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RESEARCH ARTICLE

A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes

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Abstract

Background To compare insulin glargine with NPH human insulin for basal insulin supply in adults with type 1 diabetes.

Methods People with type 1 diabetes ($n = 585$), aged 17–77 years, were randomized to insulin glargine once daily at bedtime or NPH insulin either once- (at bedtime) or twice-daily (in the morning and at bedtime) according to their prior treatment regimen and followed for 28 weeks in an open-label, multicentre study. Both groups continued with pre-meal unmodified human insulin.

Results There was no significant difference between the two insulins in change in glycated haemoglobin from baseline to endpoint (insulin glargine $0.21 \pm 0.05\%$ (mean $\pm$ standard error), NPH insulin $0.10 \pm 0.05\%$). At endpoint, self-monitored fasting blood glucose (FBG) had decreased similarly in each group (insulin glargine -1.17 ± 0.12 mmol/L, NPH insulin -0.89 ± 0.12 mmol/L; $p = 0.07$). However, people on >1 basal insulin injection per day prior to the study had a clinically relevant decrease in FBG on insulin glargine versus NPH insulin (insulin glargine -1.38 ± 0.15 mmol/L, NPH insulin -0.72 ± 0.15 mmol/L; $p < 0.01$). No significant differences in the number of people reporting ≥ 1 hypoglycaemic episode were found between the two groups, including severe and nocturnal hypoglycaemia. Insulin glargine was well tolerated, with a similar rate of local injection and systemic adverse events versus NPH insulin.

Conclusions A single, bedtime, subcutaneous dose of insulin glargine provided a level of glycaemic control at least as effective as NPH insulin, without an increased risk of hypoglycaemia. Copyright © 2005 John Wiley & Sons, Ltd.

Keywords type 1 diabetes; basal insulin; insulin glargine; NPH insulin; blood glucose control; hypoglycaemia

Introduction

Insulin therapy in people with type 1 diabetes seeks to recreate the normal physiological pattern of insulin secretion (that is, a steady basal insulin level with a short-lived enhancement of secretion at meal time) [1] by tailoring insulin doses to changing insulin requirements throughout the day. The aim of this type of insulin regimen is to keep blood glucose levels close enough to the normal range in order to minimize

the long-term risk of microvascular complications associated with hyperglycaemia [2], while avoiding hypoglycaemia as far as is possible.

Traditionally available intermediate- or long-acting insulin preparations do not provide a constant and reliable 24-h basal insulin supply. Neutral Protamine Hagedorn (NPH) insulin, introduced in 1946, has an early peak of absorption around 4–6 h after subcutaneous administration, followed by a steady decline in plasma insulin concentrations [3], while the longer-acting ultralente insulins are limited by erratic insulin absorption [4]. As a result, these insulins are associated with a high incidence of much-feared nocturnal hypoglycaemia. Consequently, the bedtime insulin dose cannot be increased sufficiently to prevent elevated pre-breakfast blood glucose levels, which then compromise blood glucose control during the rest of the day. Furthermore, previously available intermediate- or long-acting insulins are provided as a suspension, and variability in the mixing and administration of these has been shown [5]. Insulin glargine (LANTUS®; Aventis Pharma, Frankfurt, Germany) is a long-acting basal insulin analogue with a prolonged and stable absorption rate and without a pronounced peak that offers a near-24-h basal insulin supply [3,6] and a reduced risk of hypoglycaemia compared with NPH insulin [7].

To compare the effects of insulin glargine and NPH insulin on overall blood glucose control and safety, a large-scale, open, multicentre, randomized, controlled study was carried out in Europe in people with type 1 diabetes for a treatment period of 28 weeks.

Methods

People

The study was performed at 63 centres in 12 European countries. Ethics committee approval was obtained for each centre, and all participants gave written, informed consent.

Of the 655 people entering the screening phase, 602 were randomized and 585 were treated with study medication – 292 with insulin glargine and 293 with NPH insulin (147 people received once-daily NPH insulin and 146 received twice-daily NPH insulin). Baseline characteristics were comparable between the treatment groups, with respect to sex, age, duration of diabetes, and prior blood glucose control (Table 1). Late diabetic complications present at entry, including retinopathy (30%) and neuropathy (17%), were similarly distributed between the treatment groups.

All participants were judged by the investigators to have type 1 diabetes and post-prandial serum C-peptide levels of <0.50 nmol/L or <1.50 μg/L when the capillary blood glucose level was ≥ 5.5 mmol/L (≥ 100 mg/dL) at the first visit. All had been treated with insulin for at least 1 year. Basal insulin was NPH insulin in 89% of people and human ultralente insulin in 9%, while mealtime insulin was unmodified human insulin in 98% and insulin lispro in 13% (some people used both). These figures included pre-mixed insulins being used by 6% of the study population. Three people (0.5%) took basal insulin with no unmodified human (pre-prandial) insulin. The distribution of insulin types was similar in the two treatment groups. Insulin doses at entry to the study are given in Table 1.

Study design

This was a randomized, multicentre, open-label, controlled, parallel group study. The study treatment groups were not blinded because insulin glargine (a clear solution) and NPH insulin (a suspension) preparations look different, and because the different pharmacodynamic properties might have led people and investigators to apply different insulin dose adjustment techniques.

People who were treated previously with NPH insulin and continued to receive NPH insulin in this study remained on a regimen similar to their previous basal insulin regimen: those on once-daily injections continued

Table 1. Clinical characteristics at baseline of the people with type 1 diabetes studied

Variable	All	Insulin glargine	NPH insulin
Sex (men/women)	326/259	160/132	166/127
Age (yr)	39 ± 12	39 ± 12	39 ± 12
Duration of diabetes (yr)	16 ± 11	16 ± 12	15 ± 9
Duration of insulin treatment (yr)	15 ± 10	15 ± 11	15 ± 10
Body weight (kg)	n/a	73.2 ± 11.8	74.8 ± 12.5
BMI (kg/m^2)	24.9 ± 3.2	24.6 ± 3.1	25.1 ± 3.3
HbA_{1c} (%)[a]	7.9 ± 1.2	7.9 ± 1.2	8.0 ± 1.2
Fasting blood glucose[b] (mmol/L)	9.3 ± 2.6	9.3 ± 2.7	9.2 ± 2.4
Fasting plasma glucose[c] (mmol/L)	12.4 ± 4.9	12.7 ± 5.0	12.1 ± 4.9
Total insulin dose (U/day)	48 (16–188)	46 (18–104)	49 (16–188)
Basal insulin dose (U/day)	20 (4–64)	20 (5–63)	21 (4–64)

n, mean ± standard deviation, or median (range).
BMI, body mass index; HbA_{1c}, glycated haemoglobin; n/a, not available.
[a]HbA_{1c}, normal range 4.0–6.1%.
[b]Self-monitored.
[c]Measured at clinic visit.

on once-daily (bedtime) and those on more than once-daily injections were put on a twice-daily injection regimen (morning and at bedtime). People treated with insulin glargine were given a once-daily bedtime dose, irrespective of their previous regimen. Given the large number of centres and, therefore, the small number of people per centre, it was recognized that it was premature to enforce any algorithm for insulin dose adjustment even though the prior people/investigator experience would be likely to bias the results in favour of the comparator insulin.

Participant eligibility was assessed at a screening visit. At baseline, an independent agency randomly allocated people by central telephone contact into two equal groups for treatment with insulin glargine or NPH insulin. Outcome assessments and safety monitoring were performed at baseline and at six subsequent visits over 28 weeks (weeks 1, 4, 8, 12, 20 and 28). Insulin dose adjustment was made throughout the study based on advice from the investigators during the scheduled visits and informal contacts, and self-monitored blood glucose results between visits.

In accordance with regulatory requirements, the primary outcome measure was the change in HbA_{1c} from baseline to endpoint. Secondary variables were aspects of clinic plasma glucose, self-monitored blood glucose and hypoglycaemia (see below).

Insulins

For people randomized to once-daily insulin glargine at bedtime, the dose was determined on the first treatment day by the total basal insulin dose the day before, with investigator discretion for people transferring from twice-daily basal injections or from insulin–zinc suspensions. The protocol suggested dose titration by 10% or greater increments, according to self-monitored fasting blood glucose (FBG) levels, with a nominal target of 4.4–6.7 mmol/L (80–120 mg/dL) averaged over at least 2–4 days and an absence of nocturnal hypoglycaemia. All dose adjustments were, however, at the discretion of the investigator/person with diabetes.

The comparator, NPH human insulin (HOE 36H, Aventis Pharma), was injected either once- (at bedtime) or twice-daily according to the person's prior treatment regimen. Starting evening doses were the same as those on the immediate pre-treatment day, with subsequent adjustment as described for insulin glargine. Morning NPH insulin was adjusted as required.

Unmodified human insulin was injected before meals according to an individual's habit. The ideal titration goal was a self-monitored pre-meal blood glucose concentration of 4.4–6.7 mmol/L (80–120 mg/dL), in the absence of hypoglycaemia.

The injection sites used were determined by the habits of the person, with a preference for the abdominal wall. Separate injection sites for basal and unmodified insulin were stipulated so that injection site reactions could be attributed specifically to one type of insulin.

Measurements

Glycated haemoglobin (GHb) was measured at screening by Covance (Geneva, Switzerland). Baseline and subsequent evaluations of GHb were carried out by the Diabetes Diagnostic Laboratory (Columbia, Missouri, USA). GHb was measured by affinity chromatography of total GHb (Primus HPLC, Kansas City, MO, USA). The results were standardized to the Diabetes Control and Complications Trail (DCCT) assay and are, therefore, reported as HbA_{1c} (normal range 4.0–6.1%). At study visits at baseline, 8, 20, and 28 weeks, people attended in the fasting state and prior to insulin injection for the measurement of plasma glucose (Covance).

People were trained to use the One Touch II blood glucose meter (LifeScan, Neckargemünd, Germany) for self-measurement of FBG on the 7 consecutive days immediately preceding baseline and the 8-, 20- and 28-week visits. On the day immediately preceding each of these visits, the participants were asked to perform a 24-h blood glucose profile at 03:00 hours, just prior to and 2 h after breakfast, lunch and dinner, and at bedtime. Self-monitored FBG results from the 7 consecutive days prior to the study visit and the day of the study visit (i.e. eight values) were averaged prior to statistical analysis.

Hypoglycaemia was recorded by review of study diaries and by direct questioning at each study visit. Hypoglycaemia was categorized as symptomatic (clinical symptoms confirmed by blood glucose <2.8 mmol/L [<50 mg/dL]) or asymptomatic (confirmed by blood glucose <2.8 mmol/L (<50 mg/dL) without symptoms). Severe symptomatic hypoglycaemia was defined as an event consistent with symptomatic hypoglycaemia requiring the assistance of another person, with either a blood glucose level <2.8 mmol/L [50 mg/dL] or prompt recovery after administration of oral carbohydrate, intravenous glucose or glucagon. Nocturnal symptomatic hypoglycaemia was defined as symptomatic hypoglycaemia occurring during sleep between bedtime and rising in the morning, or before the morning pre-breakfast self-blood glucose measurement and the morning insulin injection. Only participants with confirmed blood glucose <2.0 mmol/L (<36 mg/dL) were considered clinically relevant.

Adverse events

A full clinical examination was performed on each person at the beginning and end of the study. At each study visit, people were formally asked about any possible adverse events, and the responses were recorded. Hypoglycaemia was recorded separately (see above).

Standard laboratory haematology and biochemistry profiles, including blood lipids, were performed at study entry and at weeks 0, 8, 20 and 28 (Covance). *Escherichia coli* and insulin antibodies were determined at the same visits (Aventis Preclinical Development, Frankfurt am

Main, Germany). A clinically relevant change in insulin antibodies was pre-defined as ≥20% binding.

Seven-field fundus photography was used to document diabetic retinopathy. Photographs were taken at baseline and the study endpoint. In addition, people with moderate non-proliferative diabetic retinopathy or worse at baseline (Early Treatment Diabetic Retinopathy Study [ETDRS] level ≥43) were re-photographed 12 weeks after randomization. The primary analysis variable for the progression of diabetic retinopathy was the proportion of people with a clinically relevant change, defined as the development of proliferative retinopathy (ETDRS level ≥61), development of clinically significant macular oedema, or ≥3-step progression on the ETDRS scale [8].

Statistical analysis

All statistical tests were two-sided and were performed at a significance level of $\alpha = 5\%$. The primary efficacy variable was defined as the change in HbA_{1c} from baseline to study endpoint using baseline-adjusted analysis of covariance (ANCOVA). ANCOVA was also performed for the secondary efficacy variables versus baseline values – HbA_{1c} at each visit, fasting plasma glucose (FPG) and self-monitored blood glucose, nocturnal blood glucose concentration and 24-h blood glucose profile. Rates of hypoglycaemia were compared between treatment groups using rank analysis of variance (ANOVA). The frequency of people experiencing at least one episode of symptomatic hypoglycaemia, nocturnal symptomatic hypoglycaemia or severe symptomatic hypoglycaemia was compared using the Cochrane–Mantel–Haenszel test. Separate analyses were performed for hypoglycaemia reported for the first month of the treatment phase, the remainder of the treatment phase and the entire treatment phase to evaluate safety during the most critical stages of changing to a new basal insulin. In addition, the subset of hypoglycaemic episodes with a recorded blood glucose value available was summarized for the two categories of blood glucose values, namely <2.8 mmol/L (<50 mg/dL) and <2.0 mmol/L (<36 mg/dL). Exploratory post hoc analyses of the primary (HbA_{1c}) and secondary (hypoglycaemia, FBG and FPG) efficacy variables were also performed. In these analyses, the efficacy of insulin glargine relative to NPH insulin was characterized in the subgroup of participants previously receiving a once-daily basal insulin regimen and the subgroup of participants previously receiving more than once-daily basal insulin.

Results

Withdrawals

After treatment initiation, 37 people withdrew and 548 (91%) of the randomized people completed the treatment phase. There was no significant difference between the number of people who withdrew from the two treatment groups ($n = 16$ [5%] and $n = 21$ [7%] for insulin glargine and NPH insulin, respectively). The principal reason for withdrawal in both groups was that the person did not wish to continue (insulin glargine, $n = 7$; NPH insulin, $n = 10$). Total people exposure to insulin glargine was 151.1 patient–years. Study treatment was permanently discontinued because of adverse events in two people in the insulin glargine treatment group (loss of hypoglycaemia awareness and gastric carcinoma), and in two people who were receiving NPH insulin (allergy to NPH insulin and recurrent serious hypoglycaemia).

Insulin dose

At 1 month, the median change in daily total insulin dose in the insulin glargine group was −2.0 U (range −22.0 to 22.0 U, $p < 0.01$ vs baseline), due almost entirely to a fall in the daily basal insulin dose in the people previously using twice-daily NPH insulin (median change 0.0 U [−37.0 to 19.0 U], $p < 0.01$). By the end of the study, there was a decrease in both daily total insulin dose (−2.0 U [−24.0 to 39.0 U]; $p = 0.03$) and daily basal insulin dose (−1.0 U [−25.0 to 13.0 U], $p < 0.01$) in the insulin glargine group. For the NPH insulin group, there was no change in either daily total or basal insulin doses (Table 2).

Blood glucose control

There was no statistically significant difference in the effect of insulin glargine and NPH insulin on change from baseline to endpoint in HbA_{1c}, either for the whole study population group or when analysed by prior basal insulin regimen (Table 3). Although people treated with insulin glargine exhibited a significantly greater change from baseline to endpoint in HbA_{1c} compared to those people treated with NPH insulin at week 20

Table 2. Change in daily insulin dose (randomization–endpoint) during the study for the total treatment population and for people previously treated with once-daily basal insulin or more than once-daily basal insulin

	Change in daily insulin dose (U)	
	Insulin glargine	NPH insulin
All people		
Total insulin	−2.0 (−24, 39)	0.0 (−49, 35)
Basal insulin	−1.0 (−25, 13)	0.0 (−36, 38)
Meal-time insulin	0.0 (−20, 34)	0.0 (−26, 31)
Prior once-daily basal		
Total insulin	−1.0 (−24, 39)	0.0 (−40, 24)
Basal insulin	0.0 (−15, 13)	0.0 (−32, 11)
Meal-time insulin	−1.0 (−20, 34)	0.0 (−23, 26)
Prior more than once-daily basal		
Total insulin	−2.0 (−23, 28)	1.0 (−31, 35)
Basal insulin	−3.0 (−25, 10)	1.0 (−15, 28)
Meal-time insulin	2.0 (−20, 34)	0.0 (−20, 31)

Median (range).
No change was statistically significant.

Table 3. Change in measures of blood glucose control from baseline to endpoint in people with type 1 diabetes treated with insulin glargine- or NPH insulin-based regimens

	Insulin glargine	NPH insulin	Difference	*p*-value
All people				
HbA_{1c} (%)	0.21 ± 0.05	0.10 ± 0.05	0.11 (−0.03, 0.24)	NS
FPG (mmol/L)	−0.82 ± 0.30	−0.79 ± 0.31	−0.04 (−0.82, 0.75)	NS
FBG (mmol/L)	−1.17 ± 0.12	−0.89 ± 0.12	−0.29 (−0.60, 0.03)	0.071
Prior once-daily basal insulin				
HbA_{1c} (%)	0.20 ± 0.07	0.07 ± 0.08	0.13 (−0.08, 0.33)	NS
FPG (mmol/L)	−0.45 ± 0.41	−0.27 ± 0.43	−0.18 (−1.35, 0.98)	NS
FBG (mmol/L)	−0.95 ± 0.16	−1.03 ± 0.16	0.07 (−0.38, 0.52)	NS
Prior twice or more daily basal insulin				
HbA_{1c} (%)	0.26 ± 0.07	0.15 ± 0.07	0.11 (−0.07, 0.30)	NS
FPG (mmol/L)	−1.02 ± 0.37	−1.08 ± 0.39	0.06 (−0.99, 1.11)	NS
FBG (mmol/L)	−1.02 ± 0.37	−1.08 ± 0.39	0.06 (−0.99, 1.11)	NS

Mean ± standard error or mean (95% CI).
HbA_{1c}, glycated haemoglobin; FPG, fasting plasma glucose at study visit; FBG, self-monitored fasting blood glucose; NS, not significant.

(0.16 ± 0.05 vs 0.03 ± 0.05%, $p = 0.043$), this difference was not detected at study endpoint. FPG measured at clinic visits also did not differ between insulin glargine- and NPH-treated groups, whether considering all people or prior basal insulin regimen (Table 3).

Self-monitored FBG did not differ between insulin glargine- and NPH insulin-treated groups. However, a trend to lower glucose levels in the insulin glargine-treated group was apparent in the total treated population. This was accounted for by a 0.7 mmol/L (95% confidence interval [CI] 0.2–1.1) greater decrease in FBG with insulin glargine compared with NPH insulin in people who had previously been taking more than a once-daily basal insulin injection ($p < 0.01$).

Examination of the blood glucose profiles collected immediately before the final visit demonstrated no difference between treatment groups in blood glucose levels at any other time point during the day (Figure 1).

Hypoglycaemia

Throughout the entire treatment period, very similar proportions of people in the two treatment groups experienced at least one episode of symptomatic hypoglycaemia (Table 4). Slightly more people reported symptomatic hypoglycaemia with insulin glargine in the first month of the treatment phase than with NPH insulin, although this difference was not statistically significant ($p = 0.08$).

The difference in the number of people with at least one episode of symptomatic hypoglycaemia was most marked in people transferred from a twice or more prior daily insulin regimen. Of these people, more insulin glargine-treated (74.8%) than twice-daily NPH insulin-treated (66.2%) people reported symptomatic hypoglycaemia during the first month of treatment, although a similar number of people from each treatment group had symptomatic hypoglycaemia confirmed by a blood glucose level below 2.0 mmol/L during this study period (insulin glargine: 17.3%; NPH insulin: 20.0%).

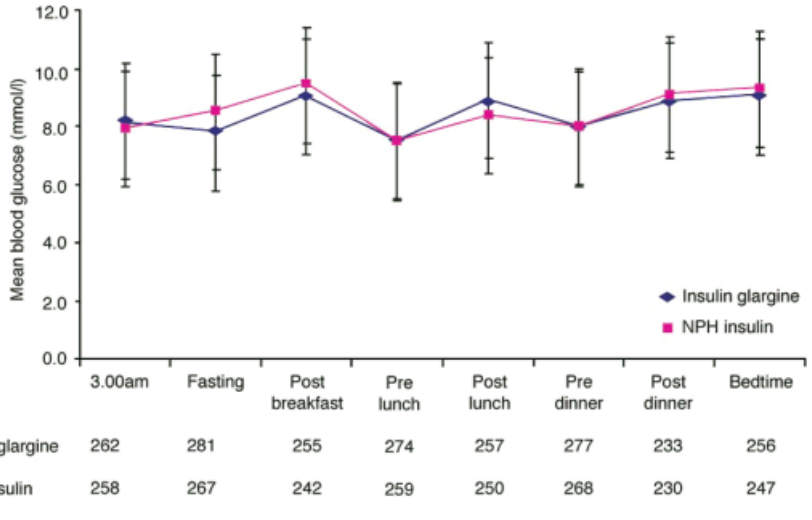

Figure 1. 24-h self-monitored whole blood glucose profile at endpoint in people with type 1 diabetes treated with insulin glargine or NPH insulin

Table 4. Hypoglycaemia endpoints (number [%] of people with at least one episode) in people with type 1 diabetes treated with insulin glargine- or NPH insulin-based regimens

	Insulin glargine	NPH insulin	*p*-value
All regimens			
Symptomatic hypoglycaemia			
First month	214 (73.3)	198 (67.6)	0.08
Month 2–end	240 (83.0)	233 (82.6)	NS
Entire period	260 (89.0)	248 (84.6)	NS
Nocturnal hypoglycaemia			
First month	103 (35.3)	96 (32.8)	NS
Month 2–end	154 (53.3)	161 (57.1)	NS
Entire period	178 (61.0)	179 (61.1)	NS
Severe hypoglycaemia			
First month	10 (3.4)	16 (5.5)	NS
Month 2–end	28 (9.7)	35 (12.4)	NS
Entire period	31 (10.6)	44 (15.0)	NS
Prior once-daily basal insulin			
Symptomatic hypoglycaemia			
First month	110 (71.9)	89 (67.9)	NS
Month 2–end	124 (81.6)	104 (81.3)	NS
Entire period	132 (86.3)	110 (84.0)	NS
Nocturnal hypoglycaemia			
First month	39 (25.5)	42 (32.1)	NS
Month 2–end	75 (49.3)	72 (56.3)	NS
Entire period	82 (53.6)	82 (62.6)	NS
Severe hypoglycaemia			
First month	9 (5.9)	10 (7.6)	NS
Month 2–end	14 (9.2)	20 (15.6)	NS
Entire period	17 (11.1)	25 (19.1)	NS
Prior twice or more daily basal insulin			
Symptomatic hypoglycaemia			
First month	104 (74.8)	86 (66.2)	NS
Month 2–end	116 (84.7)	103 (84.4)	NS
Entire period	128 (92.1)	111 (85.4)	0.10
Nocturnal hypoglycaemia			
First month	64 (46.0)	40 (30.8)	0.01
Month 2–end	79 (57.7)	69 (56.6)	NS
Entire period	96 (69.1)	75 (57.7)	0.07
Severe hypoglycaemia			
First month	1 (0.7)	3 (2.3)	NS
Month 2–end	14 (10.2)	9 (7.4)	NS
Entire period	14 (10.1)	12 (9.2)	NS

p-values by the Cochran–Mantel–Haenszel test stratified by pooled centre.
NS, not significant

In the first month of treatment, there was also a significantly higher proportion of people treated with insulin glargine with at least one episode of nocturnal hypoglycaemia compared with those treated with NPH insulin ($p = 0.01$). However, this difference was not statistically significant from month 2 to end and overall, a similar proportion of people in the two treatment groups reported at least one episode of nocturnal hypoglycaemia (Table 4). In addition, the proportion of people who experienced nocturnal hypoglycaemia confirmed by a blood glucose level <2.8 mmol/L (<50 mg/dL) and <2.0 mmol/L (<36 mg/dL) in the entire treatment period did not differ significantly between the insulin glargine (46.6% and 15.4%, respectively) and NPH insulin (51.2% and 19.1%, respectively) treatment groups.

The number of people with severe hypoglycaemic events was too small to judge whether the apparent advantage in favour of insulin glargine was real (Table 4).

Insulin antibodies

While there was no difference in baseline-adjusted insulin antibody levels at endpoint between the two insulin groups (Table 5), levels of insulin antibody binding to human insulin were significantly lower in the insulin glargine-treated group than the NPH insulin-treated group at 28 weeks (baseline-adjusted difference −1.3 [−2.6, −0.1] %B/T, $p = 0.042$). While the difference was not statistically significant, the same trend was found with measurements of antibody binding of insulin glargine (−1.0 [−2.2, +0.2] %B/T, $p = 0.10$). The number of people treated with insulin glargine (8/284, 2.8%) who had greater than the pre-defined increase (20%B/T) in antibodies binding insulin glargine was the same as the number having a decrease of the same order (9/284, 3.2%), but higher than the number showing an increase with NPH insulin in the same period (1/276 [0.4%], $p = 0.038$). In the eight people showing increased

Table 5. Change in insulin antibodies (percent binding) between baseline and endpoint in people treated with insulin glargine- or NPH insulin-based regimens (ANCOVA results from ITT population)

Antibody type	Insulin glargine	NPH insulin	Difference	*p*-value
Insulin glargine	−1.12 ± 0.510	−0.45 ± 0.511	−0.67 (−1.99, 0.64)	NS
Human insulin	−1.55 ± 0.511	−0.70 ± 0.512	−0.86 (−2.18, 0.46)	NS

Mean ± standard error or mean (95% confidence interval); ANCOVA, analysis of covariance ITT, intent to treat NS, not significant.

binding, there were no consistent effects on insulin dose or HbA_{1c}.

Adverse events, excluding hypoglycaemia

Both insulin glargine and NPH insulin treatments were well tolerated with no differences in common adverse events during the treatment periods. Thirteen percent of adverse events in both groups were judged by the investigators to be possibly related to the study treatments, and there was no trend to more frequent injection site reactions in the insulin glargine-treated people (Table 6). Statistical analysis of the laboratory data, reports of the clinically noteworthy abnormal laboratory values, electrocardiograms and vital signs (heart rate, blood pressure, body weight) did not reveal any special issues with regard to safety.

Treatment-emergent adverse events classified as serious were reported in 53 (9%) of all people treated, and were similar in type and frequency for the two treatment groups (9% and 10% for insulin glargine- and NPH insulin-treated people, respectively).

The number of people who developed a retinopathy severity level >61 (ETDRS), clinically significant macular oedema and/or a three step progression on the ETDRS retinopathy scale was similar in the two treatment groups (data not shown). There were no differences between the treatment groups in the numbers of people with *E. coli* antibodies (data not shown).

Discussion

In this study, no significant difference was observed between the glycaemic control (in terms of HbA_{1c}, FBG, and hypoglycaemia) afforded by once-daily insulin glargine and that of once- or twice-daily NPH insulin. Furthermore, this was also true for the change in HbA_{1c} from baseline to endpoint, irrespective of the prior basal insulin regimen used (once- or twice-daily NPH insulin). This is consistent with the study reported by Ratner and colleagues, who found comparable overall glycaemic control between insulin glargine and NPH insulin in people with type 1 diabetes in a United States (US) multicentre Phase 3 study [7].

Table 6. Adverse events (*n* [%]) considered by the investigators to be at least possibly related to the study treatment in two or more of the people studied

	Insulin glargine	NPH insulin
People randomized and treated	292 (100)	293 (100)
People with possibly related adverse events	37 (13)	39 (13)
Hypoglycaemic reaction	9 (3)	15 (5)
Injection site mass	8 (3)	9 (3)
Injection site reaction	3 (1)	6 (2)

The results were similar for insulin glargine and NPH insulin treatment with respect to all secondary variables evaluated. The exception to this was a statistically significant difference observed between insulin glargine and NPH insulin treatment in the change in HbA_{1c} from baseline at week 20, a difference that was no longer significant at the study endpoint. There was a trend towards lower self-monitored FBG levels in people treated with insulin glargine compared with NPH insulin; however, this difference was significant only in those people receiving once-daily insulin glargine who had previously been on more than once-daily basal insulin.

The biggest differences between the groups in terms of secondary efficacy variables were observed in people who had switched from twice-daily NPH insulin to once-daily insulin glargine. For example, a significantly higher incidence of nocturnal hypoglycaemia was observed in the first month of treatment with insulin glargine in people who switched from twice-daily NPH insulin. This difference was not significant after the first month and, overall, there were no clinically relevant differences observed between insulin glargine and NPH insulin treatment with respect to the number of people reporting severe or nocturnal episodes of hypoglycaemia. It is likely that the difference in hypoglycaemia observed during the first month of treatment was a consequence of people adjusting to the study drugs and regimens. Indeed, it was during this period of the study that the biggest change in daily basal insulin dose was observed in people randomized to insulin glargine who had been treated previously with twice-daily NPH insulin. In this study, the people with diabetes and the investigators advising them would have had no prior experience of insulin dose adjustment when using insulin glargine-based regimens. It is possible that the initial hypoglycaemia observed with insulin glargine in the first month may have been minimized by a reduction in basal insulin dosage upon switching from NPH insulin to insulin glargine. Indeed, it is now recommended that a dose reduction of 20–30%

of the NPH insulin dose be used in patients on more than once-daily insulin upon the initiation of insulin glargine therapy [9]. The use of many centres with small numbers of people enrolled in each, and people who were treated for clinically short periods, also precludes the adequate accumulation of such expertise. In contrast, investigators would have a wealth of experience of adjusting the dose of NPH insulin, and the patients would normally have had the opportunity of years of self-monitoring to optimize their use of this insulin. No algorithm of dose adjustment was employed in this study, as it was partly exploratory in that regard.

There was a trend towards a lower rate of severe hypoglycaemia in people treated with insulin glargine compared with NPH insulin, but this difference was not statistically significant. In the US study reported by Ratner and colleagues, in which insulin glargine and NPH insulin treatment provided comparable glycaemic control, insulin glargine therapy resulted in significantly fewer episodes of all symptomatic, nocturnal and severe hypoglycaemia [7]. The reason the results in the current study differ from those of the US study could relate to the diversity of attitudes to diabetes care in the different countries in Europe. In the US, physicians and perhaps patients might be expected to be more homogeneous in this regard and are often willing to accept a higher risk of hypoglycaemia in response for better glycaemic control in people with type 1 diabetes [10].

The current study has a number of weaknesses inevitable for such a large, regulatory Phase III clinical trial in the early phase of development of a new insulin. Similar problems affected the pivotal Phase III studies of insulin lispro [11,12] and insulin aspart [13,14] such that their true clinical advantages only came to be recognized as a result of the lessons learnt in these major studies. The open-label nature of the trial is a study limitation that can influence the titration of a new or unfamiliar therapeutic agent.

This study did not reveal any differences in safety between the two insulins studied. This applies to special issues including retinopathy and injection site reactions. A similar proportion of people treated with insulin glargine and NPH insulin experienced adverse events that were deemed by the investigators to be possibly related to treatment, and these adverse events were also similar in nature. Treatment discontinuation due to serious adverse events was rare, and occurred at the same rate in people treated with insulin glargine or NPH insulin. In addition, there was no significant change from baseline to endpoint in the levels of insulin antibodies in either group, nor was there any difference between the treatment groups in the levels of *E. coli* antibodies.

In addition to the data reported here, treatment satisfaction and psychological well-being were evaluated in the participants of the current study, and these data have been reported elsewhere [15]. While psychological well-being improved irrespective of the study medication (as judged by mean scores in the Well-being Questionnaire [W-BQ]), advantages were observed for insulin glargine treatment compared with NPH insulin treatment with respect to improved treatment satisfaction (assessed by the Diabetes Treatment Satisfaction Questionnaire [DTSQ]). Treatment satisfaction improved compared with baseline at weeks 8, 20 and 28, and at the study endpoint for people receiving insulin glargine, but deteriorated slightly with NPH insulin treatment; this difference between insulin glargine and NPH insulin treatment remained statistically significant throughout the study. In addition, people treated with insulin glargine had a significantly lower 'Perceived Frequency of Hyperglycaemia' compared to those treated with NPH insulin, and this was not associated with any significant increase in the 'Perceived Frequency of Hypoglycaemia'.

In conclusion, once-daily insulin glargine provides a level of glycaemic control that is comparable to that provided by once- or twice-daily NPH insulin and is not associated with an increased risk of hypoglycaemia or other treatment-related safety issues. While the data presented here demonstrate equivalence for insulin glargine and NPH insulin with respect to safety and efficacy, insulin glargine has an advantage with respect to psychological outcomes, since people are apparently more satisfied with treatment with insulin glargine compared with NPH insulin. Insulin glargine is, therefore, a suitable candidate for a once-daily basal insulin replacement as part of a meal-time plus basal regimen in people with type 1 diabetes.

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