaemic control to neutral protamine hagedorn insulin with fewer hypoglycaemic events, they remain less than ideal basal-replacement strategies.¹⁹ Hence, many patients are not treated optimally.²⁰ Insulin degludec was developed as a basal insulin with pharmacokinetic properties resulting in an ultra-long action profile.⁷ On the basis of this protracted profile, new applications of this basal insulin such as alternate-day or three times a week injection become possible (panel).

In this trial, total weekly doses were much the same for three treatment groups but were higher in the insulin degludec once a day group B at the end of trial. The low rates of hypoglycaemia reported in this study might be partly attributed to the short duration of

Panel: Research in context**Systematic review**

We searched Medline, Embase, Current Contents Search, and Biosis databases for review and meta-analysis articles published between January, 2007, and December, 2010, without language restrictions with search terms “insulin therapy”, “insulin treatment”, “insulin regimen”, “insulin analogue”, “insulin analog”, “detemir” OR “glargine”. We did not set any criteria for assessment of quality.

Interpretation

Physiological replacement of insulin in diabetes is challenging and remains an elusive goal, as evidenced by the many patients who do not achieve recommended treatment targets. In basal insulin replacement, the presently used insulin analogues glargine and detemir have some advantages over human neutral protamine hagedorn insulin. Insulin degludec has a half-life longer than 24 h² and was developed to provide a more appropriate basal pharmacokinetic profile. In this proof-of-concept phase 2 study in patients with type 2 diabetes, insulin degludec provided much the same glycaemic control as did insulin glargine when injected once a day. Because of its ultra-long action profile, insulin degludec could also be injected three-times weekly and still provide comparable glycaemic control to insulin glargine once a day. This new basal insulin analogue might be a valuable addition to clinical practice.

diabetes in this cohort. The higher mean reported rate of hypoglycaemic episodes in the three-dose per week insulin degludec group than in the other groups might be because larger doses of insulin had to be given at every injection to cover the weekly insulin requirements. However, the higher hypoglycaemic event rate in this group was not statistically significant compared with the other treatment groups and might be partly attributable to two participants having nine and six hypoglycaemic episodes each. Irrespectively, the proportion of participants who had one or more hypoglycaemic episodes was the same in the insulin degludec three times a week group and the insulin glargine group.

Ours is a novel clinical study reporting the use of a three dose per week insulin regimen in the treatment of type 2 diabetes, a regimen that was made possible because of insulin degludec's ultra-long action profile and unique mechanism of protraction. A three times a week, weekend-off, dosing regimen might appeal to some people with type 2 diabetes who are inadequately controlled on oral antidiabetic drug treatments, potentially helping with acceptance and early initiation of insulin therapy. The applicability and acceptance of such a dosing regimen needs to be assessed.

This proof-of-concept trial has several limitations inherent to phase 2 regulatory studies. Caution should be exercised in drawing of firm conclusions from the data.

The open-label design that was used to accommodate the different insulin-injection systems could have affected efforts to attain blood glucose control and reporting of hypoglycaemia and adverse events.

In summary, findings from this trial show that insulin degludec can provide equivalent glycaemic control to insulin glargine without new or increased rates of adverse events in insulin-naïve people with type 2 diabetes. The safety, efficacy, and optimum use of treatment regimens for insulin degludec need to be established.

Contributors

BZ helped to design the study, obtain data, interpret the data, and prepare the final report. PVR, NT, AL, JR, and MP helped to obtain and interpret data and prepare the final report. GF, LAE, and CM helped to design the study, interpret data, and prepare the final report. TJ was the International Medical Director for the trial and helped to design the study, interpret the data, and prepare the final report. RL prepared the first draft of the report, edited subsequent revisions, and helped to interpret data. All authors approved the final version of the report.

Conflicts of interest

LAE, TJ, and RL are employees of Novo Nordisk and own stock in the company. BZ has received fees for consultancy and honoraria for membership of advisory boards from Novo Nordisk, GlaxoSmithKline, Merck, Eli Lilly, Amylin, and Boehringer Ingelheim and grant support from Novo Nordisk, GlaxoSmithKline, and Merck. BZ has also received travel and accommodation expenses from Novo Nordisk to attend an investigators' meeting and expense coverage from Novo Nordisk to attend scientific meetings. GF has received fees for consultancy and honoraria for membership of advisory boards from Novo Nordisk, Sanofi-Aventis, Eli Lilly, Merck/Schering-Plough, AstraZeneca, Novartis, and Boehringer Ingelheim. PVR has received research support, fees for consultancy, and honoraria for membership of advisory boards from Novo Nordisk and DiabetOmics; travel and accommodation expenses from Novo Nordisk to attend an investigators' meeting; and is a board member of DiabetOmics. AL has received fees for consultancy, honoraria for membership on advisory boards, and research support from Novo Nordisk, GlaxoSmithKline, Sanofi-Aventis, Merck, Daiichi-Sankyo, Forest Laboratories, Roche, Vivus, Abbott, Novartis, Takeda, Hollis-Eden, Phenomix, Surface Logix, Akros Pharma, ActivX Bioscience, and Amylin; and travel and accommodation expenses from Novo Nordisk to attend an investigators' meeting. JR received fees for consultancy, honoraria for membership of advisory boards, and research support from Novo Nordisk, GlaxoSmithKline, Sanofi-Aventis, Amylin, Daiichi-Sankyo, Forest Labs, Roche, Novartis, Takeda, Pfizer, Eli Lilly, MannKind, Johnson and Johnson, and Boehringer Ingelheim; research support from AstraZeneca, Merck, and Bristol-Myers Squibb; and travel and accommodation expenses from Novo Nordisk to attend an investigators' meeting. MP has received fees for consultancy and honoraria for membership of advisory boards from Novo Nordisk and Roche; fees for consultancy from Medtronic MiniMed and Ypsomed; and travel and accommodation expenses from Novo Nordisk to attend an investigator's meeting. CM has received fees for consultancy and honoraria for membership of advisory boards from Novo Nordisk, Pfizer, Eli Lilly, Sanofi-Aventis, Johnson and Johnson, Mannkind, and Novartis. NT has received travel and accommodation expenses from Novo Nordisk to attend an investigators' meeting.

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