

Title: A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes
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Abstract

Aims/hypothesis: This 52-week multinational, randomised, open-label, parallel-group, non-inferiority trial compared clinical outcomes following supplementation of oral glucose-lowering drugs with basal insulin analogues detemir and glargine in type 2 diabetic patients. **Methods:** Insulin-naive adults ($n=582$, HbA_{1c} 7.5–10.0%, $BMI \leq 40.0$ kg/m²) were randomised 1:1 to receive insulin detemir or glargine once daily (evening) actively titrated to target fasting plasma glucose (FPG) ≤ 6.0 mmol/l. An additional morning insulin detemir dose was permitted if pre-dinner plasma glucose (PG) was >7.0 mmol/l after achieving FPG <7.0 mmol/l. Due to labelling restrictions, no second glargine dose was allowed. **Results:** Baseline HbA_{1c} decreased from 8.6 to 7.2 and 7.1% (NS) with detemir and glargine, respectively. FPG improved from 10.8 to 7.1 and 7.0 mmol/l (NS), respectively. With detemir, 45% of participants completed the study on once daily dosing and 55% on twice daily dosing, with no difference in HbA_{1c} . Overall, 52% of participants achieved $HbA_{1c} \leq 7.0\%$: 33% (detemir) and 35% (glargine) without hypoglycaemia. Within-participant variability for self-monitored FPG and pre-dinner PG did not differ by insulin treatment, nor did the relative risk of overall or nocturnal hypoglycaemia. Modest reductions in weight gain were seen with detemir vs glargine in completers (3.0 vs 3.9 kg, $p=0.01$) and in the intention-to-treat population (2.7 vs 3.5 kg, $p=0.03$), primarily related to completers on once daily detemir. Mean daily detemir dose was higher (0.78 U/kg [0.52 with once daily dosing, 1.00 U/kg with twice daily dosing]) than glargine (0.44 IU/kg). Injection site reactions were more frequent with detemir (4.5 vs 1.4%). **Conclusions/interpretation** Supplementation of oral agents with detemir or glargine achieves clinically important improvements in glycaemic control with low risk of hypoglycaemia. Non-inferiority was demonstrated for detemir using higher insulin doses (mainly patients on twice daily dosing); weight gain was somewhat reduced with once daily insulin detemir. ClinicalTrials.gov ID no.: NCT00283751.

Keywords: Body weight, Fasting plasma glucose, Glucose variability, Glucose control, Hypoglycaemia, Insulin detemir, Insulin glargine, Insulin supplementation, Oral glucose-lowering agents, Type 2 diabetes

Abbreviations:

FPG: fasting plasma glucose
ITT: intention-to-treat
LOCF: last observation carried forward
NPH: NPH insulin
PG: plasma glucose

Introduction

People with type 2 diabetes inadequately controlled by oral glucose-lowering drugs can achieve clinically relevant improvements in HbA_{1c} with the addition of insulin therapy [1–3]. However, patients and healthcare providers are often reluctant to initiate insulin due to concerns over injections, fear of hypoglycaemia and additional weight gain, and also because insulin treatment is perceived as complex and an added burden to diabetes management [4, 5]. Moreover, once insulin is initiated, recommended targets for glycaemic control ($HbA_{1c} <6.5$ – 7.0%) are often not met [5–7]. In recent years, the basal insulin analogues glargine and detemir have been introduced. These were developed to improve upon the limitations of NPH insulin (NPH) and other conventional basal insulins, which have an inadequate duration of action, a marked peak glucose-lowering effect and variability in response from one injection to another [8]. These analogues might help to overcome some of the barriers to insulin initiation and optimisation, including concerns over hypoglycaemia and weight gain. Several recent studies have assessed basal insulin as an add-on therapy to oral glucose-lowering drugs, comparing either insulin glargine or insulin detemir with NPH, and using titration algorithms based on glucose monitoring [1, 9–13]. These studies have demonstrated that simple regimens involving a once or twice daily injection of a basal insulin analogue can achieve clinically important improvements in glycaemic control similar to those achievable with NPH, but with less risk of hypoglycaemia. Insulin detemir has consistently shown less body weight gain than NPH when used in this way, as well as when used in basal plus mealtime insulin therapy [14, 15], whereas a weight advantage has been reported in

only a few of the comparative trials of glargine vs NPH, as for example in the recent LANMET study [11]. Insulin glargine is licensed only for once daily use as a basal insulin for people with diabetes. Insulin detemir, in contrast, is available for once or twice daily use. Glucose clamp comparisons between these insulins have given contradictory information on whether their duration of effect is comparable [16, 17]. The only direct comparison in patients with type 2 diabetes suggests very similar pharmacodynamic profiles at clinically relevant doses [16], but methodological issues remain controversial. The objective of the current study was to compare treatment with insulin detemir and insulin glargine in line with their licensed indications as add-on therapy to oral glucose lowering agents in insulin-naive patients with type 2 diabetes.

Methods

Study protocol

This 52-week, parallel-group trial was conducted in 2003 and 2004 at 80 sites in Europe and the USA and included 582 insulin-naive people with type 2 diabetes, who were randomised (1:1) and treated with insulin detemir (Levemir; Novo Nordisk, Bagsværd, Denmark) or insulin glargine (Lantus; sanofi-aventis, Paris, France) as add-on therapy to oral glucose-lowering drugs. The trial was conducted in accordance with the Declaration of Helsinki and principles for Good Clinical Practice and was approved by ethics committees/review boards in all countries. All participants gave written informed consent. Concealed randomisation was carried out by an automatic telephone response system and was stratified according to oral glucose-lowering drug mono- or combination-therapy at entry. An open-label design was required to allow twice daily administration of insulin detemir if needed, according to the dosing algorithm targets for pre-dinner plasma glucose (PG) concentrations (Table 1). Glargine was only administered once daily at bedtime as per study protocol and in accordance with its licence [18]. To reduce potential bias, HbA_{1c} results were only disclosed to investigators at randomisation and at trial end.

Participants

Insulin-naive men and women with type 2 diabetes and the following characteristics were recruited: ≥ 18 years old, ≥ 12 months disease duration, BMI ≤ 40.0 kg/m² and HbA_{1c} 7.5–10.0%. For inclusion, they had to be receiving one or two oral agents (metformin, insulin secretagogues, α -glucosidase inhibitors) ≥ 4 months on at least one-half the maximum recommended dose, according to local guidelines. Exclusion criteria included treatment with thiazolidinediones (due to labelling restrictions in Europe), use of more than two oral agents within 6 months, hypoglycaemic unawareness or other medical conditions likely to interfere with trial conduct. Withdrawal criteria included pregnancy, HbA_{1c} $> 11.0\%$ after the first 12 weeks of treatment and initiation of medication interfering with glucose metabolism.

Study medications

Oral glucose-lowering therapy, diet and physical activity were recommended to remain stable during the study; no meal-time insulin was allowed. Basal insulin was initiated once daily in the evening at a dose of 12 U and titrated according to a structured treatment algorithm. In line with its licence, people allocated to insulin detemir were allowed to receive an additional morning insulin dose if pre-dinner PG was > 7.0 mmol/l, but only if pre-breakfast PG was < 7.0 mmol/l or nocturnal hypoglycaemia (major episode or PG ≤ 4.0 mmol/l) precluded achievement of the fasting plasma glucose (FPG) target. Insulin detemir was administered with a pen-injector (FlexPen, Novo Nordisk) 1 h before to 1 h after dinner, and if needed within 30 min of breakfast. Glargine was given once daily at bedtime, via a pen-injector in the EU (OptiPen Pro 1, sanofi-aventis) and with syringes in the USA. The evening dose of insulin detemir was administered somewhat earlier than that of insulin glargine, to allow for the possibility that recipients might be switched to a twice daily schedule, in which case a more even distribution of the dose across 24 h would be achieved.

Titration of basal insulin

Participants attended 16 scheduled visits and nine telephone contacts over 1 year. Evening insulin doses were titrated throughout the trial to a FPG target ≤ 6.0 mmol/l in the absence of hypoglycaemia. An identical pre-dinner glucose target was applied for people administering a morning dose of insulin detemir (Table 1). Participants measured capillary PG using glucose meters (Medisense Xtra; Abbott, Wiesbaden, Germany). Dose adjustments were to be based on the average of three self measurements before breakfast (and before dinner if on twice daily insulin detemir). During the first 12 weeks, participants had weekly investigator contact. A titration committee monitored the algorithm for insulin dose optimisation and reviewed prescribed insulin doses periodically. This committee was not informed of the treatment insulin being used, but this would have been evident for participants on twice daily insulin detemir.

Outcome measures

The primary endpoint was baseline-adjusted HbA_{1c} at end of treatment. Secondary variables included clinic FPG, within-participant variation in PG, ten-point self-measured PG profiles, proportion of participants achieving HbA_{1c} ≤7.0% with and without hypoglycaemia, change in body weight, incidence of hypoglycaemia, adverse events and standard safety parameters.

Analyses and assessments

HbA_{1c} was analysed by HPLC (Bio Rad, Munich, Germany [EU analyses] and Bio Rad, Hercules, CA, USA [US analyses], DCCT-harmonised), with a reference range 4.3–6.1%. Clinic FPG was measured centrally by a hexokinase method (Gluco-quant; Roche, Mannheim, Germany). Body weight was measured using calibrated scales. Participants recorded ten-point PG profiles during the last week of treatment. Hypoglycaemia was classified as 'major' if assistance from another person was required, 'minor' if confirmed by PG <3.1 mmol/l or 'symptoms only' if PG ≥3.1 mmol/l or no measurement was made.

Statistical analyses

The sample size was based on noninferiority of insulin detemir relative to insulin glargine for HbA_{1c} after 52 weeks. To achieve a power of 95% with an expected SD for change in HbA_{1c} of 1.1% and allowing a dropout rate of 15%, it was originally planned to randomise 466 patients. However, this was extended to 566 patients to allow for potential regional differences between the EU and US. The possibility of a treatment × region interaction was tested, but eliminated from the model as no significant interaction was found. Non-inferiority was accepted if the upper limit of the two-sided 95% CI for the difference in HbA_{1c} (detemir–glargine) was less than 0.4%-units, a value decided in discussion with the Food and Drug Administration (FDA) for the entire insulin detemir phase III study programme.

Unless otherwise specified, all analyses were based on the intention-to-treat (ITT) population, this being all randomised patients exposed to insulin detemir or insulin glargine. A significance level of 5% was used for all analyses. Participants were regarded as being on once- or twice-daily insulin detemir according to the regimen used at trial completion. Statistical analyses were not made for these subsets of patients, as this was non-randomised and protocol-determined; results are given for observational comparison only.

Analyses of HbA_{1c}, clinic FPG and change in weight after 52 weeks were by ANOVA with treatment, region and oral glucose-lowering therapy as fixed effects and baseline (randomisation) value as covariate. The last observation carried forward (LOCF) principle was specified for HbA_{1c} and clinic FPG in non-completers treated ≥12 weeks (time of the first on-treatment measurements). Change in weight was estimated based on all participants completing the trial. Additional weight analyses were prepared for the ITT population, applying the same LOCF principle or using imputed data, by treatment-specific linear regression, from week 12 onwards to account for continuing weight change and limit the influence of differences in withdrawal rates and times between treatments. Fisher's exact test was used to compare the numbers of patients on insulin detemir and insulin glargine with an HbA_{1c} ≤7.0% without symptomatic hypoglycaemia confirmed by PG <4.0 mmol/l or any single value <3.1 mmol/l during the last 3 months of treatment. The ten-point self-monitored PG profiles were analysed for parallelism using repeated measures ANOVA depending on treatment, region, oral glucose-lowering therapy, time and treatment × time interaction as fixed effects. Within-participant variation in self-measured fasting and pre-dinner PG was determined from four measurements for each during the last week of treatment. Hypoglycaemic episodes during the 52 week treatment period were analysed as recurrent events in a Cox regression analysis using a gamma frailty model (Splus 2000; Insightful, Seattle, WA, USA). Nocturnal episodes (2300 to 0600 hours) were analysed separately. Adverse events were summarised using descriptive statistics. All other analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA).

Results

Participants

Of 892 patients screened, 582 were randomised, while 289 did not fulfil the selection criteria and 21 withdrew consent. In each treatment arm, 291 patients were randomised and treated, of whom 231 (79%) and 252 (87%) completed the trial on insulin detemir and insulin glargine, respectively (Fig. 1). The higher withdrawal rate observed with insulin detemir was partly due to adverse events, ten of which were considered possibly or probably related to trial drug (Electronic supplementary material [ESM] Table 1). These included two cases of possible cutaneous allergy, five of injection site reactions and one

each of injection site inflammation, hypoglycaemia and weight increase. Adverse event withdrawals with possible or probable relation to glargine included one case each of pruritus, myalgia, hyperglycaemia and hypoglycaemia. Details of all adverse events leading to withdrawal are provided in ESM Table 2. Other diabetes-related reasons for withdrawal with insulin detemir included HbA_{1c} 12.0% (n=1) and multiple hypoglycaemic episodes (n=1). Other reasons for withdrawal included the closure of a trial site and various circumstantial events unrelated to the trial medications.

Baseline characteristics (Table 2) were comparable between the two treatment groups. Participants completing the trial on once or twice daily insulin detemir had a baseline HbA_{1c} of 8.60 and 8.66%, respectively.

Insulin dosing

Of participants treated with insulin detemir, 104 (45%) completed the trial on one daily injection, while 129 (55%) administered an additional morning dose. The majority of patients administering insulin detemir twice daily (n=103) were transferred to this regimen within 12 weeks of treatment. At the time of transfer, about two thirds of the patients adding a morning injection fulfilled the formal dose transfer guidelines, the other one-third were changed through investigator discretion. Participants using insulin detemir twice daily administered about 40% of their daily insulin dose before breakfast. After 52 weeks the mean daily dose of insulin detemir (n=227) was 0.78 U/kg (0.52 U/kg on once daily [n=102] and 1.00 U/kg on twice daily [n=125]) and the mean daily dose of glargine (n=248) was 0.44 IU/kg.

Glycaemic control

HbA_{1c} decreased by 1.5% with both insulins and was comparable after 52 weeks at 7.2% (n=268) and 7.1% (n=275) for detemir and glargine respectively (Table 3), with an estimated difference of 0.05 (−0.11, 0.21)%, thereby meeting the criteria for non-inferiority for insulin detemir vs glargine. HbA_{1c} was similar in participants completing the study on once or twice daily insulin detemir (7.1 and 7.1%). Clinic FPG was 10.8 mmol/l at baseline in both arms and was comparable at end of treatment with insulin detemir and insulin glargine (7.1 and 7.0 mmol/l) (Table 3). The profile of change in HbA_{1c} and FPG was very similar (Fig. 2a). Mean self-monitored FPG was comparable between treatments, being 6.1 mmol/l with insulin detemir and 6.0 mmol/l with insulin glargine; self-monitored PG predinner (6.8 and 7.0 mmol/l) was also similar.

Within-participant variation in self-monitored PG pre-breakfast and pre-dinner did not differ significantly between insulin detemir and insulin glargine (Table 3). The overall shape of the ten-point self-monitored PG profiles during the last week of treatment was parallel for insulin detemir (n=218) and insulin glargine (n=246) (NS) and appeared identical, regardless of treatment regimen (Fig. 2b).

Of participants in both arms, 52% achieved HbA_{1c} ≤7.0%, while 33% treated with insulin detemir and 35% treated with insulin glargine did so in the absence of hypoglycaemia. Fasting and pre-dinner PG targets of ≤6.0 mmol/l were achieved by 25 and 20% of participants treated with insulin detemir and insulin glargine (NS), respectively; the pre-breakfast target alone was achieved by 46 and 58% (p<0.01) and the pre-dinner target by 38 and 30%, respectively (p<0.05).

Hypoglycaemia

The risk of hypoglycaemia of any type was comparable between treatments (Table 4). The overall rate of hypoglycaemia was low at 5.8 vs 6.2 episodes per patient-year with insulin detemir versus insulin glargine (relative risk: 0.94 [96% CI 0.71, 1.25]), while the rate of nocturnal hypoglycaemia was only 1.3 episodes per patient-year with both insulins. Adjustment for HbA_{1c} did not affect the outcome of the analyses. Major hypoglycaemic episodes were rare with both insulins, especially at night, and could not be statistically analysed.

Body weight

Weight gain in participants completing 52 weeks of treatment was lower with insulin detemir (n=230) than with insulin glargine (n=252) (3.0 [SE=0.4] vs 3.9 [SE=0.4] kg, p=0.01). Change in weight analysed by LOCF (detemir n=268, glargine n=275) confirmed this lower weight gain (2.7 vs 3.5 kg, p=0.03), as did analysis with imputation for non-completers (2.8 vs 3.5 kg, p=0.04). Patients completing the study on once daily insulin detemir (n=104) had a weight gain of 2.3 (SE=0.5) kg, whereas those treated twice daily (n=126) gained 3.7 (SE=0.4) kg, similar to glargine (Fig. 3).

Adverse events and other safety measures

Serious adverse events were less frequent with insulin detemir (42 patients with 47 events) than with glargine (53 patients with 73 events). However, only five serious events with insulin detemir (two hypoglycaemia, one each of hypothyroidism, injection-site reaction and a motor vehicle accident) and four with glargine (three hypoglycaemia, one hyperglycaemia) were considered by local investigators to be probably or possibly related to trial products. A participant treated with insulin detemir was found dead in bed (no autopsy report available), but had a history of myocardial infarction. A patient using glargine was hospitalised after the study for pulmonary fibrosis and died of cryptogenic fibrosing alveolitis. Adverse events recorded as serious tended to be of a wide-ranging disparate nature, with no clear pattern of between-treatment differences. Full details of all serious adverse events and events recorded as possibly or probably related to the study insulins are given as in the ESM Tables 1, 2, 3, and 4).

The only differences in adverse events, judged as possibly or probably related to trial drugs, between treatments were: injection-site disorders (13 patients [4.5%] on insulin detemir compared with four [1.4%] on glargine), allergic reactions (three patients on detemir vs one on glargine) and skin disorders including pruritus and rash (six patients on insulin detemir vs one on glargine). There were no differences in standard safety parameters between treatments.

Discussion

The results of this first head-to-head comparison of insulin detemir and insulin glargine as add-on for treatment with oral glucose-lowering agents in people with type 2 diabetes using forced insulin titration suggest that clinically significant and similar improvements in glycaemic control can be achieved with both analogues, together with a similarly low risk of hypoglycaemia. Insulin doses were higher with insulin detemir overall, partly as a result of the doses used by those taking it twice daily. The withdrawal rate appeared to be higher with insulin detemir (21 vs 13%), which was partly accounted for by adverse events (8 vs 4%), this excess being primarily due to injection site reactions. Insulin detemir was associated with a modest relative reduction in weight gain, consistent with observations in previous comparisons of this analogue with NPH in type 2 diabetes [12, 13, 19, 20]. In the present study, the between-treatment difference in weight was primarily accounted for by those patients completing the study on once-daily insulin detemir. It is, however, possible that differences in eating pattern were contributory factors in both the insulin detemir dosing schedule and the different levels of weight gain observed between the two insulin detemir dosing schedules. The mechanism(s) responsible for relatively lower weight gain observed here and previously with insulin detemir remain the object of speculation [14, 15, 21, 22].

The present study was designed to compare the two basal insulin analogues as they had been used in previous studies and according to label. Thus, insulin glargine was given once daily at bedtime regardless of glycaemic profile, while for insulin detemir an option was provided for adding a second dose, primarily based on pre-dinner blood glucose level following a structured insulin titration protocol. The decision to use twice-daily insulin detemir could not be attributed to hypoglycaemia, as patients who were switched to a twice-daily regimen had on average 3.7 hypoglycaemic episodes per patient-year prior to transfer, compared with 4.7 episodes per patient-year in patients completing treatment on once-daily insulin detemir. The frequency of nocturnal hypoglycaemia was also lower in relevant patients before transfer (0.7 vs 0.9 episodes per patient-year).

Interestingly, the initiation of insulin with once-daily insulin detemir has recently been tested by Philis-Tsimikas et al. in type 2 diabetes patients on oral glucose-lowering agents, resulting in HbA_{1c} reductions of 1.5% (morning injection) and 1.6% (evening injection) from baseline values of 9.1 and 8.9%, respectively [13]. These improvements in glycaemic control approach the magnitude of HbA_{1c} reduction shown in the current study and in previous studies of once-daily insulin glargine [9–11], although the insulin detemir doses were higher at trial-end and the absolute HbA_{1c} values achieved at trial-end were relatively high.

The design of the current study does not allow definitive conclusions for comparison of once and twice daily dosing with insulin detemir, although these post hoc observations do suggest that once daily administration can be an appropriate starting regimen for people using insulin detemir as add-on to oral glucose-lowering drug therapy. However, with dose optimisation, a significant proportion of patients may eventually need a twice-daily regimen, guided by structured glucose monitoring. Further studies are required to better define the differences between these two basal insulin analogues on the basis of a similar insulin administration

regimen, once daily only, for both insulins. Alternatively, if the option of adding a second insulin dose is available for both insulins, then a properly designed study protocol should allow addition of this second insulin injection only when a normal or much lower FPG target is achieved. Indeed, the use of lower FPG targets (e.g. ≤ 5.5 mmol/l, as has been used previously) should also enable a higher proportion of patients to reach guideline HbA_{1c} targets.

In conclusion, the use of insulin detemir or insulin glargine as add-on to oral glucose-lowering therapy resulted in comparable HbA_{1c} improvements and a similarly low risk of hypoglycaemia. Further comparisons of detemir and glargine are required to fully understand how each may relatively benefit defined groups of patients starting on insulin.

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References

1. Riddle MC (2004) Timely initiation of basal insulin. *Am J Med* 116:3S–9S
2. Wright A, Burden ACF, Paisey RB, Cull CA, Holman RR, for the UK Prospective Diabetes Study Group (2002) Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 25:330–336
3. Marre M (2002) Before oral agents fail: the case for starting insulin early. *Int J Obes* 26(Suppl 3):S25–S30
4. Korytkowski M (2002) When oral agents fail: practical barriers to starting insulin. *Int J Obes* 26:S18–S24
5. Davies M (2004) The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges. *Int J Obes Relat Metab Disord* 28(Suppl 2):S14–S22
6. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO (2004) Glycaemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes. *Diabetes Care* 27:17–20
7. Turner RC, Cull CA, Frighi V, Holman RR, for the UK Prospective Diabetes Study (UKPDS) Group (1999) Glycaemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 281:2005–2012
8. Heise T, Nosek L, Ronn BB et al (2004) Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 53:1614–1620
9. Riddle MC, Rosenstock J, Gerich J, on behalf of the Insulin Glargine 4002 Study Investigators (2003) The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080–3086
10. Eliaschewitz FG, Calvo C, Valbuena H et al, HOE 901/4013 LA Study Group (2006) Therapy in type 2 diabetes: insulin glargine vs Diabetologia (2008) 51:408–416 415 NPH insulin both in combination with glimepiride. *Arch Med Res* 37:495–501
11. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M et al (2006) Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 49:442–451
12. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P (2006) A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 29:1269–1274

13. Philis-Tsimikas A, Charpentier G, Clauson P, Martinez Ravn G, Roberts VL, Thorsteinsson B (2006) Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 28:1569–1581
14. Home P, Kurtzhals P (2006) Insulin detemir: from concept to clinical experience. *Expert Opin Pharmacother* 7:325–343
15. Hermansen K, Davies M (2007) Does insulin detemir have a role in reducing risk of insulin-associated weight gain. *Diabetes Obes Metab* 9:209–217
16. Klein O, Lyngé J, Endahl L, Damholt B, Nosek L, Heise T (2007) Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time–action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes Obes Metab* 9:290–299
17. Porcellati F, Rossetti P, Busciantella Ricci N et al (2007) Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: A double-blind, randomized, crossover study. *Diabetes Care* 30:2447–2452
18. sanofi aventis (2005) Lantus label information, NDA 21-081/S-017. Available from <http://www.fda.gov/cder/foi/label/2005/21081s017lbl.pdf>, accessed 1 July 2007
19. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N (2004) Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract* 66:193–201
20. Haak T, Tiengo A, Draeger E, Suntum M, Waldhäusl W (2005) Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab* 7:56–65
21. Raslova K, Tamer SC, Clauson P, Karl D (2007) Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. *Clin Drug Investig* 27:279–85
22. Russell-Jones D, Khan R (2007) Insulin-associated weight gain in diabetes—causes, effects and coping strategies. *Diabetes Obes Metab* 9:799–812

Table 1 Algorithm used for insulin dose titration

	Adjustment of insulin dose (U)	
	If positive response to previous dose adjustment	If no response to previous dose adjustment ^a
Evening insulin dose adjustment		
Average pre-breakfast self-monitored PG		
>10.0 mmol/l	+12	+12
9.1–10.0 mmol/l	+8	+10
8.1–9.0 mmol/l	+6	+8
7.1–8.0 mmol/l	+4	+6
6.1–7.0 mmol/l	+2	+2
If one self-monitored PG measurement		
3.1–4.0 mmol/l	–2	–2
<3.1 mmol/l	–4	–4
Morning insulin dose adjustment ^b		
Average pre-dinner self-monitored PG		
>10.0 mmol/l	+8	+8
9.1–10.0 mmol/l	+6	+8
8.1–9.0 mmol/l	+4	+6
7.1–8.0 mmol/l	+2	+4
6.1–7.0 mmol/l	+2	+2
If one self-monitored PG measurement:		
3.1–4.0 mmol/l	–2	–2
<3.1 mmol/l	–4	–4

^a Non-responses: the average self-monitored PG level is increased and/or within the same range as at the last contact

^b Some insulin detemir-treated participants only

Table 2 Clinical characteristics of type 2 diabetic participants

	Detemir	Glargine
Randomised/Exposed/ITT, <i>n</i> (%)	291 (100)	291 (100)
Men:women, <i>n</i>	166:125	171:120
Ethnicity (<i>n</i>)		
Black	22	12
White	250	263
Asian-Pacific islander	7	7
Other	12	9
Oral glucose-lowering drugs, <i>n</i> (%)		
Monotherapy	73 (25)	70 (24)
Metformin	32 (11)	33 (11)
Insulin secretagogues	41 (14)	37 (13)
Combination therapy	218 (75)	221 (76)
Metformin + secretagogue	212	215
Metformin + alpha glucosidase inhibitor	3	1
Secretagogue + alpha glucosidase inhibitor	3	4
Secretagogue + secretagogue (SU + glinide)	–	1
Age (years)	58.4 (10.2)	59.4 (9.6)
Weight (kg) ^a	87.4 (16.6)	87.4 (17.4)
BMI (kg/m ²)	30.6 (4.8)	30.5 (4.6)
Duration of diabetes (years)	9.1 (6.1)	9.1 (6.4)
HbA _{1c} (%) ^a	8.64 (0.78)	8.62 (0.77)
C-peptide (nmol/l)	0.87 (0.56)	0.85 (0.55)

Values are *n* (%) or mean (SD). ^aBefore randomisation SU, sulfonylurea

Table 3 Glycaemic control in type 2 diabetic patients treated with insulin detemir or insulin glargine

	Detemir		All	Glargine	Difference (95% CI) (detemir–glargine)	<i>p</i> value
	Completers on once daily	Completers on twice daily		All		
HbA _{1c} (%) ^a	7.12 (0.11)	7.06 (0.10)	7.16 (0.08)	7.12 (0.08)	0.05 (−0.11, 0.21]	–
<i>n</i>	104	127	268	275		
Clinic FPG (mmol/l) ^a	7.27 (0.31)	6.73 (0.25)	7.14 (0.21)	6.98 (0.21)	0.16 (−0.26, 0.58)	–
<i>n</i>	104	127	268	272		
HbA _{1c} ≤7.0 %, <i>n</i> (%)	52 (51)	69 (54)	129 (52)	135 (52)	–	1.00
<i>n</i>	103	127	248	259		
HbA _{1c} ≤7.0 % without hypoglycaemia, <i>n</i> (%)	31 (30)	48 (38)	82 (33)	90 (35)	–	0.71
<i>n</i>	103	127	248	259		
Within-participant variation (mmol/l)						
Pre-breakfast (mmol/l) ^b	0.93 (15.0)	1.15 (19.6)	1.06 (17.5)	1.03 (17.3)	–	0.45
<i>n</i>	103	125	238	257		
Pre-dinner (mmol/l) ^b	1.27 (19.8)	1.84 (26.4)	1.60 (23.6)	1.55 (22.0)	–	0.41
<i>n</i>	103	125	238	258		

^aMean (SE); *n*=number of patients for whom data are available

^bWithin-participant SD (CV%)

Table 4 Hypoglycaemic episodes in type 2 diabetic patients treated with insulin detemir or insulin glargine

Events	Insulin detemir (n=291)			Insulin glargine (n=291)			Relative risk (detemir/glargine) (95% CI)
	Participants, n (%)	Episodes (n)	Rate (per patient- year)	Participants, n (%)	Episodes (n)	Rate (per patient- year)	
All	182 (63)	1521	5.8	191 (66)	1670	6.2	0.94 (0.71–1.25)
Nocturnal	95 (33)	352	1.3	93 (32)	350	1.3	1.05 (0.69–1.58)
Major	5 (2)	9	0.0	8 (3)	8	0.0	–
Nocturnal	3 (1)	5	0.0	4 (1)	4	0.0	–
Minor	135 (46)	737	2.9	151 (52)	786	2.9	1.05 (0.75–1.46)
Nocturnal	73 (25)	212	0.8	71 (24)	192	0.7	1.17 (0.75–1.83)
Symptoms only	137 (47)	760	3.0	133 (46)	866	3.2	0.88 (0.61–1.25)
Nocturnal	48 (17)	128	0.5	49 (17)	151	0.6	0.88 (0.50–1.54)

No statistical analyses were performed on the small numbers of major events

Fig. 1 Patient disposition during the trial and consequent analysis sets

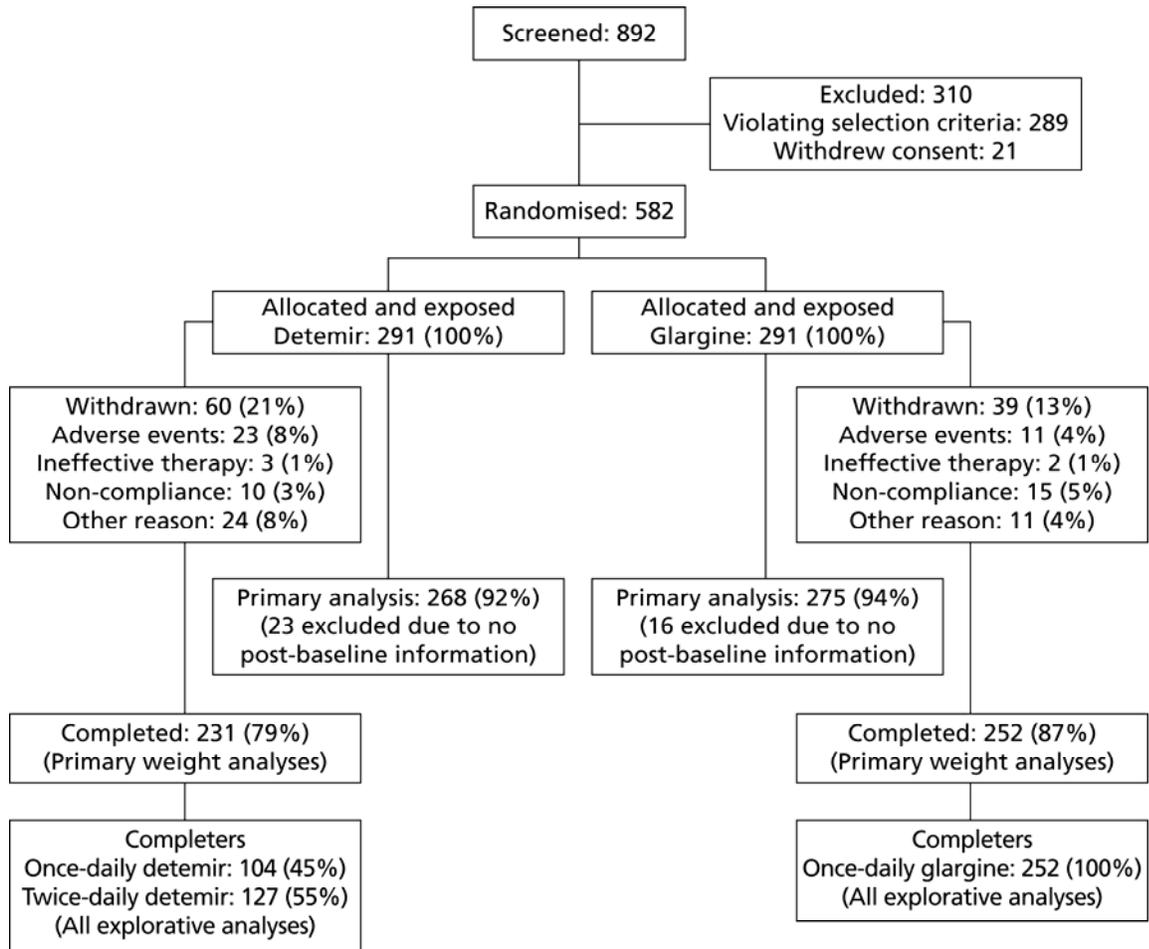


Fig. 2 Change in HbA_{1c} with time (a). Black circles, insulin detemir; white circles, insulin glargine. **b** Mean ten-point self-monitored PG profiles during the last week of treatment. White triangles, insulin detemir (once daily); black squares, insulin detemir (twice daily); black circles, insulin detemir (all patients); white circles, insulin glargine

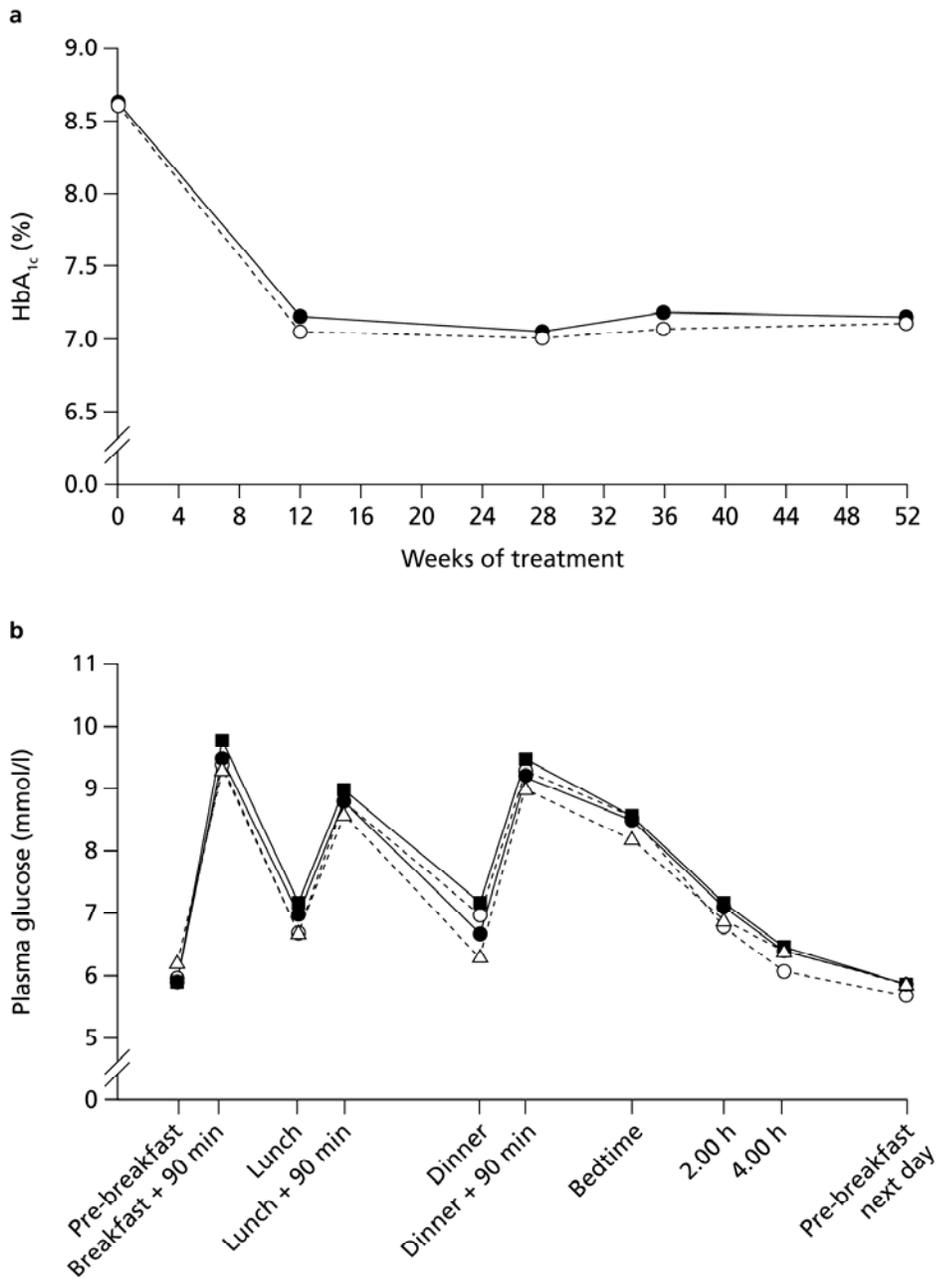
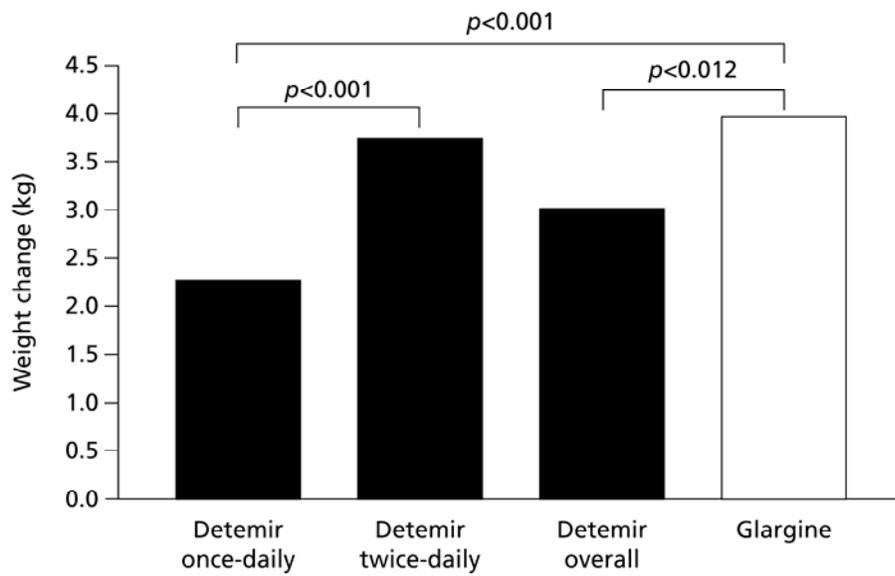


Fig. 3 Mean weight change from baseline at week 52 in patients completing treatment on insulin detemir once or twice daily (and overall) and insulin glargine. *** $p < 0.001$;

† $p < 0.012$



ESM Table 1. Treatment emergent adverse events probably or possibly related to trial product by system organ class, ITT cohort.

	ITT analysis set	Detemir		Glargine	
		N	(%) E	N	(%) E
	291			291	
Adverse Event		40 (13.7)	56	32 (11.0)	53
APPLICATION SITE DISORDERS		13 (4.5)	13	4 (1.4)	5
INJECTION SITE HAEMATOMA		1 (0.3)	1	2 (0.7)	2
INJECTION SITE INFLAMMATION		3 (1.0)	3	0 (0.0)	0
INJECTION SITE PAIN		0 (0.0)	0	2 (0.7)	2
INJECTION SITE REACTION		9 (3.1)	9	1 (0.3)	1
BODY AS A WHOLE - GENERAL DISORDERS		8 (2.7)	9	7 (2.4)	9
ABDOMEN ENLARGED		0 (0.0)	0	1 (0.3)	1
ALLERGIC REACTION		0 (0.0)	0	1 (0.3)	1
ALLERGY		3 (1.0)	3	0 (0.0)	0
ASTHENIA		1 (0.3)	1	1 (0.3)	2
FATIGUE		3 (1.0)	3	2 (0.7)	2
OEDEMA PERIPHERAL		2 (0.7)	2	3 (1.0)	3
CENTR & PERIPH NERVOUS SYSTEM DISORDERS		7 (2.4)	10	11 (3.8)	22
CONVULSIONS		1 (0.3)	1	0 (0.0)	0
DIZZINESS		1 (0.3)	1	3 (1.0)	4
GAIT ABNORMAL		0 (0.0)	0	1 (0.3)	1
HEADACHE		5 (1.7)	7	5 (1.7)	13
HYPOAESTHESIA		1 (0.3)	1	0 (0.0)	0
NEURALGIA		0 (0.0)	0	1 (0.3)	1
TREMOR			0 (0.0) 0		1 (0.3)
2					
VISUAL FIELD DEFECT		0 (0.0)	0	1 (0.3)	1
METABOLIC AND NUTRITIONAL DISORDERS		6 (2.1)	7	6 (2.1)	6
HYPERGLYCAEMIA		0 (0.0)	0	1 (0.3)	1

HYPOGLYCAEMIA	2 (0.7)	2	3 (1.0)	3
HYPOKALAEMIA	1 (0.3)	1	0 (0.0)	0
LIPODYSTROPHY	2 (0.7)	2	1 (0.3)	1
OBESITY	1 (0.3)	1	0 (0.0)	0
WEIGHT INCREASE	1 (0.3)	1	1 (0.3)	1
SKIN AND APPENDAGES DISORDERS	6 (2.1)	6	1 (0.3)	1
PRURITUS	3 (1.0)	3	1 (0.3)	1
RASH	1 (0.3)	1	0 (0.0)	0
RASH ERYTHEMATOUS	1 (0.3)	1	0 (0.0)	0
SWEATING INCREASED	1 (0.3)	1	0 (0.0)	0
VISION DISORDERS	4 (1.4)	5	2 (0.7)	2
DIPLOPIA	0 (0.0)	0	1 (0.3)	1
RETINAL DISORDER	2 (0.7)	2	0 (0.0)	0
RETINAL OEDEMA	1 (0.3)	1	0 (0.0)	0
VISION ABNORMAL	2 (0.7)	2	1 (0.3)	1
PSYCHIATRIC DISORDERS	2 (0.7)	2	1 (0.3)	1
ANOREXIA	1 (0.3)	1	0 (0.0)	0
APPETITE INCREASED	1 (0.3)	1	0 (0.0)	0
SOMNOLENCE	0 (0.0)	0	1 (0.3)	1
CARDIOVASCULAR DISORDERS, GENERAL	1 (0.3)	1	0 (0.0)	0
CIRCULATORY FAILURE	1 (0.3)	1	0 (0.0)	0
ENDOCRINE DISORDERS	1 (0.3)	1	0 (0.0)	0
HYPERTHYROIDISM	1 (0.3)	1	0 (0.0)	0
MUSCULO-SKELETAL SYSTEM DISORDERS	1 (0.3)	1	2 (0.7)	2
ARTHRALGIA	1 (0.3)	1	0 (0.0)	0
ARTHRITIS	0 (0.0)	0	1 (0.3)	1
MYALGIA	0 (0.0)	0	1 (0.3)	1
SECONDARY TERMS	1 (0.3)	1	0 (0.0)	0
INJURY ACCIDENTAL	1 (0.3)	1	0 (0.0)	0
GASTRO-INTESTINAL SYSTEM DISORDERS	0 (0.0)	0	2 (0.7)	2
ABDOMINAL PAIN	0 (0.0)	0	1 (0.3)	1
NAUSEA	0 (0.0)	0	1 (0.3)	1

MYO ENDO PERICARDIAL & VALVE DISORDERS	0 (0.0)	0	1 (0.3)	1
ANGINA PECTORIS	0 (0.0)	0	1 (0.3)	1
RESPIRATORY SYSTEM DISORDERS		0 (0.0)		1 (0.3)
1				
COUGHING	0 (0.0)	0	1 (0.3)	1
VASCULAR (EXTRACARDIAC) DISORDERS	0 (0.0)	0	1 (0.3)	1
VEIN DISORDER	0 (0.0)	0	1 (0.3)	1

N: Number of subjects with adverse event

#: Proportion of subjects in analysis set having adverse event

E: Number of adverse events

ITT analysis set consists of all subjects exposed to trial product

ESM Table 2. Adverse events leading to withdrawal.

Treatment Group	Investigators Preferred term	Description/	Duration of Event (days)	Severity	Serious	Relation to study drug
Detemir	cardiac decompensation			34	SEVERE	N UNLIKELY
Detemir	cardiac insufficiency			47	SEVERE	N UNLIKELY
Detemir	recurrent diarrhea			4	MODERATE	N UNLIKELY
Detemir	myocardial infarction			25	SEVERE	Y UNLIKELY
Detemir	allergie on skin	54		MODERATE	N	POSSIBLE
Detemir	allergical exanthema at inj site	37		MODERATE	N	PROBABLE
Detemir	allergical exanthema at inj site	42		MODERATE	N	POSSIBLE
Detemir	shoulder-arm-syndrome					MODERATE N UNLIKELY
Detemir	sciatica					MODERATE N UNLIKELY
Detemir	worsening of macula degeneration	246		SEVERE	Y	UNLIKELY
Detemir	local allergic reaction	18		SEVERE	Y	PROBABLE
Detemir	Coronary Event			0	SEVERE	Y UNLIKELY
Detemir	skin irritation at injection sites	15		MILD	N	PROBABLE
Detemir	LOCALISED INFLAMATION at inj. site	20		MILD	N	PROBABLE
Detemir	prolonged period of hypoglycaemia	0		SEVERE	Y	PROBABLE
Detemir	right sided cerebral vasc. accident	30		SEVERE	Y	UNLIKELY
Detemir	aspiration pneumonia			25	MODERATE	Y UNLIKELY
Detemir	red inflammation marks injection site			MODERATE	N	UNLIKELY
Detemir	WORSENING OF NEUROPATHY			SEVERE	N	UNLIKELY
Detemir	MACULAR PAPULES AT INJECTION SITES	67		SEVERE	N	POSSIBLE
Detemir	WEIGHT GAIN	328		MODERATE	N	POSSIBLE
Detemir	increase of creatinine	118		MODERATE	N	UNLIKELY
Detemir	cutaneous reaction	279		MODERATE	N	POSSIBLE
Detemir	Cancer diagnosis hip and lungs	9		SEVERE	Y	UNLIKELY
Detemir	chest pain	14		SEVERE	Y	UNLIKELY
Detemir	Uncontrolled Hypertension	5		SEVERE	Y	UNLIKELY
Detemir	DIZZINESS	40		SEVERE	Y	UNLIKELY
Glargine	PRURIGO / PRURITUS					MODERATE N POSSIBLE
Glargine	Muscle pain			MODERATE	N	POSSIBLE
Glargine	gastrointestinal bleeding	44		SEVERE	Y	UNLIKELY
Glargine	hypertensive crisis			24	MODERATE	Y UNLIKELY
Glargine	Re Apoplex	16		MODERATE	Y	UNLIKELY
Glargine	aneurysm of abdominal aorta	72		SEVERE	Y	UNLIKELY
Glargine	hyperglycaemia	5		MODERATE	Y	POSSIBLE
Glargine	NOCTURIA	41		MILD	N	UNLIKELY
Glargine	villous tumor of colon	250		SEVERE	Y	UNLIKELY
Glargine	major hypoglycaemia	0		SEVERE	Y	PROBABLE
Glargine	pneumopathy	25		SEVERE	Y	UNLIKELY
Glargine	stroke			SEVERE	Y	UNLIKELY
Glargine	mild stroke	33		SEVERE	Y	UNLIKELY
Glargine	Colon cancer	10		SEVERE	Y	UNLIKELY

ESM Table 3. Treatment emergent serious adverse events by system organ class, ITT cohort.

	Detemir		Glargine	
	N	(%) E	N	(%) E
ITT analysis set	291		291	
Adverse Event	42 (14.4)	47	53 (18.2)	73
MYO ENDO PERICARDIAL & VALVE DISORDERS	6 (2.1)	6	7 (2.4)	7
ANGINA PECTORIS AGGRAVATED	1 (0.3)	1	1 (0.3)	1
CORONARY ARTERY DISORDER	2 (0.7)	2	6 (2.1)	6
MYOCARDIAL INFARCTION	3 (1.0)	3	0 (0.0)	0
BODY AS A WHOLE - GENERAL DISORDERS	5 (1.7)	5	8 (2.7)	10
ALLERGIC REACTION	0 (0.0)	0	1 (0.3)	1
BACK PAIN	0 (0.0)	0	2 (0.7)	2
CHEST PAIN	2 (0.7)	2	4 (1.4)	6
MALAISE	1 (0.3)	1	0 (0.0)	0
NASAL POLYP	1 (0.3)	1	0 (0.0)	0
SYNCOPE	1 (0.3)	1	1 (0.3)	1
NEOPLASM	5 (1.7)	5	5 (1.7)	5
ADENOCARCINOMA NOS	0 (0.0)	0	1 (0.3)	1
BLADDER CARCINOMA	1 (0.3)	1	0 (0.0)	0
BREAST NEOPLASM MALIGNANT FEMALE	1 (0.3)	1	1 (0.3)	1
CARCINOMA	3 (1.0)	3	0 (0.0)	0
COLON CARCINOMA	0 (0.0)	0	1 (0.3)	1
NEOPLASM NOS	0 (0.0)	0	1 (0.3)	1
OVARIAN CYST	0 (0.0)	0	1 (0.3)	1
GASTRO-INTESTINAL SYSTEM DISORDERS	4 (1.4)	4	2 (0.7)	2
ABDOMINAL PAIN	1 (0.3)	1	0 (0.0)	0
DUODENAL ULCER	1 (0.3)	1	0 (0.0)	0
GASTRITIS	1 (0.3)	1	0 (0.0)	0
GI HAEMORRHAGE	0 (0.0)	0	1 (0.3)	1

HAEMORRHAGE RECTUM	0 (0.0) 0	1 (0.3) 1
PANCREATITIS	1 (0.3) 1	0 (0.0) 0
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	3 (1.0) 3	0 (0.0) 0
DIZZINESS	1 (0.3) 1	0 (0.0) 0
HEADACHE	1 (0.3) 1	0 (0.0) 0
VERTIGO	1 (0.3) 1	0 (0.0) 0
RESPIRATORY SYSTEM DISORDERS	3 (1.0) 3	4 (1.4)
4		
BRONCHITIS	1 (0.3) 1	0 (0.0) 0
DYSPNOEA	0 (0.0) 0	1 (0.3) 1
PNEUMONIA	2 (0.7) 2	1 (0.3) 1
PULMONARY FIBROSIS	0 (0.0) 0	1 (0.3) 1
PULMONARY INFILTRATION	0 (0.0) 0	1 (0.3) 1
SECONDARY TERMS	3 (1.0) 3	3 (1.0) 3
INJURY ACCIDENTAL	2 (0.7) 2	3 (1.0) 3
OTHER EVENTS	1 (0.3) 1	0 (0.0) 0
VASCULAR (EXTRACARDIAC) DISORDERS	3 (1.0) 3	7 (2.4) 7
CEREBROVASCULAR DISORDER	1 (0.3) 1	5 (1.7) 5
PERIPHERAL ISCHAEMIA	1 (0.3) 1	2 (0.7) 2
VEIN VARICOSE	1 (0.3) 1	0 (0.0) 0
METABOLIC AND NUTRITIONAL DISORDERS	2 (0.7) 2	4 (1.4) 4
HYPERGLYCAEMIA	0 (0.0) 0	1 (0.3) 1
HYPOGLYCAEMIA	2 (0.7) 2	3 (1.0) 3
MUSCULO-SKELETAL SYSTEM DISORDERS	2 (0.7) 2	10 (3.4) 10
ARTHROPATHY	0 (0.0) 0	1 (0.3) 1
ARTHROSIS	1 (0.3) 1	2 (0.7) 2
BONE DISORDER	0 (0.0) 0	1 (0.3) 1
DUPUYTREN'S CONTRACTURE	0 (0.0) 0	1 (0.3) 1
FRACTURE BONE	1 (0.3) 1	1 (0.3) 1
FRACTURE PATHOLOGICAL	0 (0.0) 0	2 (0.7)
2		
POLYMYALGIA RHEUMATICA	0 (0.0) 0	1 (0.3) 1
RHABDOMYOLYSIS	0 (0.0) 0	1 (0.3) 1

URINARY SYSTEM DISORDERS	2 (0.7)	2	2 (0.7)	3
CYSTITIS	0 (0.0)	0	1 (0.3)	1
HAEMATURIA	0 (0.0)	0	1 (0.3)	1
RENAL CYST	1 (0.3)	1	0 (0.0)	0
RENAL PAIN	0 (0.0)	0	1 (0.3)	1
URINARY TRACT INFECTION	1 (0.3)	1	0 (0.0)	0
VISION DISORDERS	2 (0.7)	2	1 (0.3)	1
CATARACT	0 (0.0)	0	1 (0.3)	1
MACULA LUTEA DEGENERATION	1 (0.3)	1	0 (0.0)	0
RETINITIS	1 (0.3)	1	0 (0.0)	0
APPLICATION SITE DISORDERS	1 (0.3)	1	1 (0.3)	2
CELLULITIS	0 (0.0)	0	1 (0.3)	1
INJECTION SITE REACTION	1 (0.3)	1	0 (0.0)	0
SKIN NECROSIS	0 (0.0)	0	1 (0.3)	1
CARDIOVASCULAR DISORDERS, GENERAL	1 (0.3)	1	5 (1.7)	5
ANEURYSM	0 (0.0)	0	1 (0.3)	1
CARDIAC FAILURE	0 (0.0)	0	2 (0.7)	2
HYPERTENSION	1 (0.3)	1	0 (0.0)	0
HYPERTENSION AGGRAVATED	0 (0.0)	0	1 (0.3)	1
HYPOTENSION	0 (0.0)	0	1 (0.3)	1
ENDOCRINE DISORDERS	1 (0.3)	1	0 (0.0)	0
HYPERTHYROIDISM	1 (0.3)	1	0 (0.0)	0
PLATELET,BLEEDING & CLOTTING DISORDERS	1 (0.3)	2	1 (0.3)	1
EMBOLISM PULMONARY	0 (0.0)	0	1 (0.3)	1
THROMBOSIS	1 (0.3)	2	0 (0.0)	0
RESISTANCE MECHANISM DISORDERS	1 (0.3)	1	2 (0.7)	2
ABSCESS	0 (0.0)	0	1 (0.3)	1
INFECTION BACTERIAL	1 (0.3)	1	0 (0.0)	0
INFECTION WOUND	0 (0.0)	0	1 (0.3)	1
SKIN AND APPENDAGES DISORDERS	1 (0.3)	1	0 (0.0)	0
HYPERKERATOSIS	1 (0.3)	1	0 (0.0)	0
LIVER AND BILIARY SYSTEM DISORDERS	0 (0.0)	0	3 (1.0)	3

CHOLELITHIASIS	0 (0.0) 0	3 (1.0) 3
PSYCHIATRIC DISORDERS	0 (0.0) 0	1 (0.3) 1
DEPRESSION	0 (0.0) 0	1 (0.3) 1
RED BLOOD CELL DISORDERS	0 (0.0) 0	2 (0.7) 2
ANAEMIA	0 (0.0) 0	2 (0.7) 2
REPRODUCTIVE DISORDERS, MALE	0 (0.0) 0	1 (0.3) 1
HERNIA INGUINAL	0 (0.0) 0	1 (0.3) 1

N: Number of subjects with adverse event

?: Proportion of subjects in analysis set having adverse event

E: Number of adverse events

ITT analysis set consists of all subjects exposed to trial product

ESM Table 4. Treatment emergent serious adverse events preferred term, occurring in more than one subject, ITT.

	Detemir		Glargine	
	N (%)	E	N (%)	E
ITT analysis set		291		291
Adverse Event	42 (14.4)	47	53 (18.2)	73
CORONARY ARTERY DISORDER	2 (0.7)	2	6 (2.1)	6
MYOCARDIAL INFARCTION	3 (1.0)	3	0 (0.0)	0
BACK PAIN	0 (0.0)	0	2 (0.7)	2
CHEST PAIN	2 (0.7)	2	4 (1.4)	6
CARCINOMA	3 (1.0)	3	0 (0.0)	0
PNEUMONIA	2 (0.7)	2	1 (0.3)	1
INJURY ACCIDENTAL	2 (0.7)	2	3 (1.0)	3
CEREBROVASCULAR DISORDER	1 (0.3)	1	5 (1.7)	5
PERIPHERAL ISCHAEMIA	1 (0.3)	1	2 (0.7)	2
HYPOGLYCAEMIA	2 (0.7)	2	3 (1.0)	3
ARTHROSIS	1 (0.3)	1	2 (0.7)	2
FRACTURE PATHOLOGICAL	0 (0.0)	0	2 (0.7)	2
CARDIAC FAILURE	0 (0.0)	0	2 (0.7)	2
CHOLELITHIASIS	0 (0.0)	0	3 (1.0)	3
ANAEMIA	0 (0.0)	0	2 (0.7)	2

N: Number of subjects with adverse event

#: Proportion of subjects in analysis set having adverse event

E: Number of adverse events

ITT analysis set consists of all subjects exposed to trial product