Title of Trial	A 20 week multi-national, open-labelled, randomised, three-group parallel trial comparing administration of insulin detemir morning, insulin detemir evening and NPH insulin evening as add-on to oral antidiabetic drug(s) in subjects with type 2 diabetes
Trial ID	NN304-1632
Development Phase	Phase 3b
IND Number (US only)	IND No. 51789
Compound Name	Insulin detemir
Indication	Diabetes mellitus
Investigators	There were a total of 91 principal investigators in 7 countries. Dr [redacted] ([redacted]) and Dr [redacted] ([redacted]) have been designated as the signatory investigators for this trial.
Trial Sites	There were a total of 91 trial sites in: Denmark (12), France (10), Italy (9), the Netherlands (6), Norway (9), Spain (17) and the United States (28)
Trial Initiated	14 Feb 2005
Trial Completed	21 Feb 2006
Sponsor	Novo Nordisk A/S, Denmark
International Medical Officer	[redacted] Novo Nordisk A/S, Denmark
International Trial Manager	[redacted] Novo Nordisk A/S, Denmark
Local Trial Managers	[redacted] (Denmark), [redacted] (Denmark), [redacted] (France), [redacted] (Italy), [redacted] (Netherlands), [redacted] (Norway), [redacted] (Spain) and [redacted] (US)
Statisticians	[redacted], M.Sc., and [redacted], B.Sc. Clinical Reporting, Medical Information and Biostatistics, Singapore
Medical Writers	[redacted], M.Sc., and [redacted], MA Clinical Reporting, Medical Information and Biostatistics, Singapore
Report Date	21 July 2006

This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Synopsis

TITLE OF TRIAL A 20 week multi-national, open-labelled, randomised, three-group parallel trial comparing administration of insulin detemir morning, insulin detemir evening and NPH insulin evening as add-on to oral antidiabetic drug(s) in subjects with type 2 diabetes
INVESTIGATORS There were a total of 91 principal investigators in 7 countries. Dr [redacted] ([redacted]) and Dr [redacted] ([redacted]) have been designated as the signatory investigators for this trial.
TRIAL SITES There were a total of 91 trial sites in: Denmark (12), France (10), Italy (9), the Netherlands (6), Norway (9), Spain (17) and the United States (28).
PUBLICATIONS None.

TRIAL PERIOD	**DEVELOPMENT PHASE**
The trial started on 14 Feb 2005 and completed on 21 Feb 2006	Phase 3b

OBJECTIVES

Primary Objective:

To compare the glycaemic control, measured as HbA_{1c}, of insulin detemir given once daily with that of NPH insulin given once daily as add-on to current OAD treatment, in subjects with type 2 diabetes after a 20 week treatment period.

Secondary Objectives:

If both insulin detemir treatments, insulin detemir given in the morning and insulin detemir given in the evening, are shown to be non-inferior to NPH insulin given once daily with regard to HbA_{1c}, the secondary objective was to compare the glycaemic control, measured as HbA_{1c}, of insulin detemir given in the morning with that of insulin detemir given in the evening, as add-on to OAD(s) after a 20 week treatment period.

A comparison of the following will be performed between insulin detemir morning and NPH insulin and insulin detemir evening and NPH insulin:

- Proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ after 20 weeks of treatment.
- Proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ after 20 weeks of treatment without symptomatic hypoglycaemia with a plasma glucose value < 4.0 mmol/L (< 72 mg/dL) or any single plasma glucose value < 3.1 mmol/L (< 56 mg/dL), in the last four weeks of treatment.
- Glycaemic control as measured by FPG (central laboratory) after 12 and 20 weeks of treatment.
- Within-subject variation of SMPG before breakfast and dinner during the trial.
- Glycaemic control as measured by 9-point SMPG profiles during the trial.
- Body weight change during the trial.
- Incidence of hypoglycaemic episodes during the trial: nocturnal (11 pm–6 am) and over the entire day (24h).
- The safety profile as measured by occurrence of adverse events during the trial.
- The safety profile as measured by laboratory safety parameters (haematology, biochemistry and lipids), fundoscopy/fundusphotography and vital signs.
- Insulin doses during the trial.
- Possible correlation between endogenous insulin production (serum insulin and C-peptide) and insulin requirements in insulin naïve subjects.

If both insulin detemir treatments are shown to be non-inferior to NPH insulin with regard to HbA_{1c}, insulin detemir in the morning is to be compared to insulin detemir in the evening in terms of the same parameters as mentioned above.

METHODOLOGY

This was a multi-national, open-labelled, randomised parallel group trial with a 20-week treatment period which compared the efficacy and safety of add-on therapy of once daily basal insulin (insulin detemir or NPH insulin) to OAD in subjects with type 2 diabetes. Subjects were randomised 1:1:1 to treatment. Insulin detemir was administered in the morning or evening and NPH insulin was administered in the evening.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 501 subjects were planned to be enrolled in the trial. The subject disposition is shown below:
For withdrawal due to other reasons, the specifics included: withdrawal of consent, inadequate control, meeting inclusion/withdrawal criteria, non-compliance with visits, no need for insulin therapy or fear of hypoglycaemia.

	Detemir Morning N (%)	Detemir Evening N (%)	NPH Evening N (%)	All N (%)
Screened				670
Randomised[+]	168 (100)	170 (100)	166 (100)	504 (100)
Withdrawals	18 (10.7)	16 (9.4)	17 (10.2)	51 (10.1)
AE	4 (2.4)	4 (2.4)	4 (2.4)	12 (2.4)
INEFF. THERAPY	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)
NON-COMPLIANCE	7 (4.2)	5 (2.9)	9 (5.4)	21 (4.2)
OTHER	6 (3.6)	6 (3.5)	3 (1.8)	15 (3.0)
Completers	149 (88.7)	154 (90.6)	149 (89.8)	452 (89.7)
ITT analysis set	165 (98.2)	169 (99.4)	164 (98.8)	498 (98.8)
PP analysis set	138 (82.1)	142 (83.5)	130 (78.3)	410 (81.3)

[+]Subject [redacted] is a screening failure but was randomised accidentally to detemir morning.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male or female subjects at least 18 years of age who had type 2 diabetes mellitus for at least 12 months, insulin-naïve, who are currently treated with OAD, have BMI ≤ 40 kg/m^2 and HbA_{1c} between 7.5% and 11.0%, both inclusive.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Insulin detemir FlexPen (100 U/mL) was administered subcutaneously, preferably in the thigh. The injection area chosen was to remain unchanged throughout the trial with rotation in the region within the chosen injection site.
Batch numbers: PP51449 and RP51010.

DURATION OF TREATMENT

There was a 2-week screening period after which subjects were randomised to treatment. A 20-week treatment period followed, during which insulin dose was continuously titrated to achieve treatment targets of pre-breakfast or pre-dinner plasma glucose value ≤ 6.0 mmol/L (≤ 108 mg/dL).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

NPH insulin (100 IU/mL) was administered subcutaneously, preferably in the thigh. The injection area chosen was to remain unchanged throughout the trial with rotation in the region within the chosen injection site. Batch numbers: NPH insulin Penfill – RQ50154 and PQ50189; NPH insulin FlexPen – RP50257 and PP51091.

CRITERIA FOR EVALUATION – EFFICACY

HbA_{1c} after 20 weeks of treatment, fasting plasma glucose (FPG), 9-point self-monitoring plasma glucose (SMPG), change in body weight, serum insulin, C-peptide and insulin dose.

CRITERIA FOR EVALUATION – SAFETY

Incidence of hypoglycaemia and adverse events, vital signs, fundoscopy/fundusphotography, haematology, biochemistry and lipids.

STATISTICAL METHODS

Analysis Groups

Two analysis sets were defined. The modified intention-to-treat analysis set (ITT) consisted of all randomised subjects exposed to at least one dose of trial product. The per-protocol analysis set (PP) consisted of all exposed subjects who completed the trial and who: did not significantly violate the inclusion or exclusion criteria, did not violate other aspects of the protocol considered to potentially affect the efficacy results.

STATISTICAL METHODS (CONTINUED)

Efficacy Endpoints

The primary efficacy endpoint was HbA_{1c} after 20 weeks of treatment.

The secondary efficacy endpoints were:

- Body weight change after 20 weeks.
- Proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ after 20 weeks.
- Proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ after 20 weeks without symptomatic hypoglycaemia with PG value <4.0 mmol/L (<72 mg/dL) or any single PG value <3.1 mmol/L (<56 mg/dL) in the last 4 weeks of treatment.
- FPG (central laboratory analysis) after 12 and 20 weeks.
- Within-subject variation of SMPG before breakfast and dinner at baseline and after 8 and 20 weeks.
- 9-point SMPG profiles after 8 and 20 weeks.
- Insulin dose.
- Level of C-peptide and serum insulin.

Efficacy Analysis

To answer the primary objective, the non-inferiority hypothesis comparing insulin detemir evening and NPH insulin was performed first. If the test of the first hypothesis gave evidence that detemir evening was non-inferior to NPH insulin, the second hypothesis of non-inferiority between insulin detemir morning and NPH insulin was tested. The hypotheses for the non-inferiority tests used the clinical acceptable non-inferiority difference in HbA_{1c} of 0.4%. Non-inferiority for insulin detemir evening was claimed if the upper limit of the 95% confidence interval (CI) was less than 0.4%. If non-inferiority for insulin detemir evening was obtained, non-inferiority for insulin detemir morning could also be claimed using the same criteria. If both insulin detemir groups were shown to be non-inferior to the NPH insulin group with regards to HbA_{1c}, clinical equivalence between the two insulin detemir groups was tested. Unless otherwise specified, all analyses were performed at a 5% significance level.

Primary Efficacy Endpoint

For the two comparisons between insulin detemir morning or insulin detemir evening with NPH insulin evening, the analysis of the primary efficacy endpoint, HbA_{1c} after 20 weeks used the analysis of variance (ANOVA) model with treatment, OAD treatment and country as fixed effects and the corresponding baseline value as a covariate. OAD treatment was defined as OAD monotherapy or OAD combination therapy.

Secondary Efficacy Endpoints

- *Body weight and FPG*
  Body weight change after 20 weeks and FPG at week 12 and week 20 were analysed as for the primary efficacy endpoint, i.e., using the ANOVA model with treatment, OAD treatment and country as fixed effects and the corresponding baseline values as covariate.
- *Subjects achieving $HbA_{1c} \leq 7.0\%$ with/without hypoglycaemia*
  The proportion of subjects reaching $HbA_{1c} \leq 7\%$ after 20 weeks without symptomatic hypoglycaemia with PG value <4.0 mmol/L (<72 mg/dL) or any single PG value <3.1 mmol/L (<56 mg/dL) in the last 4 weeks of treatment was compared between treatment groups using Fisher's Exact Test. A treatment comparison for subjects reaching $HbA_{1c} \leq 7\%$ was also made using Fisher's Exact Test.
- *Within-subject variation of self-measured pre-breakfast and pre-dinner PG*
  Within-subject variability in pre-breakfast PG or pre-dinner values was estimated as follows: 3 measurements recorded 3 consecutive days before week 8 (Visit 4) and week 20 (Visit 6) and pre-breakfast or pre-dinner measurement from the 9-point PG profile recorded the week before week 8 (Visit 4) and week 20 (Visit 6). The estimates for within-subject variability was obtained using the ANOVA model with treatment, country, day, day by treatment, OAD treatment as fixed effects and subject as a random effect. Day and day by treatment effects referred to the 4 days where FPG was measured and its interaction with treatment. Subject was a random effect with a variance depending on treatment.

STATISTICAL METHODS (CONTINUED)

- *9-point SMPG profile after 8 and 20 weeks*
  The 9-point SMPG profile was tested for parallelism using a repeated measurements model with treatment, country, OAD treatment, time and treatment by time as fixed effects. Time and treatment by time effects referred to the PG measurements and interaction with treatment at the time-points: before 3 main meals, 90 minutes after main meals, bedtime, 3 am and before breakfast the following day.

Additional Analyses of Efficacy Endpoints

- Both insulin detemir groups were shown to be non-inferior to NPH insulin group with regards to HbA_{1c}. Hence, equivalence of the two insulin detemir groups was tested. The clinically acceptable equivalence margin in HbA_{1c} for which treatment with insulin detemir in the morning and insulin detemir in the evening was considered equal was 0.4%. Equivalence was claimed if the upper limit of the 95% CI for the difference was less than 0.4% and the lower limit of the 95% CI for the difference was greater than -0.4%.
- The analysis of the endpoint HbA_{1c} after 20 weeks of treatment was performed by an ANOVA model with treatment, OAD treatment and country as fixed effects and the corresponding baseline values (Visit 2) as a covariate.

Exploratory Analysis

Exploratory analysis was performed on change in body weight and included change in HbA_{1c} and treatment by change in HbA_{1c} interaction in the model. The proportion of subjects reaching $HbA_{1c} \leq 7\%$ after 20 weeks without symptomatic hypoglycaemia with PG value <4.0 mmol/L (<72 mg/dL) or any single PG value <3.1 mmol/L (<56 mg/dL) in the last 3 months of treatment was compared between treatment groups using Fisher's Exact Test.

Safety Endpoints

The safety endpoints were:

- Incidence of hypoglycaemic episodes (all, major, minor and symptoms only) during the trial; nocturnal (11 pm [inclusive]–6 am [exclusive]) and over the entire day (24h).
- Incidence of adverse events during the trial.
- Laboratory assessments on haematology, biochemistry and lipids, fundoscopy/fundusphotography and vital signs after 20 weeks of treatment.

Safety Analysis

- Safety analysis was performed on the ITT analysis set except for the safety analysis on hypoglycaemia, which was also performed on the PP analysis set.
- Descriptive statistics were used to analyse treatment emergent adverse events (TEAE), treatment emergent serious adverse events, fundoscopy, vital signs, laboratory assessment on haematology, biochemistry and lipids.
- Hypoglycaemic episodes were analysed according to the categories: all, major, minor and symptoms only over the entire day as well as for nocturnal episodes. The incidence of hypoglycaemic episodes was evaluated by modelling reported episodes and deriving the relative risk of having a hypoglycaemic episode in the insulin detemir morning group compared to the NPH insulin group and insulin detemir evening group with the NPH insulin group. On an informal basis, the ratio of these two relative risks was obtained yielding the third relative risk between the two insulin detemir groups. Hypoglycaemic episodes was analysed as recurrent events using a gamma frailty model. The Cox regression model with treatment and OAD treatment as covariate extended with a random effect (following a gamma distribution), acts multiplicatively on the baseline hazard function describing the excess risk (or frailty) for a subject.
- Exploratory analysis was carried out on a separate frailty model fitted with treatment and HbA_{1c} as covariates. HbA_{1c} measurements at end of trial were used for hypoglycaemic episodes. The analysis was performed for four categories of hypoglycaemia: all, major, minor and symptoms only.

DEMOGRAPHY OF TRIAL POPULATION

Subject characteristics at screening is summarised in **Table 1**. Subject characteristics were comparable in all treatment groups. The majority (~92%) of subjects were white. Slightly more than half (~57%) of the subjects were male. Subjects in all treatment groups were comparable in mean age (~58 yrs), BMI (~30 kg/m^2), duration of diabetes (~10 yrs) and HbA_{1c} (~9%). HbA_{1c} and body weight was slightly higher in the NPH insulin evening group.

Other Characteristics at Screening or Baseline

- In all treatment groups, comparable results on subjects' vital signs, safety laboratory parameters (biochemistry,

haematology and lipids) were observed.

- Also, the majority (~93%) of subjects in all treatment groups had normal outcomes for physical examination of the various body systems.
- With regards to prior diabetes treatment, combination therapy (~76%) was the most common type of treatment in all groups. Of the remaining ~24% who were treated with monotherapy, slightly more subjects indicated that they had been receiving OHA monotherapy other than metformin (~15%) while ~9% had been receiving metformin monotherapy.
- The incidence of diabetic complications ranged from 8.3–17.6%. All treatment groups had comparable incidence of retinopathy (~15%) and neuropathy (~15%). The incidence of nephropathy was 8.3% in the insulin detemir evening group, 11.5% in the insulin detemir morning group and 10.4% in the NPH insulin group. The incidence of macroangiopathy was 17.6% in the insulin detemir morning group, 12.4% in the insulin detemir evening group and 12.8% in the NPH insulin evening group.

Table 1. Subject Characteristics, ITT

	Detemir Morning	Detemir Evening	NPH Evening
ITT analysis set (N)	165 (100)	169 (100)	164 (100)
Sex (N (%))			
Female	67 (40.6)	78 (46.2)	70 (42.7)
Male	98 (59.4)	91 (53.8)	94 (57.3)
Ethnic Origin (N (%))			
AMERICAN INDIAN - ALASKA NATIVE	2 (1.2)	7 (4.1)	10 (6.1)
ASIAN	2 (1.2)	0 (0.0)	2 (1.2)
BLACK OR AFRICAN AMERICAN	0 (0.0)	5 (3.0)	5 (3.0)
OTHER	0 (0.0)	2 (1.2)	3 (1.8)
WHITE	161 (97.6)	155 (91.7)	144 (87.8)
Age (years)			
Mean (SD)	58.3 (10.4)	58.7 (10.2)	58.4 (11.0)
Min - Max	29 - 84	34 - 89	32 - 84
Weight (kg)			
N	164	169	164
Mean (SD)	83.1 (17.6)	83.5 (19.3)	85.3 (17.8)
BMI (kg/m^2)			
Mean (SD)	29.8 (5.0)	29.7 (5.1)	30.4 (4.8)
Min - Max	19.6 - 40.4	15.9 - 40.0	20.6 - 40.3
Duration of diabetes (years)			
Mean (SD)	10.5 (7.6)	10.5 (7.0)	10.0 (6.9)
Min - Max	1.2 - 46.9	1.1 - 37.3	1.2 - 37.3
HbA1c (%)			
Mean (SD)	9.08 (0.97)	8.88 (0.95)	9.15 (1.00)
Min - Max	7.30 - 11.80	7.30 - 11.20	7.20 - 11.30
Other Characteristics			
C-peptide nmol/L			
N	163	163	157
Mean (SD)	0.9 (0.5)	0.9 (0.5)	1.0 (0.6)
Median	0.9	0.9	1.0
Min - Max	0.01 - 2.58	0.08 - 2.43	0.02 - 2.98
Serum Insulin uIU/mL			
N	162	164	159
Mean (SD)	12.9 (9.0)	12.4 (9.4)	14.0 (10.9)
Median	10.7	10.0	10.9
Min - Max	0.60 - 56.00	2.10 - 57.50	1.60 - 58.10

Baseline body weight and baseline HbA1c are taken from visit 2. If visit 2 data are not available then the visit 1 value is used, respectively.

EFFICACY RESULTS

Primary endpoint:

- Treatment with insulin determir evening was non-inferior to NPH insulin evening as measured by the primary endpoint, HbA_{1c} after 20 weeks. Mean difference (insulin detemir evening – NPH insulin evening) = 0.104% (95% C.I.: -0.081–0.289). Similar result was observed for the PP analysis.
    - HbA_{1c} after 20 weeks of treatment was estimated to 7.43% with insulin detemir evening and 7.33% with NPH insulin evening.
- Treatment with insulin determir morning was non-inferior to NPH insulin evening as measured by the primary endpoint, HbA_{1c} after 20 weeks. Mean difference (insulin detemir morning – NPH insulin evening) = 0.127% (95% C.I.: -0.071–0.324). Similar result was observed for the PP analysis.
    - HbA_{1c} after 20 weeks of treatment was estimated to 7.48% with insulin detemir morning and 7.36% with NPH insulin evening.

Secondary endpoints:

- The proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ after 20 weeks of treatment was comparable between insulin detemir morning treatment and NPH insulin evening treatment (p=0.343), and between insulin detemir evening treatment and NPH insulin evening treatment (p=0.351).
- The proportion of subjects achieving an $HbA_{1c} \leq 7.0\%$ after 20 weeks of treatment without symptomatic hypoglycaemia, with a plasma glucose value < 4.0 mmol/L (< 72 mg/dL) or any single plasma glucose value < 3.1 mmol/L (< 56 mg/dL), during the last four weeks of treatment, was comparable between insulin detemir morning treatment and NPH insulin evening treatment (p=0.365), and between insulin detemir evening treatment and NPH insulin evening treatment (p=1.000).
- The estimated mean FPG of NPH insulin evening treated subjects was significantly lower than insulin detemir morning treated subjects (7.44 versus 8.32 mmol/L, p=0.003), but comparable with insulin detemir evening treated subjects (7.50 versus 7.04 mmol/L, p=0.124), after 20 weeks of treatment.
    - Similar trends were observed after 12 weeks of treatment: the estimated mean FPG of NPH insulin evening treated subjects was significantly lower than insulin detemir morning treated subjects (7.28 versus 8.77 mmol/L, p<0.0001), but comparable with insulin detemir evening treated subjects (7.26 versus 7.06 mmol/L, p=0.465).
- The within-subject variation in pre-breakfast PG was comparable between insulin detemir morning treatment versus NPH insulin evening treatment (SD=1.23 versus 1.25 mmol/L, p=0.631) as well as between insulin detemir evening treatment and NPH insulin evening treatment (SD=1.28 versus 1.26 mmol/L, p=0.735), after 20 weeks of treatment.
- The within-subject variation in pre-dinner PG was comparable between insulin detemir morning treatment versus NPH insulin evening treatment (SD=1.91 versus 2.00 mmol/L, p=0.378), as well as between insulin detemir evening treatment versus NPH insulin evening treatment (SD=1.84 versus 1.98 mmol/L, p=0.125), after 20 weeks of treatment.
- The overall shape of the plasma glucose profile of the NPH insulin evening group was significantly different from that of the insulin detemir morning group (p<0.001), but comparable with that of the insulin detemir evening group (p=0.717), after 20 weeks of treatment.
    - The mean glucose levels in the insulin determir morning group were lower before dinner and higher before-breakfast, 90-minutes-after-breakfast, and the following day before breakfast, as compared to the NPH insulin evening group.
    - The mean glucose levels in the insulin determir evening group were comparable to the NPH insulin evening group for all time-points.
- The estimated mean increase in body weight after 20 weeks of treatment was significantly lower with insulin detemir evening treatment than with NPH insulin evening treatment (estimated mean change: 0.69 versus 1.60 kg, p=0.005), but comparable between insulin detemir morning treatment and NPH insulin evening treatment (estimated mean change: 1.14 versus 1.50 kg, p=0.273).

EFFICACY RESULTS (CONTINUED)

- The median daily basal insulin dose was highest in the insulin detemir morning group, followed by the insulin detemir evening group and the NPH insulin evening group.
- There did not appear to be any association between endogenous insulin production (serum insulin and C-peptide) with insulin requirement.

SAFETY RESULTS

- The incidence of adverse events was comparable between NPH insulin (50.0%) and both insulin detemir regimens (42.4% in morning and 39.6% in evening dose). In all treatment groups, most of the incidence was assessed as unlikely related to trial product and mild in severity. Mild nasopharyngitis was commonly reported in ~6% subjects in all treatment groups. Mild headache was more frequently reported in insulin detemir evening (5.9%) and NPH insulin evening (5.5%) than in insulin detemir morning (1.8%).
    - The incidence of potentially allergic adverse events was slightly higher in the insulin detemir groups than with NPH insulin whereas the incidence of application site disorders was slightly higher with the insulin detemir evening regimen. No more than 3 subjects experienced these adverse events with the same preferred term. Hypersensitivity was only reported in insulin detemir morning. There were no reports of lipodystrophy in this trial.
    - A total of 22 subjects reported 22 serious adverse events; 8, 5 and 9 subjects in the insulin detemir morning and evening regimens and NPH insulin, respectively. All 22 events were assessed as unlikely related to trial product. Two subjects died of cerebrovascular accident, one each in insulin detemir evening and NPH insulin evening. The incidence related to cardiac disorders was more common in both insulin detemir morning (2.4%) and NPH insulin evening (1.8%) than insulin detemir evening (0.6%).
    - 12 subjects reporting 15 adverse events were withdrawn with similar withdrawal rates in all treatment groups: 4 subjects in each group. Ten of the AE withdrawals were serious in nature, four events each in insulin detemir morning and NPH insulin evening, and two events in insulin detemir evening; one of which was fatal (cerebrovascular accident in NPH insulin evening), and all these events were assessed as unlikely related to trial products. Four events were possibly related to insulin detemir evening: moderate rash, injection site swelling and fatigue, and mild memory impairment.
- The incidence of hypoglycaemia was higher for NPH insulin compared to the two insulin detemir regimens. Only two major hypoglycaemic episodes were reported, both in the insulin detemir evening group.
    - There was no significant difference between insulin detemir and NPH insulin with regard to the risk of overall hypoglycaemia or symptoms only hypoglycaemia.
    - The risk of minor hypoglycaemic episodes was 53% lower for insulin detemir evening than NPH insulin evening ($p=0.019$).
- The incidence of nocturnal hypoglycaemia was higher for NPH insulin compared to both insulin detemir regimens. There were no reports of major nocturnal episodes in any treatment groups.
    - The risk of nocturnal hypoglycaemia was 73% and 59% lower for insulin detemir morning than for NPH insulin evening ($p<0.001$) or insulin detemir evening ($p=0.016$).
    - The risk of minor nocturnal episodes was 87% lower for insulin detemir morning ($p<0.001$) and 65% lower for insulin detemir evening ($p=0.031$) when compared to NPH insulin evening.
    - The risk of symptoms only nocturnal episodes was 61% and 57% lower for insulin detemir morning than for NPH insulin evening ($p=0.031$) or insulin detemir evening ($p=0.048$).
- No clinically relevant changes were observed with regards to vital signs, clinical laboratory parameters of biochemistry, haematology, lipids or fundoscopy/fundusphotography results.

CONCLUSIONS

After 20 weeks of once-daily treatment with insulin detemir morning or insulin detemir evening or NPH insulin evening as an add-on to current OAD treatment in subjects with type 2 diabetes:

- Glycaemic control with insulin detemir was as effective as NPH insulin, as measured by HbA_{1c}.
- Consistent with the reductions in HbA_{1c} observed in all 3 treatment groups, reductions in FPG were also observed in all 3 treatment groups, with both evening insulin regimens providing a statically significantly lower mean FPG level at the end of treatment compared to the morning regimen.
- Variability in within-subject variation in pre-breakfast or pre-dinner plasma glucose values was comparable between insulin detemir and NPH insulin..
- Weight gain was significantly less in the insulin detemir evening group than in the NPH insulin evening group but comparable between insulin detemir morning and NPH evening group.
- The risk of all hypoglycaemia was similar in the 3 treatment groups but treatment with insulin detemir morning was associated with a reduced risk of nocturnal hypoglycaemia compared to NPH insulin evening.
- The overall safety profile of insulin detemir was similar to that of NPH insulin.
- This trial has demonstrated that the timing of insulin detemir can be flexible, and given in the morning or evening.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.