# Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naive patients with type 2 diabetes: results of two phase 3, 26 week, randomised, open-label, treat-to-target, non-inferiority trials

*Bernard Zinman, J Hans DeVries, Bruce Bode, David Russell-Jones, Lawrence A Leiter, Alan Moses, Thue Johansen, Robert Ratner, on behalf of the NN1250-3724 (BEGIN:EASY AM) and NN1250-3718 (BEGIN:EASY PM) Trial Investigators*

## Summary

**Background** Results of an exploratory phase 2 study showed that insulin degludec, a basal insulin with an action profile of longer than 42 h, provided similar glycaemic control when injected three times a week (IDeg 3TW) to once-daily insulin glargine (IGlar OD). To provide further evidence, we did two phase 3 trials to compare the efficacy and safety of IDeg 3TW with IGlar OD in insulin-naive patients with type 2 diabetes.

**Methods** In two 26 week, randomised, open-label, parallel group, non-inferiority trials IDeg was injected Monday, Wednesday, and Friday before breakfast (IDeg 3TW$_{AM}$) in the AM trial (94 sites in seven countries) or with the evening meal (IDeg 3TW$_{PM}$) in the PM trial (89 sites in seven countries), and compared with IGlar OD. Adults with type 2 diabetes (HbA$_{1c}$ 7·0–10·0%; body-mass index ≤45 kg/m²) were randomly allocated (1:1) without stratification by a central interactive response system to IDeg 3TW or IGlar OD. Both groups continued taking metformin with or without dipeptidyl peptidase-4 inhibitors. Insulin was titrated to achieve a prebreakfast self-monitored blood glucose (SMBG) concentration of between 3·9 and less than 5·0 mmol/L. The primary outcome was non-inferiority of IDeg 3TW compared with IGlar OD, as assessed by change in HbA$_{1c}$ from baseline to 26 weeks (non-inferiority limit of 0·4%) by ANOVA in an intent-to-treat analysis (full analysis set). These trials are registered with ClinicalTrials.gov, numbers NCT01068678 and NCT01076647.

**Findings** We recruited 460 patients for the AM trial (IDeg 3TW$_{AM}$, n=230; IGlar OD, n=230) and 467 patients for the PM trial (IDeg 3TW$_{PM}$, n=233; IGlar OD, n=234). After 26 weeks, mean HbA$_{1c}$ decreased by 0·9% (IDeg 3TW$_{AM}$) and 1·3% (IGlar OD) in the AM trial, and by 1·1% (IDeg 3TW$_{PM}$) and 1·4% (IGlar OD) in the PM trial. Non-inferiority was not confirmed in either trial (estimated treatment difference [IDeg 3TW$_{AM}$–IGlar OD] 0·34%, 95% CI 0·18–0·51; [IDeg 3TW$_{PM}$–IGlar OD] 0·26%, 0·11–0·41). Across the two trials, rates of confirmed hypoglycaemia (SMBG <3·1 mmol/L or severe [needing assistance]) ranged from 1·0 to 1·6 episodes per patient-year and were similar for IDeg 3TW$_{AM}$ and IGlar OD (estimated rate ratio [ERR] 1·04, 95% CI 0·69–1·55), but higher for IDeg 3TW$_{PM}$ than for IGlar OD (ERR 1·58, 1·03–2·43). The rate of nocturnal confirmed hypoglycaemia was higher for IDeg 3TW$_{AM}$ than for IGlar OD (ERR 2·12, 1·08–4·16); we noted no significant difference between IDeg 3TW$_{PM}$ and IGlar OD (ERR 0·60, 0·21–1·69).

**Interpretation** The inferior glycaemic control and increased risk of hypoglycaemia with IDeg 3TW compared with IGlar OD do not support a three-times-weekly dosing regimen.

**Funding** Novo Nordisk.

Published **Online** July 9, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70013-5

**Samuel Lunenfeld Research Institute, Mount Sinai Hospital** (Prof B Zinman MDCM) **and Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael's Hospital** (Prof L A Leiter MD), **University of Toronto, Toronto, Canada; Department of Internal Medicine, Academic Medical Centre, Amsterdam, Netherlands** (J Hans DeVries MD); **Atlanta Diabetes Associates, Atlanta, GA, USA** (B Bode MD); **Royal Surrey County Hospital, Guildford, Surrey, UK** (Prof D Russell-Jones MD); **Novo Nordisk, Princeton, NJ, USA** (A Moses MD); **Novo Nordisk, Søborg, Denmark** (T Johansen MD); **and Georgetown University School of Medicine, Washington, DC, USA** (R Ratner MD)

Correspondence to:
Prof Bernard Zinman, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, M5T 3L9, Canada
**zinman@lumenfield.ca**

## Introduction

Insulin degludec is a basal insulin analogue that forms a soluble depot of multihexamers after subcutaneous injection,[1] resulting in a long half-life (about 25 h) and a consistent glucose-lowering effect that lasts longer than 42 h.[2–4] Results of phase 3a treat-to-target trials in patients with type 1 and type 2 diabetes have shown that once-daily insulin degludec provides similar glycaemic control to insulin glargine but with lower rates of hypoglycaemia, particularly during the night.[5–8] Insulin degludec is approved for once-daily dosing in the European Union, Japan, and Mexico and is under regulatory review in other countries; the US Food and Drug Administration (FDA) has requested additional cardiovascular data from a dedicated cardiovascular outcomes trial before their review can be completed.

On the basis of the ultra-long pharmacokinetic and pharmacodynamic profile of insulin degludec, a three-times-weekly dosing regimen was explored in a 16 week, proof-of-concept phase 2, treat-to-target trial in patients with type 2 diabetes.[9] In that trial, insulin degludec injected three times a week (IDeg 3TW) provided similar glycaemic control to once-daily insulin glargine (IGlar OD), with similar rates of hypoglycaemia.[9] Because a three-times-weekly dosing schedule might, for some patients, be an appealing alternative to the

once-daily dosing regimens required by basal insulin analogues, larger, phase 3 trials to further test this treatment and dosing schedule were deemed important.

The objective of this study was to analyse the data from two 26 week, phase 3 trials that compared the efficacy and safety of IDeg 3TW with IGlar OD in previously insulin-naive patients with type 2 diabetes inadequately controlled by oral antidiabetic (OAD) treatments.

## Methods

### Study design and participants

Both phase 3 trials were of identical design (26 week, randomised, treat-to-target, two-arm, parallel group, and open-label), differing only in terms of whether insulin degludec was administered in the morning before the first meal of the day (AM trial) or with the main evening meal (PM trial). The AM trial was done at 94 sites in seven countries (Canada, Czech Republic, Israel, Slovakia, South Africa, UK, and USA) from February to November, 2010; the PM trial was done at 89 sites in seven countries (Bulgaria, Canada, France, Hungary, Netherlands, Romania, and USA) from March to December, 2010. Trial sites included hospitals, specialist diabetes clinics, and general practices. Trial protocols were approved by independent ethics committees or institutional review boards (informed consent was obtained before participants entered the trial) and undertaken according to the Declaration of Helsinki[10] and Good Clinical Practice.[11]

Patient inclusion and exclusion criteria were identical for both trials: adults (aged ≥18 years) with type 2 diabetes mellitus for 6 months or longer, $HbA_{1c}$ concentration of 7·0–10·0% (53–86 mmol/mol; inclusive), and body-mass index of 45 kg/m² or less. Participants had to be insulin-naive (previous short-term insulin treatment of ≤14 days permitted), and were excluded if they had taken glucagon-like peptide-1 receptor agonists or thiazolidinediones within 3 months of screening (appendix).

See Online for appendix

### Randomisation and masking

Eligible participants were randomly assigned (1:1) by a simple sequential allocation from a blocked randomisation schedule (without stratification) via a central interactive voice response or web response system. Participants were assigned to receive either insulin degludec on Monday, Wednesday, and Friday (IDeg 3TW) or insulin glargine once daily (IGlar OD) at any time during the day (but at the same time each day) as chosen by participant and investigator, according to local product labelling[12] (the time of dosing was not recorded). In the AM trial, insulin degludec was administered in the morning, anytime between waking and the first meal of the day (IDeg $3TW_{AM}$); in the PM trial, insulin degludec was administered with the main evening meal (IDeg $3TW_{PM}$). Treatment group assignment was masked for titration surveillance personnel, safety committee members (an internal safety committee provided by the sponsor that was responsible for safety surveillance, and an independent committee that adjudicated cardiovascular events according to the predefined classifications of the insulin degludec phase 3 development programme), and personnel involved in defining analysis sets until data were locked for statistical analysis.

### Procedures

Insulin degludec (200 U/mL, 3 mL PDS290, Novo Nordisk, Bagsvaerd, Denmark) and insulin glargine (100 U/mL, 3 mL SoloSTAR, Sanofi, Paris, France) were injected subcutaneously. At randomisation, participants discontinued all OADs except metformin and dipeptidyl peptidase-4 (DPP4) inhibitors; these drugs were maintained at pretrial doses and dosing frequency (DPP4 inhibitors were continued only in countries where combination treatment with insulin had regulatory approval [South Africa and USA]). Starting doses were 10 U (IGlar OD) or 20 U (IDeg 3TW) to achieve similar initial weekly doses. On the basis of prebreakfast self-measured blood glucose (SMBG) measurements (mean value from 3 consecutive days), insulin doses were titrated individually once a week to a plasma glucose concentration of 3·9 to less than 5·0 mmol/L with a common algorithm (IDeg 3TW dose adjustments were twice those of IGlar OD; appendix). Participants used a glucose meter (Abbott Diabetes Care, Abbott Park, IL, USA), calibrated to plasma values, to measure their blood glucose concentration.

### Outcome measures

The primary endpoint was change in $HbA_{1c}$ concentration from baseline to week 26 of treatment. Secondary efficacy endpoints included achievement of an $HbA_{1c}$ concentration of less than 7·0%, changes in laboratory-measured fasting plasma glucose (FPG), insulin dose, 9-point SMBG profiles, and health-related quality of life (HRQoL) assessed with the Short Form 36 (SF-36v2) questionnaire.[13] Safety assessments included adverse events (incidence and severity), hypoglycaemic episodes, injection-site reactions, bodyweight, laboratory analyses, physical examination, vital signs, fundoscopy, and electrocardiogram (ECG). Regional central laboratories (Quintiles Laboratories in UK, USA, and South Africa) did laboratory analyses, including assessment of $HbA_{1c}$ and FPG concentrations. $HbA_{1c}$ was measured using a National Glycohemoglobin Standardization Program-certified high-performance liquid chromatography method. Confirmed hypoglycaemia was defined as an episode confirmed by a plasma glucose value of less than 3·1 mmol/L (irrespective of symptoms) or a severe episode (needing assistance). Confirmed hypoglycaemia with onset between 0001 h and 0559 h (inclusive) was classified as nocturnal.

### Statistical analyses

The primary objective of both trials was to confirm non-inferiority of IDeg 3TW compared with IGlar OD,

assessed by change in $HbA_{1c}$ concentration from baseline to week 26. For each trial we calculated sample size with a one-sided *t* test with α=0·025 (used because non-inferiority is a one-sided hypothesis), assuming a mean treatment difference of 0, and an SD of 1·3% for $HbA_{1c}$. Assuming a 15% dropout rate, 450 participants needed to be randomly assigned for at least 85% power in the per-protocol analysis set.

Statistical analyses of $HbA_{1c}$, FPG, SMBG, HRQoL, and hypoglycaemia included all randomly assigned participants (full analysis set), following the intention-to-treat principle. We assessed safety endpoints in participants exposed to treatment. Missing values were imputed using last observation carried forward.[14]

We assessed treatment differences in changes in $HbA_{1c}$ concentration from baseline to week 26 with an ANOVA model, in which treatment, antidiabetic therapy at screening, sex, and region were fixed factors, and age and baseline value were covariates. Non-inferiority was confirmed if the upper limit of the 95% CI for the treatment difference was 0·4% or lower as per FDA guidelines.[14] We analysed the proportion of participants attaining an $HbA_{1c}$ of less than 7·0% with a logistic regression model with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and baseline $HbA_{1c}$ as covariates.

Changes in FPG and HRQoL from baseline to week 26 were analysed with a similar ANOVA model to that used for the primary endpoint. We used this model also for a post-hoc analysis of week 26 prebreakfast SMBG concentrations on the first, second, and third days after the previous injection of insulin degludec. We defined the mean of the 9-point SMBG profile as the area under the profile calculated by the trapezoidal method divided by the time from first to ninth measurement.

We calculated rate ratio estimates of hypoglycaemic episodes with a negative binomial regression model including treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age as a covariate.

We report data with 95% CI and p values for two-sided testing at α=0·05 (for the primary endpoint [$HbA_{1c}$], the one-sided test of non-inferiority was assessed at α=0·025). All statistical analyses were as described in the trial protocols (apart from the post-hoc analysis) and were run with SAS version 9.1.3.

These trials are registered with ClinicalTrials.gov, numbers NCT01068678 and NCT01076647.

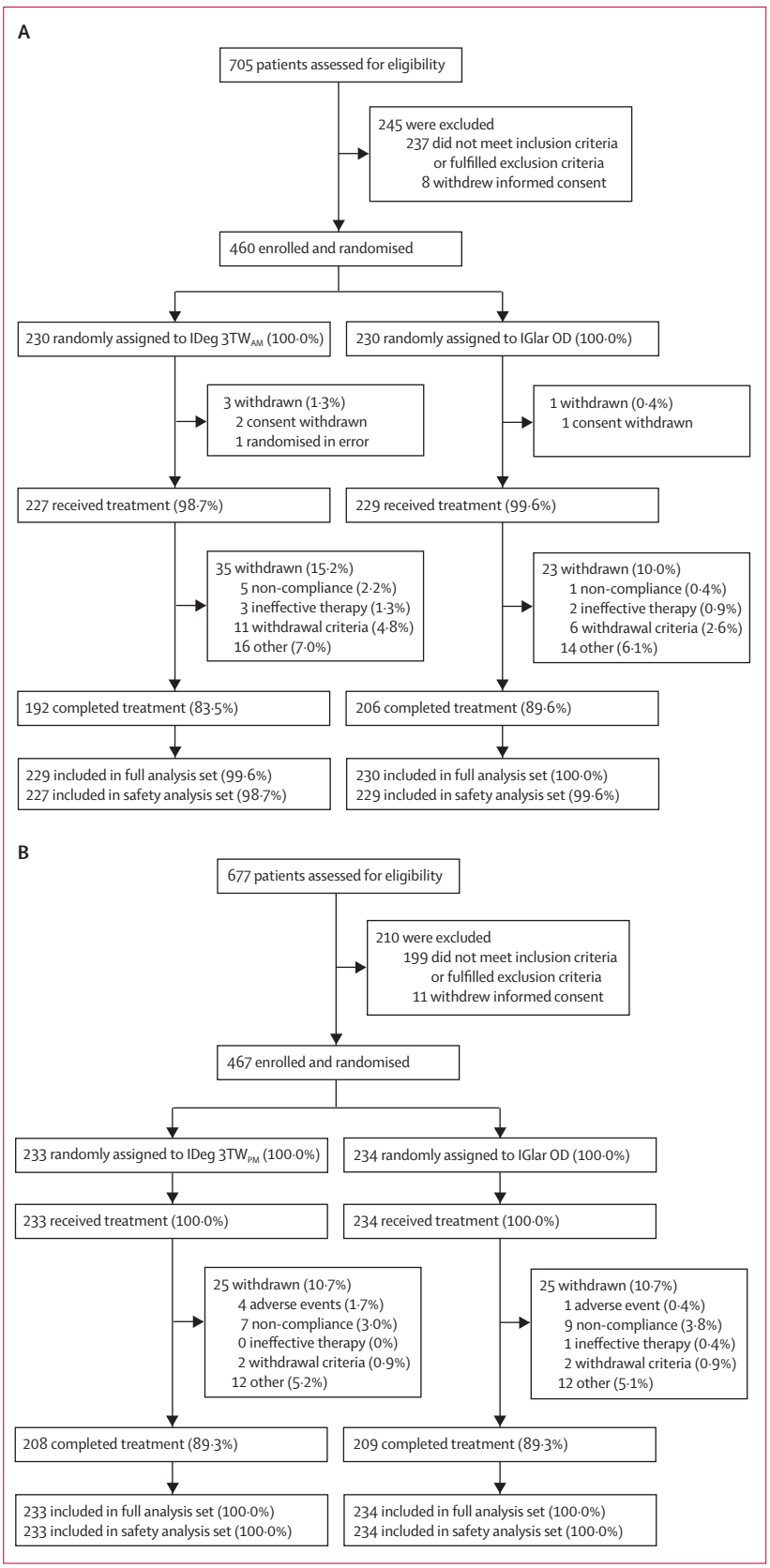


***Figure 1*: Trial profiles**

(A) Trial profile for AM trial (insulin degludec administered in the morning). (B) Trial profile for PM trial (insulin degludec administered in the evening). Percentages are the proportions of randomly assigned participants at each stage. IDeg 3TW$_{AM}$=insulin degludec administered three times weekly between waking up and the first meal of the day. IDeg 3TW$_{PM}$=insulin degludec administered three times weekly with the main evening meal. IGlar OD=insulin glargine administered once daily.

### Role of funding source

The sponsor of the study was responsible for trial design, trial product supply, monitoring, data collection, statistical analyses, and preparation of the trial report. DR-J and LAL were signatory investigators for the AM and PM trial reports, respectively, had access to the raw data, reviewed the trial report, and approved the final version. All authors reviewed and discussed data at an author meeting before the writing process began and were given full access to the trial reports. All authors had final responsibility for manuscript content and the decision to submit for publication.

## Results

Of the 705 participants screened in the AM trial, and the 677 participants screened in the PM trial, 460 (AM) and 467 (PM) were randomly assigned to treatment (figure 1). Similar proportions of participants completed treatment in each trial (figure 1). Within each trial, baseline and demographic characteristics in the full analysis set (ie, all randomised patients excluding one patient in the IDeg 3TW$_{AM}$ trial who was randomised in error) were well matched between groups, except for slight differences in race and bodyweight in the AM trial (table 1). Baseline variables were similar between trials, apart from differences in the proportion of participants on different prestudy OAD treatment regimens (table 1).

After 26 weeks, mean HbA$_{1c}$ concentration had decreased in patients receiving IDeg 3TW and those receiving IGlar OD (figure 2A and 2B). In the AM trial, the estimated mean change in HbA$_{1c}$ from baseline was –0·93% with IDeg 3TW$_{AM}$ and –1·28% with IGlar OD (estimated mean treatment difference [ETD; IDeg 3TW$_{AM}$–IGlar OD] 0·34%, 95% CI 0·18–0·51). In the PM trial, the estimated mean change in HbA$_{1c}$ from baseline was –1·09% with IDeg 3TW$_{PM}$ and –1·35% with IGlar OD (ETD [IDeg 3TW$_{PM}$–IGlar OD] 0·26%, 0·11–0·41). Thus, non-inferiority of IDeg 3TW to IGlar OD was not shown in either trial. The robustness of the primary analyses was supported by sensitivity analyses (appendix). In both trials, a significantly lower proportion of participants achieved an HbA$_{1c}$ target of less than 7·0% with IDeg 3TW than with IGlar OD (AM trial, 48% [110 of 229 patients] *vs* 58% [134 of 230 patients], p=0·0177; PM trial, 46% [107 of 233 patients] *vs* 54% [127 of 234 patients], p=0·0183).

Mean laboratory-measured FPG values decreased from baseline in all groups (figure 2C and 2D). In both trials, IGlar OD was associated with a significantly greater reduction in FPG than was IDeg 3TW after 26 weeks (AM trial, ETD [IDeg 3TW$_{AM}$–IGlar OD] 0·72 mmol/L, 95% CI 0·29–1·14, p=0·001; PM trial, ETD [IDeg 3TW$_{PM}$–IGlar OD] 0·50 mmol/L, 0·10–0·90, p=0·0144).

Mean 9-point SMBG profile improved from baseline in all groups (appendix). After 26 weeks, the estimated overall mean SMBG concentration of the 9-point profile was significantly lower for IGlar OD in both the AM trial (ETD [IDeg 3TW$_{AM}$–IGlar OD] 0·5 mmol/L, 95% CI 0·16–0·83; p=0·0035) and the PM trial (ETD [IDeg 3TW$_{PM}$–IGlar OD] 0·43 mmol/L, 0·12–0·74; p=0·0064). With IDeg 3TW (AM or PM), mean prebreakfast SMBG concentrations in week 26 of the trial were similar to those in the IGlar OD group on the day after dosing, but significantly higher at 2 and 3 days after the previous injection of insulin degludec (post-hoc analysis; figure 3).

Insulin doses were adjusted during the trial to aim for a prebreakfast SMBG target of between 3·9 and less than 5·0 mmol/L. In the AM trial, 22 (9·6%) of 229 participants in the IDeg 3TW group and 38 (16·6%) of 229 participants in the IGlar OD group met this titration target, compared with 33 (14·2%) of 233 and 62 (26·5%) of 234 participants, respectively, in the PM trial.

In terms of mean calculated daily insulin dose (weekly IDeg 3TW dose divided by 7), the insulin degludec starting dose was about 85% of the mean daily dose of IGlar OD in both trials (appendix). Mean calculated daily doses (insulin degludec) and actual daily doses (insulin glargine) increased in all groups during the trials but did so at a lower rate with IDeg 3TW than with IGlar OD throughout the treatment period (appendix). The end-of-trial mean calculated daily insulin dose in the AM

| | AM trial | | PM trial | |
|---|---|---|---|---|
| | IDeg 3TW$_{AM}$ | IGlar OD | IDeg 3TW$_{PM}$ | IGlar OD |
| n | 229 | 230 | 233 | 234 |
| Female | 105 (45·9%) | 93 (40·4%) | 101 (43·3%) | 99 (42·3%) |
| Race | | | | |
| White | 182 (79·5%) | 202 (87·8%) | 212 (91·0%) | 210 (89·7%) |
| Black | 23 (10·0%) | 12 (5·2%) | 16 (6·9%) | 17 (7·3%) |
| Asian | 20 (8·7%) | 15 (6·5%) | 3 (1·3%) | 5 (2·1%) |
| Other | 4 (1·7%) | 1 (0·4%) | 2 (0·9%) | 2 (0·9%) |
| Hispanic or Latin American ethnicity | 17 (7·4%) | 16 (7·0%) | 25 (10·7%) | 33 (14·1%) |
| Age (years) | 58·4 (9·9) | 57·9 (9·7) | 57·3 (9·6) | 57·5 (10·7) |
| Bodyweight (kg) | 90·8 (18·6) | 95·7 (19·0) | 92·3 (18·3) | 91·4 (18·7) |
| Body-mass index (kg/m$^2$) | 31·9 (5·1) | 33·0 (5·4) | 32·3 (5·1) | 31·9 (5·5) |
| Duration of diabetes (years) | 9·2 (6·4) | 8·5 (5·7) | 8·4 (6·2) | 9·2 (0·6) |
| HbA$_{1c}$ (%) | 8·2 (0·8) | 8·3 (0·9) | 8·3 (0·8) | 8·3 (0·8) |
| HbA$_{1c}$ (mmol/mol)* | 66 | 67 | 67 | 67 |
| Fasting plasma glucose (mmol/L) | 9·3 (2·4) | 9·6 (2·4) | 9·9 (2·2) | 9·9 (2·4) |
| Fasting plasma glucose (mg/dL) | 167·6 (43·2) | 173·2 (4·8) | 178·1 (40·5) | 177·9 (43·9) |
| Prestudy treatment | | | | |
| Metformin monotherapy | 67 (29·3%) | 70 (30·4%) | 54 (23·2%) | 54 (23·1%) |
| Metformin + DPP4 inhibitor ± sulphonylurea or glinides ± α-glucosidase inhibitor | 52 (22·7%) | 52 (22·6%) | 40 (17·2%) | 35 (15·0%) |
| Metformin ± sulphonylurea or glinides ± α-glucosidase inhibitor | 110 (48·0%) | 108 (47·0%) | 139 (59·7%) | 145 (62·0%) |

Data are number (%) or mean (SD). IDeg 3TW$_{AM}$=insulin degludec administered three times a week between waking up and first meal of day. IGlar OD=insulin glargine administered once daily. IDeg 3TW$_{PM}$=insulin degludec administered three times a week with the main evening meal. DPP4=dipeptidyl peptidase-4. *Calculated by the following formula: HbA$_{1c}$ (mmol/mol)=[HbA$_{1c}$ (%)–2·15]×10·929.

***Table 1*: Baseline characteristics of patients in the full analysis set**

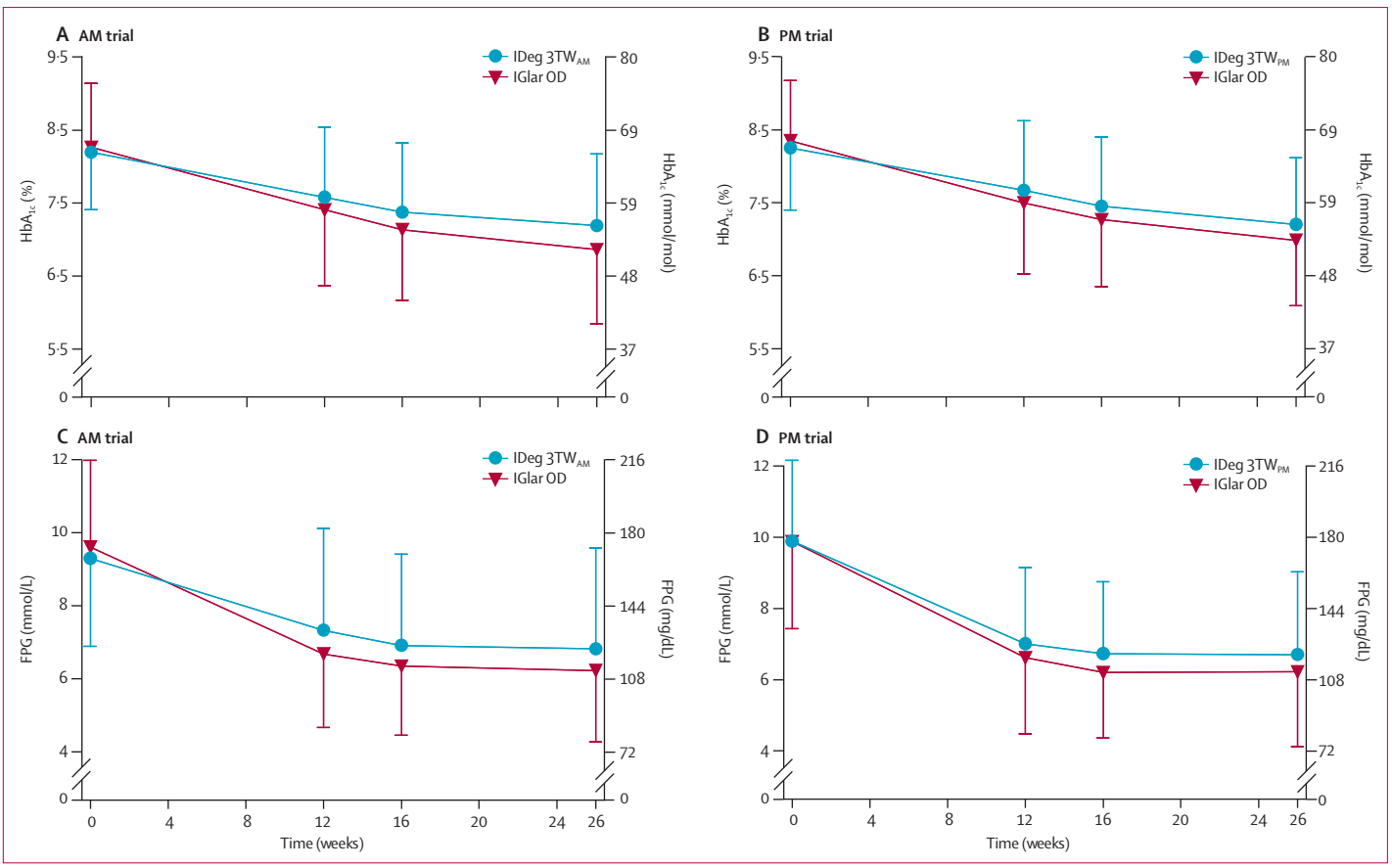


***Figure 2*: Glycaemic efficacy**

Mean HbA$_{1c}$ concentration over time in the AM trial (A) and PM trial (B). Mean FPG over time in the AM trial (C) and PM trial (D). Missing postbaseline data were imputed using the last observation carried forward approach. Results of analysis of data obtained at 26 weeks were p=0·251 for one-sided test of non-inferiority evaluated at the 2·5% level for (A); p=0·03 for one-sided test of non-inferiority evaluated at the 2·5% level for (B); p=0·001 for the estimated treatment difference evaluated at the 5% level for (C); and p=0·0144 for the estimated treatment difference evaluated at the 5% level for (D). Datapoints show mean; lines show SD. FPG=fasting plasma glucose. IDeg 3TW$_{AM}$=insulin degludec administered three times weekly between waking up and the first meal of the day. IDeg 3TW$_{PM}$=insulin degludec administered three times weekly with the main evening meal. IGlar OD=insulin glargine administered once daily.

trial was 50 U in the IDeg 3TW$_{AM}$ group versus an actual daily dose of 62 U in the IGlar OD group; in the PM trial it was 51 U (IDeg 3TW$_{PM}$) versus 56 U (IGlar OD).

Mean weight gain (baseline to end of trial) was similar between groups in each trial: 0·8 kg (IDeg 3TW$_{AM}$) and 1·2 kg (IGlar OD) in the AM trial (ETD –0·41 kg, 95% CI –1·08 to 0·26; p=0·2317), and 0·8 kg (IDeg 3TW$_{PM}$) and 0·5 kg (IGlar OD) in the PM trial (ETD 0·27 kg, –0·42 to 0·96; p=0·4423).

For both trials, differences in domain scores (change from baseline to end of trial) of the HRQoL questionnaire (SF-36) did not differ significantly between the IDeg 3TW and IGlar OD groups (appendix).

Table 2 shows the proportion of participants who reported at least one confirmed hypoglycaemic episode. Severe hypoglycaemia was rare: two episodes occurred in the AM trial (one in each of the IDeg 3TW$_{AM}$ and IGlar OD groups) and one episode occurred in the PM trial (IDeg 3TW$_{PM}$). Across the two trials, rates of confirmed hypoglycaemia ranged from 1·0 to 1·6 episodes per patient-year of exposure (table 2), and were similar for both the IDeg 3TW$_{AM}$ and IGlar OD groups (estimated rate ratio [ERR] 1·04, 95% CI 0·69–1·55; p=0·8583) but were significantly higher for IDeg 3TW$_{PM}$ than for IGlar OD (ERR 1·58, 1·03–2·43; p=0·0365). No significant difference in the rate of nocturnal confirmed hypoglycaemia was recorded between IDeg 3TW$_{PM}$ and IGlar OD (ERR 0·60, 0·21–1·69; p=0·3357); however, the rate of nocturnal confirmed hypoglycaemia was significantly higher in the IDeg 3TW$_{AM}$ group than in the IGlar OD group (ERR 2·12, 1·08–4·16; p=0·0291).

In both trials, results of post-hoc analyses showed that the number of nocturnal confirmed hypoglycaemic episodes in the IDeg 3TW group in the first 24 h (roughly) after each insulin degludec injection was about two to three times higher than in the subsequent 24 h (figure 4).

In the AM trial, 140 (61·7%) of 227 participants receiving insulin degludec and 151 (65·9%) of 229 participants receiving insulin glargine reported at

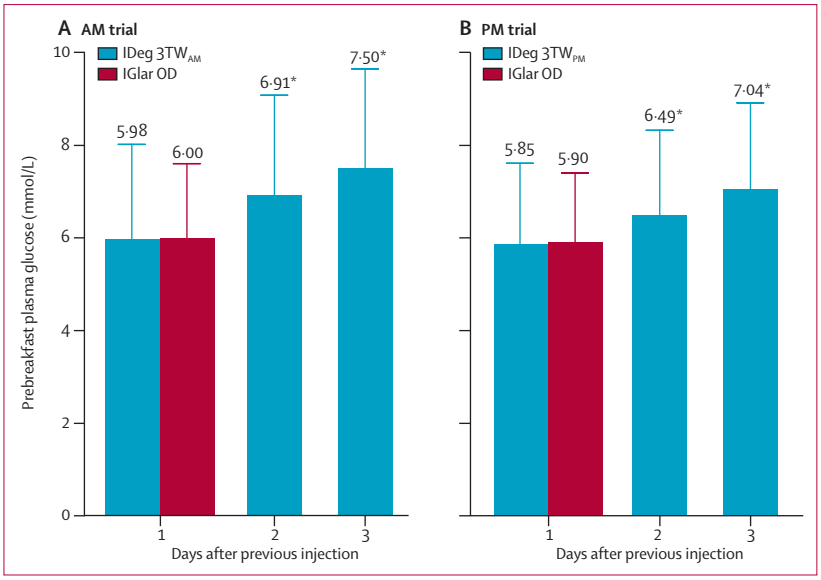


***Figure 3*: Mean prebreakfast plasma glucose**

Mean prebreakfast self-monitored blood glucose (SMBG) in the AM trial (A) and PM trial (B). SMBG measurements were made on the 3 days before the visit on week 26. Data presented for IDeg 3TW represent mean of measurements made on Tuesday, Thursday, and Saturday (ie, 1 day after previous injection); Wednesday, Friday, and Sunday (2 days after previous injection); and Monday (3 days after previous injection). Data presented for insulin glargine represent overall mean prebreakfast SMBG measured in week 26. Participants with no week 26 data had their data imputed by the last observation carried forward method. Bars show mean; lines show SD. IDeg 3TW$_{AM}$=insulin degludec administered three times weekly between waking up and the first meal of the day. IDeg 3TW$_{PM}$= insulin degludec administered three times weekly with the main evening meal. IGlar OD=insulin glargine administered once daily. *p<0·0001 for pairwise comparison versus IGlar OD.

| | Confirmed hypoglycaemia | | | Confirmed nocturnal hypoglycaemia† | | |
|---|---|---|---|---|---|---|
| | Number of participants | Number of events | Rate‡ | Number of participants | Number of events | Rate‡ |
| **AM trial** | | | | | | |
| IDeg 3TW$_{AM}$ | 62/227 (27·3%) | 136 | 1·3 | 26/227 (11·5%) | 39 | 0·4 |
| IGlar OD | 65/229 (28·4%) | 127 | 1·2 | 17/229 (7·4%) | 19 | 0·2 |
| **PM trial** | | | | | | |
| IDeg 3TW$_{PM}$ | 75/233 (32·2%) | 175 | 1·6 | 10/233 (4·3%) | 26 | 0·2 |
| IGlar OD | 50/234 (21·4%) | 110 | 1·0 | 16/234 (6·8%) | 25 | 0·2 |

IDeg 3TW$_{AM}$=insulin degludec administered three times weekly between waking up and first meal of day. IGlar OD=insulin glargine administered once daily. IDeg 3TW$_{PM}$=insulin degludec administered three-times weekly with the main evening meal. *Occurring on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment. †Confirmed hypoglycaemia with an onset between 0001 h and 0559 h (inclusive). ‡Unadjusted event rate (episodes per patient-year of exposure).

***Table 2*: Summary of hypoglycaemic episodes***

least one adverse event, compared with 139 (59·7%) of 233 and 119 (50·9%) of 234 in the PM trial (appendix). For both trials, most adverse events (>90%) were mild or moderate in severity; nasopharyngitis, headache, and diarrhoea were most frequently reported. No treatment-specific adverse event patterns were apparent and no adverse events were fatal. Five adverse events were adjudicated as major adverse cardiovascular events in the AM trial: three in the IDeg 3TW$_{AM}$ group (one case of stroke and two cases of acute coronary syndrome) and two in the IGlar OD group (two cases of acute coronary syndrome). Three adverse events were adjudicated as major adverse cardiovascular events in the PM trial: one in the IDeg 3TW$_{PM}$ group (acute coronary syndrome) and two in the IGlar OD group (two cases of acute coronary syndrome). All events were judged by the investigator as unlikely to be related to trial treatment.

In the AM trial, 27 (11·9%) of 227 participants in the IDeg 3TW group and 30 (13·1%) of 229 participants in the IGlar OD group reported injection-site reactions compared with 15 (6·4%) of 233 and seven (3·0%) of 234, respectively, in the PM trial.

No differences were noted in standard laboratory measurements, physical examination findings, vital signs, ECG, or fundoscopy between the treatment groups of each trial.

## Discussion

In both trials, clinically relevant improvements in long-term glycaemic control (HbA$_{1c}$) were recorded for IGlar OD and IDeg 3TW, although the HbA$_{1c}$ reduction was greater with IGlar OD. Indeed, irrespective of whether insulin degludec was injected in the morning or evening, non-inferiority to IGlar OD with respect to change in HbA$_{1c}$ from baseline was not established. IDeg 3TW was also inferior to IGlar OD in terms of reductions from baseline in laboratory-measured FPG and SMBG concentrations. IDeg 3TW resulted in similar prebreakfast SMBG concentrations to IGlar OD on the day after injection. However, mean concentrations measured on the second and third days after the previous injection of insulin degludec were progressively higher than with IGlar OD, suggesting a waning of effect with time that probably explains, at least in part, why non-inferiority of insulin degludec to insulin glargine in overall glycaemic control was not met.

The inferior glycaemic control provided by IDeg 3TW might also be attributable to the lower calculated mean daily doses of insulin degludec given throughout both trials compared with insulin glargine. This probably resulted from the higher risk of hypoglycaemia with IDeg 3TW and greater caution in the adjustment of doses of the new drug (insulin degludec), particularly since starting doses per injection (and dose adjustments) were twice that of insulin glargine. In addition to standard monitoring, specific Novo Nordisk staff masked to the treatment allocation visited most sites to ensure that the dosing algorithm was being followed as closely as possible. For both trials, doses prescribed by investigators corresponded well with the titration algorithm, as did prescribed doses and actual doses administered by the patients. Furthermore, compliance with the three-times-weekly and once-daily dosing regimens was high, with no apparent differences between regimens. The lower doses associated with IDeg 3TW throughout the trial were also partly the result of the dose adjustment algorithm, which was based on

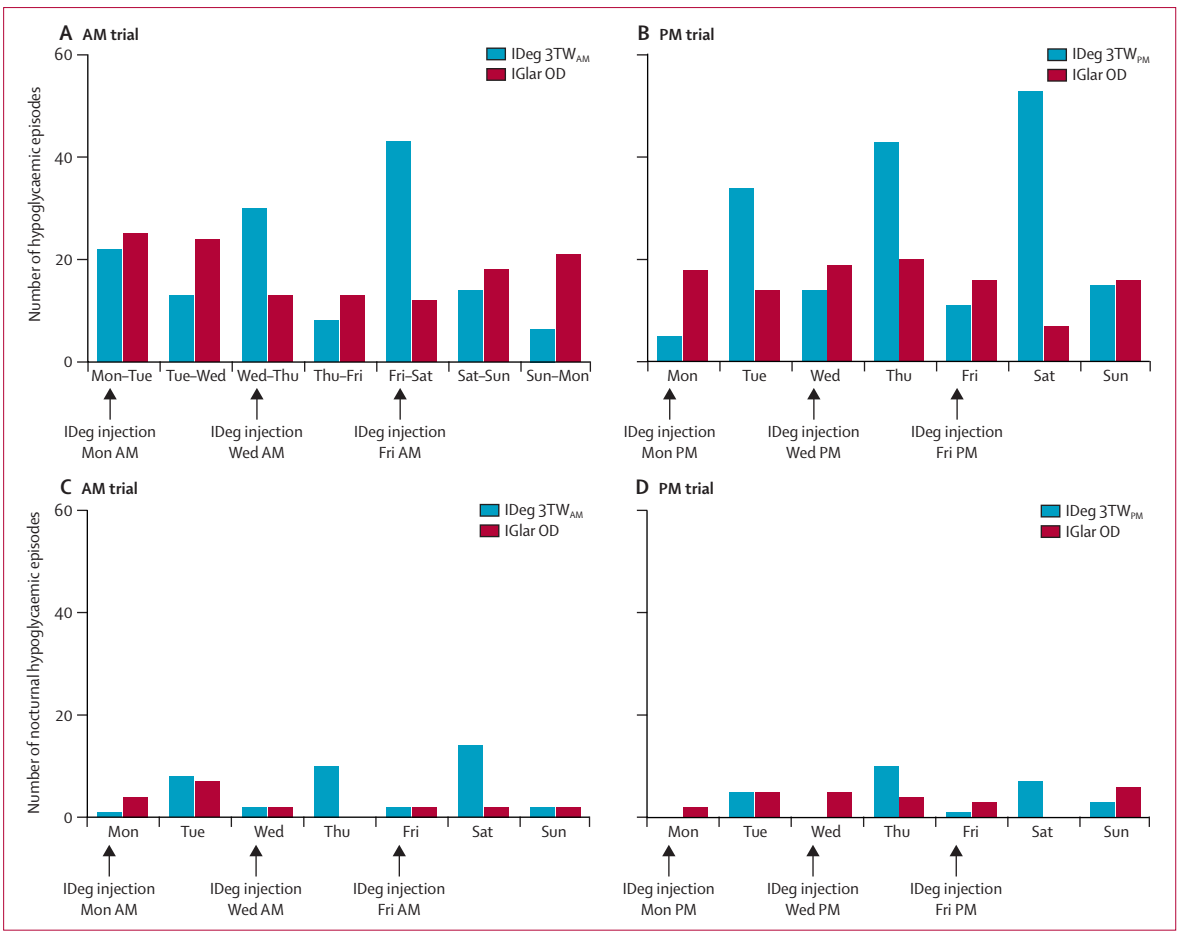


***Figure 4*: Number of confirmed hypoglycaemic episodes by day**

Overall number of episodes of confirmed hypoglycaemia reported in the AM trial (A) and in the PM trial (B). Overall number of episodes of nocturnal confirmed hypoglycaemia (ie, confirmed hypoglycaemia with an onset between 0001 h and 0559 h, inclusive) in the AM trial (C) and in the PM trial (D). Because insulin degludec was injected in the morning in the AM trial, hypoglycaemic episodes are presented in intervals from noon on one day to noon the following day in (A) to show the overall number of episodes in the first 24 h interval after injection. For (B–D), the interval measured is from midnight to midnight the following day. IDeg 3TW$_{AM}$=insulin degludec administered three times weekly between time of waking up and the first meal of the day. IDeg 3TW$_{PM}$=insulin degludec administered three times weekly with the main evening meal. IGlar OD=insulin glargine administered once daily.

the lowest, rather than the average, of three consecutive prebreakfast SMBG measurements. As defined by the protocol, starting doses of insulin degludec (60 U per week) were roughly 15% lower than IGlar (70 U per week). Hence, the cumulative effect of this difference is likely to be responsible for the overall differences in doses recorded by the end of each trial. Nonetheless, since rates of hypoglycaemia were low but generally higher with IDeg 3TW, if IDeg 3TW dose adjustment was more aggressive, we might have seen even greater differences in hypoglycaemia between treatments. We chose an SMBG titration target of a plasma glucose concentration of between 3·9 and less than 5·0 mmol/L (shown to be safely achieved in an earlier trial[15]) because we wanted to approximate normoglycaemia at the prebreakfast (fasting) timepoint. We expected that an insulin with a consistent glucose-lowering effect, such as insulin degludec, would allow a low titration target (approaching normoglycaemia) to be reached safely, potentially with less hypoglycaemia. Although a low proportion of patients achieved the titration target at the end of trial SMBG measurement, it was notable that about 30–40% of patients on IDeg 3TW achieved the target at least once during the trial compared with about 55–60% of patients on IGlar OD (results not shown).

In both trials, the number of overall and nocturnal confirmed hypoglycaemic episodes was two to three times higher for insulin degludec in the first 24 h after injection compared with the subsequent 24 h. This distribution of hypoglycaemic episodes suggests that when given in a three-times-weekly schedule, insulin degludec plasma concentrations reach a peak within about 24 h after dosing and then decline until the next injection is given. Thus, unlike once-daily dosing of insulin degludec, which is associated with a flat and consistent pharmacokinetic

### *Panel:* Research in context

**Systematic review**

We searched Medline for meta-analyses or reviews published in English between January, 2007, and April, 2013) with the terms "type 2 diabetes", "NPH", "glargine", "detemir", and "degludec". No criteria to assess quality were set. Basal insulin is an effective therapeutic option for initiating insulin therapy in patients with type 2 diabetes inadequately controlled on oral antidiabetic agents or incretin therapy.[17] Insulin degludec (IDeg) is a basal insulin that has a long half-life and a consistent biological activity exceeding 42 h,[2–4] suggesting that it might be suitable for less than once-daily administration. This hypothesis was previously explored in a small, proof-of-concept study,[9] in which insulin degludec injected three times a week (IDeg 3TW) was shown to provide similar glycaemic control to once-daily insulin glargine (IGlar OD) at a similar rate of hypoglycaemia.

**Interpretation**

In both of our trials, IDeg 3TW was statistically inferior to IGlar OD with respect to the primary endpoint (change in $HbA_{1c}$ from baseline) and associated with a higher incidence of hypoglycaemia in the immediate 24 h after injection. By contrast, all phase 3 trials comparing once-daily insulin degludec with insulin glargine have shown insulin degludec to be statistically non-inferior to insulin glargine with respect to reductions in $HbA_{1c}$ concentrations, and to be associated with a lower rate of hypoglycaemia, particularly during the night.[5–8] We therefore conclude that the overall benefit-to-risk relation of IDeg 3TW in these phase 3 trials does not support three-times-weekly dosing, and recommend that insulin degludec should only be used in a once-daily dosing regimen.

profile at steady state,[3] the combination of a longer interval between injections and a dose per injection that is two times higher for the three-times-weekly regimen seems to create an action profile with a higher peak-to-trough ratio between doses that is more reminiscent of available basal insulins.[16] Such an action profile is probably responsible for the inferior glycaemic efficacy and higher rate of hypoglycemia (*vs* IGlar OD) when insulin degludec is given three-times weekly.

Given the use of different insulin delivery systems for insulin degludec and insulin glargine, a blinded, double-dummy trial design was impractical. As a result, participants and clinical staff might have been more vigilant in recalling and reporting adverse events (and other endpoints needing personal judgment) for the investigational drug in this open-label trial. However, because the study population was insulin-naive before entering the trial (and equally unfamiliar with insulin degludec, insulin glargine, and the dosing regimens used), we believe that such bias would have been minimal compared with a patient population who had previously received the comparator insulin. However, to minimise any potential reporting bias for hypoglycaemia, we used biochemically confirmed hypoglycaemia (SMBG <3·1 mmol/L or severe episodes) instead of hypoglycaemic symptoms to compare rates between treatment groups. In common with other trials in patients with type 2 diabetes, physical activity and diet are potential confounders. We did not wish to impose any special or intensive limitations on diet or physical activity because we wished our trials to reflect clinical reality. Thus, apart from normal standards of care, no specific attempts were made to control physical activity and nutrition.

In conclusion, the overall benefit-to-risk relation in these phase 3 trials does not support a three-times-weekly dosing regimen (panel).

#### Contributors

BB, DR-J, JHDV, LAL, and RR were trial investigators and helped to obtain data. TJ provided medical oversight during the trials. All authors were involved in reviewing and interpreting the data, proposing post-hoc analyses, preparing the first draft of the manuscript, and providing further comments and revision. All authors approved the final version of the manuscript and take full responsibility for the content.

#### Conflicts of interest

BZ has served on advisory panels for Amylin, AstraZeneca, Boehringer Ingelheim, Lilly, Novo Nordisk, Bristol-Myers Squibb, Merck, and Sanofi, and received research support from Boehringer Ingelheim, Novo Nordisk, and Merck. JHDV is a board member for Johnson & Johnson, Novo Nordisk, and Roche Diagnostics; has received research support from Dexcom, GluMetrics, Novartis Pharmaceuticals, Novo Nordisk, and Sanofi; and has attended speakers' bureaux for Dexcom, Lilly, and Novo Nordisk. BB has served on medical advisory boards and acted as consultant for Novo Nordisk, Lilly, and Sanofi. He has received research support from Novo Nordisk, Lilly, Sanofi, Merck, and Johnson & Johnson and served on speakers' bureaux for Novo Nordisk, Lilly, Sanofi, Merck, and Amylin/Bristol-Myers Squibb. DR-J has received research support from Lilly, Novo Nordisk, Boehringer Ingelheim, and Serono. He has served on speakers' bureaux for Lilly, Novo Nordisk, and Sanofi and served as consultant and on advisory panels for Lilly and Novo Nordisk. LAL has received honoraria or research support from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Servier, and Takeda. AM and TJ are employed by Novo Nordisk and own stocks and shares in the company. RR has received research funding from, and participated on advisory boards for, Novo Nordisk and Sanofi.

#### Acknowledgments

We thank the investigators, trial staff, and participants for their participation. We also thank Pei-Ling Chu and Kamilla Begtrup (both Novo Nordisk) for statistical support, Paul G Drake (Novo Nordisk) for medical writing support, and Daria Renshaw of Watermeadow Medical (sponsored by Novo Nordisk) for assisting with the submission.

#### References

1 Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund PO, Ribel U. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharm Res* 2012; **29**: 2104–14.

2 Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab* 2012; **14**: 859–64.

3 Heise T, Nosek L, Bottcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes Metab* 2012; **14**: 944–50.

4 Kurtzhals P, Heise T, Strauss HM, et al. Multi-hexamer formation is the underlying basis for the ultra-long glucose-lowering effect of insulin degludec. *Diabetologia* 2011; **54**: S426.

5 Garber AJ, King AB, Del Prato S, et al, for the NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; **379:** 1498–507.

6 Heller S, Buse J, Fisher M, et al, for the BEGIN Basal-Bolus Type 1 Trial Investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; **379:** 1489–97.

7 Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012; **35:** 2464–71.

8 Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013; **15:** 175–184.

9 Zinman B, Fulcher G, Rao PV, et al. 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. *Lancet* 2011; **377:** 924–31.

10 World Medical Association. Declaration of Helsinki. ethical principles for medical research involving human subjects. *J Indian Med Assoc* 2009; **107:** 403–05.

11 International Conference on Harmonisation (ICH). ICH harmonised tripartite guideline: guideline for Good Clinical Practice. *J Postgrad Med* 2001; **47:** 199–203.

12 European Medicines Agency. Lantus: European Public Assessment Report—annex I: summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000284/WC500036082.pdf (accessed Dec 1, 2010).

13 Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. Users manual for the SF-36v2 health survey, 2nd edn. Lincoln, RI: QualityMetric Incorporated, 2007.

14 US Food and Drug Administration. Guidance for industry—diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. Draft guidance. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf (accessed Dec 1, 2010).

15 Blonde L, Merilainen M, Karwe V, Raskin P. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets—the TITRATE study. *Diabetes Obes Metab* 2009; **11:** 623–31.

16 Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes Obes Metab* 2007; **9:** 648–59.

17 Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012; **55:** 1577–96.