Integrated Clinical Trial Report

Trial ID: NN304-1659

A multi-centre, open-labelled, randomized, two-group parallel, treat-to-target trial comparing the weight change in overweight and obese subjects with type 2 diabetes after 26 weeks of treatment with insulin detemir once daily versus insulin NPH once daily, both with insulin aspart in the mealtime.

(PREDICTIVE-BMI study)

A Phase 3b Trial

Author:
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Title of Trial	A multi-centre, open-labelled, randomized, two-group parallel, treat-to-target trial comparing the weight change in overweight and obese subjects with type 2 diabetes after 26 weeks of treatment with insulin detemir once daily versus insulin NPH once daily, both with insulin aspart in the mealtime. (PREDICTIVE-BMI study)
Trial ID	NN304-1659
Development Phase	Phase 3 b
IND Number (US only)	Not applicable
Compound Name	Insulin detemir
Indication	Diabetes mellitus
Investigator(s)	44 principal Investigators in Spain. Coordinating Investigator: Dr. [redacted]
Trial Site(s)	44 centres in Spain (41 Active sites that enrolled patients and 3 inactive sites)
Trial Initiated	27-09-2005
Trial Completed	21-12-2006
Sponsor	Novo Nordisk Pharma S.A. (Spain) C/ Caleruega 102 28033 Madrid
International Medical Officer	[redacted]. Novo Nordisk SA.
International Trial Manager	N/A
Local Trial Manager(s)	[redacted]/[redacted]. Novo Nordisk Pharma S.A. (Spain)
Statistician	[redacted] (C.R.O. [redacted])
Medical Writer	[redacted], MD. (C.R.O. [redacted])
Report Date(s)	08 October 2007

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

Synopsis

TITLE OF TRIAL

A multi-centre, open-labelled, randomized, two-group parallel, treat-to-target trial comparing the weight change in overweight and obese subjects with type 2 diabetes after 26 weeks of treatment with insulin detemir once daily versus insulin NPH once daily, both with insulin aspart in the mealtime. (PREDICTIVE-BMI study)

INVESTIGATOR(S)

44 principal Investigators in Spain. Coordinating Investigator: Dr. [redacted]

TRIAL SITE(S)

44 centres in Spain (41 Active sites that enrolled patients and 3 inactive sites).

PUBLICATIONS

Not applicable

TRIAL PERIOD:	**DEVELOPMENT PHASE:**
27 September 2005 to 21 December 2006	Phase 3b

OBJECTIVES

Primary objective

To compare weight change during 26 weeks of treatment with insulin detemir versus NPH insulin, in obese or overweight type 2 diabetic subjects.

Secondary objectives

To compare both insulin regimens (detemir versus NPH), according to the following variables:

• *Efficacy*:

o HbA1c at the start and after 12 and 26 weeks of treatment.
o Fasting plasma glucose at the start and after 12 and 26 weeks of treatment.
o 7-point glucose profiles during the 26 weeks of treatment
o Intra-variability of detemir and NPH insulin during 26 weeks of treatment
o Proportion of subjects reaching glycaemic control (HbA1c ≤ 7.0%) at the end of the trial
o Proportion of subjects reaching pre and postprandial targets according to titration guidelines at the end of the trial.
o Relationship between BMI and required daily dose of insulin detemir

• *Safety*:

o Incidence of hypoglycaemia in the 26 weeks of treatment
o Lipid profile at the start and after 26 weeks of treatment
o Incidence of Adverse events during the trial
o Safety profile as measured by laboratory safety parameters (haematology, biochemistry, glycosuria) and physical examination/vital signs before and at the end of treatment
o Insulin resistance measured by the HOMA-IR at the start and at the end of the trial.

METHODOLOGY

This trial was a phase 3b, multi-centre, open-labelled, randomized, two-group parallel, treat-to-target clinical trial comparing insulin detemir and NPH in intensive insulin regimens in subjects with type 2 diabetes who were obese or overweight.

Subjects requiring bolus-basal insulin therapy and who fulfilled the inclusion criteria were recruited in this study and randomized to receive either:

• Insulin detemir once daily plus multiple prandial insulin analogue injections with insulin aspart during 26 weeks
or
• NPH insulin administered once daily plus multiple prandial insulin analogue injections with insulin aspart during 26 weeks.

NUMBER OF SUBJECTS PLANNED AND ANALYZED

Planned number of subjects to be screened was 313 and planned number of subjects to be randomized was 272. Finally 345 patients were screened and 277 randomized. The subject disposition is shown in the following table:

	Detemir N (%)	NPH N (%)	All N (%)
Screened			345
Randomized	126(45.5)	151(54.5)	277(100)
Withdrawals	7 (5.6)	12(7.9)	19(6.9)
Adverse Event	1 (0.8)	2(1.3)	3(1.1)
Ineffective therapy	0 (0.0)	2(1.3)	2(0.7)
Non-compliance with protocol	3 (2.4)	3(2.0)	6(2.2)
Other	3(2.4)	5(3.3)	8(2.9)
Completers	119(94.4)	139(92.1)	258(93.1)
ITT analysis set (Exposed)	125(99.2)	146(96.7)	271(97.8)
PP analysis set	115(91.3)	136(90.1)	251(90.6)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male or female subjects with type 2 diabetes, age ≥ 18 years, who have been treated with 2 doses of insulin (one of them must be a premix) for at least 3 months prior to inclusion with a BMI ≥25 kg/m2 and ≤40 kg/m2 and a HbA1c ≥7.5% and ≤11.0% at screening, based on analysis from central laboratory. All of them gave their informed consent before any trial-related activity was performed. Subjects were excluded from the trial if they were treated with any OAD (Oral Antidiabetic Drug) in the last six months (excepting metformin), had proliferative retinopathy or maculopathy that had required acute treatment within six months prior to study start, uncontrolled hypertension (treated or untreated) as judged by the investigator, known or suspected allergy to trial product(s) or related products, total daily insulin dose ≥ 2 IU/kg, any disease or condition (such as renal, hepatic or cardiac) that according to the judgment of the investigator made the subject unsuitable for participation in the trial, anticipated change in concomitant medication known to interfere with glucose metabolism (systemic steroids, non-selective beta-blockers or mono amine oxidase (MAO) inhibitors), pregnant, breast-feeding or the intention of becoming pregnant or not using adequate contraceptive measures, mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation, any condition the Investigator felt would interfere with trial participation or evaluation of the results and receipt of any investigational drug within 1 month prior to this trial.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Insulin detemir FlexPen® 100 U/ml solution for subcutaneous injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S. Insulin aspart was supplied as mealtime insulin in FlexPen® 100 U/ml solution for subcutaneous injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S. Dose was individualized and titrated during the trial according to a protocol titration guideline (Appendix C of the protocol) to get some preset glycaemic targets.
Batch number (insulin Detemir): RP50873; Batch number (Insulin Aspart): RP50736

DURATION OF TREATMENT: 26 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Isophane (NPH) Insulin FlexPen® 100 IU/ml suspension for subcutaneous injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S. Insulin aspart was supplied as mealtime insulin in FlexPen® 100 U/ml solution for subcutaneous injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S. Dose was individualized and titrated during the trial according to a protocol titration guideline (Appendix C of the protocol) to get some preset glycaemic targets.
Batch number (insulin NPH): RP50931; Batch number (Insulin Aspart): RP50736

CRITERIA FOR EVALUATION – EFFICACY

Weight change; HbA1c; Fasting Plasma Glucose; 7- Point Plasma Glucose Profiles; Self Monitoring Fasting Plasma Glucose (SMFPG) for intra-subject variation; Percentage of subjects that achieved pre and postprandial targets according to titration and percentage that achieved the target of HbA1c ≤ 7%; relationship between BMI and daily dose of detemir; Treatment satisfaction and quality of life (objective not initially included in protocol). Comparison of insulin doses (not initially planned).

CRITERIA FOR EVALUATION – SAFETY

Incidence of Adverse Events; hypoglycaemic episodes (minor, major or symptoms only); change in laboratory assessments (haematology, biochemistry and lipids); physical examination; vital signs.

STATISTICAL METHODS

EFFICACY: The aim of the analysis of the **primary endpoint** was to test whether the mean weight of the subjects between both treatments was statistically different from each other. The hypothesis was tested by fitting one-way analysis of covariance model (ANCOVA) to the primary endpoint with treatment as fixed effect and weight at baseline as a covariate. Differences in weight changes could be attributable not only to differences among the treatments but also to the initial differences in baseline weight. To control this source of variation, the effect of the baseline weight was removed from the weight change by using the regression method. Then the F test could be performed on the adjusted weight changes. This analysis was performed on the ITT and PP population. Other efficacy objectives: **HbA1c**: Mean HbA1c after 26 weeks of treatment was compared between the groups by fitting an ANCOVA, similar to that used for the primary efficacy endpoint, with treatment as fixed factor and baseline HbA1c as covariate. In case of missing data, LOCF (last observation carried forward) was used. **Fasting Plasma Glucose**: The secondary endpoint, FPG, was analyzed at Visit 7, using an ANCOVA model with treatment as fixed effect and the corresponding baseline values as a covariate. A 95% two-sided confidence interval was constructed for the difference between the means from the two treatment groups in comparison in these analyses. **Within-Subject Variation of Self-Measured Fasting Plasma Glucose**: The within-subject variation was measured as the CV (%) of the last six fasting plasma glucose measures performed by the subjects 4 weeks prior to Visits 2, 5 and 7. The within-subject variation of values was compared between the two treatment groups using variance-component models. **7-Point Plasma Glucose Profiles (mg/dL)** The 7-point SMPG profiles were compared after 26 weeks of treatment. The repeated measures ANOVA with treatment, time and treatment-by-time as fixed effects were used to compare the group means on PG (dependent variable) across repeated measurements of time. **Proportions of subjects that achieved HbA1c ≤ 7.0% and pre and postprandial targets according to titration** after 26 weeks of treatment were compared between the two groups using Fisher's exact test. **Relationship between BMI and required daily dose of insulin Detemir**: The analysis of association between BMI and daily dose of detemir was based upon a Spearman rank-order correlation by lack of normality. **Treatment Satisfaction**: Though not included as a protocol objective, it was finally analyzed. The change in SF-36 and DTSQ scores to week 26 was analyzed by fitting an ANCOVA model with treatment as fixed factor and the baseline score as a covariate. **Insulin doses** at the end of trial were compared between groups although this was not an objective of the trial.

***SAFETY*: Hypoglycemic Episodes:** The incidence of hypoglycemia was compared between the groups after 26 weeks of treatment by estimating the relative risk of having an hypoglycemic episode in the insulin Detemir group compared to the insulin NHP group. Three categories of hypoglycemic episodes were analyzed separately for 24h episodes and nocturnal episodes: all episodes; major episodes; minor episodes. The treatment emergent hypoglycemic episodes were analyzed as recurrent events using a semiparametric proportional means model. Also the relative risk based on time to the first episodes was estimated using an ordinary Cox regression model. Only a limited number of major hypoglycemic episodes occurred during the treatment period. Therefore no statistical analysis was performed on this endpoint.

Lipid profile was analyzed at Visit 7, using an ANCOVA model with treatment as fixed effect and the corresponding baseline values as a covariate. A 95% two-sided confidence interval was constructed for the difference between the means from the two treatment groups in comparison.

Adverse Events AEs and SAEs emerging during the treatment period were summarized and presented. The incidence of AEs was compared between the groups by means of descriptive statistics. No formal statistical analysis was performed.

Laboratory Safety The laboratory safety parameters were compared between the groups by means of descriptive statistics.

Vital Signs, Funduscopy or Fundusphotography. Descriptive statistics by Visit were presented for vital signs and funduscopy/fundusphotography. Subjects with only baseline data recorded were excluded from the summary statistics and the graphics aiming to illustrate change over time. No formal comparison was performed.

DEMOGRAPHY OF TRIAL POPULATION

Baseline characteristics of trial population were rather similar in both groups and are shown below:

	Detemir	NPH	All
ITT analysis set (N)	125 (100.0)	146 (100.0)	271 (100.0)
Sex (N (%))			
Male	47 (37.6)	63 (43.2)	110 (40.6)
Female	78 (62.4)	83 (56.8)	161 (59.4)
Age (years)			
Mean (SD)	62.06(9.25)	61.79 (8.26)	61.92(8.72)
Weight (kg)			
Mean (SD)	79.45 (11.9)	82.23(12.2)	80.94 (12.1)
Height (m)			
Mean (SD)	1.59 (0.09)	1.60 (0.08)	1.59 (0.08)
BMI (kg/m^2)			
Mean (SD)	31.61(4.25)	32.02(4.17)	31.83(4.20)
Duration of diabetes (years)			
Mean (SD)	16.18(8.69)	16.40(7.43)	16.30(8.02)
FPG (g/L)			
Mean (SD)	1.94(0.63)	1.82(0.65)	1.87(0.64)
HbA1c (%)			
Mean (SD)	8.85(0.87)	8.78(0.96)	8.81(0.92)

At baseline 49.6% of patients of the detemir group were treated only with insulin and 50.4% with insulin and metformin. Corresponding figures for the NPH group were 42.5% and 57.5% respectively.

EFFICACY RESULTS: Results are given for ITT population (excepting for the primary objective where results were also analyzed for PP population). SE: standard error.

1. Primary objective: Weight change after 12 and 26 weeks of treatment: For ITT population, after 12 weeks of treatment, mean weight change from baseline was –0.02 Kg (SE 0.22) in detemir group vs. 1.09 (0.20) in the NPH group (p= 0.0003). After 26 weeks of treatment corresponding figures were 0.42 (0.28) vs. 1.94 (0.26) in the NPH group (p= 0.0001). Results for PP population were: -0.07 (0.23) in detemir group vs. 1.13 (0.21) in NPH group (p= 0.0002) after 12 weeks of treatment and 0.35 Kg (0.30) vs. 1.99 (0.28) in NPH group (p= 0.0001) after 26 weeks.
Change in BMI after 26 weeks of treatment was also significantly lower in the detemir group: 0.16 Kg/m^2 (0.11) vs. 0.77 (0.10) in the NPG group (p<0.0001).
2. HbA1c: after 12 weeks of treatment mean HbA1c in detemir group was 8.0% (0.08) vs. 7.9% (0.07) in NPH group (p = 0.4476). After 26 weeks of treatment corresponding figures were 7.8% (0.09) vs. 7.8 (0.08), p = 0.8562.
3. Fasting Plasma Glucose (FPG): after 12 weeks of treatment mean FPG was 150.5 mg/dl (SE 5.1) in detemir group vs. 154.6 mg/dl (4.7) in NPH group (p= 0.5597); corresponding figures after 26 weeks of treatment were 156.8 (4.6) vs. 161.6 (4.3) mg/dl, p= 0.4488.
4. 7- Point Plasma Glucose Profiles: the following table shows the results for 7-point plasma glucose profiles after 26 weeks of treatment: No significant differences were found between treatment groups (p=0.2527).

	Detemir Mean (SE)	NPH Mean (SE)	Detemir - NPH Mean 95%CI	p-value
Determir vs NPH	162.46(3.28)	157.30(3.07)	5.16 (-3.701 , 14.012)	0.2527*
Time-point				<0.0001**
Before Breakfast	135.23(3.71)	138.63(3.48)	-3.97(-13.417 , 6.623)	
90 Min. after Breakfast	163.45(5.44)	170.37(5.08)	-6.92(-21.585 , 7.743)	
Before Lunch	138.39(4.68)	140.80(4.38)	-2.41(-15.033 ,10.208)	
90 Min. after Lunch	167.43(5.27)	160.04(4.95)	7.39(-6.848 ,21.624)	
Before Dinner	178.54(5.34)	161.06(5.00)	17.48(3.070 ,31.895)	
90 Min. after Dinner	195.22(6.11)	182.51(5.66)	12.71(-3.696 ,29.112)	
At 3:0 A.M.	158.93(5.06)	147.69(4.81)	11.24(-2.514 ,24.993)	
Treatment*time-point				0.0737***
Test for Reduction of Variance Structure				<0.0001****

The analysis was a two-way repeated measures ANOVA on SMPG after 26 weeks of treatment with treatment (between-subject factor), time (within-subject factor) and treatment-by-time interaction as fixed effects.
*p-value of between-subject main effect (difference in treatment);
**p-value of within-subject main effect (difference over time);
***p-value of time by treatment group interaction effect

****p-value for null model likelihood ratio, indicating that the unstructured covariance matrix is preferred to the diagonal one of the ordinary least-squares null model.

5. Intra-subject variation for self monitoring fasting plasma glucose (SMFPG): Mean SMFPG was 142.7 mg/dl

± 47.6 with a CV 33.3% in the detemir group vs. 146.5 ± 50.5 mg/dl with a CV 34.5% in the NPH group; p < 0.0001 (p-value: Likelihood ratio test for the model with a common residual variance component for each treatment group, against the alternative model with varying residual variance components). Thus, there was a lower within-subject variability of self measured FPG in the detemir group.

6. Subjects that achieved HbA1c <= 7.0 % after 26 Weeks of Treatment (without having any symptomatic hypoglycaemia with a plasma glucose value < 4.0 mmol/L or any single plasma glucose value < 3.1 mmol/L in the last four weeks of treatment): similar results were obtained in both treatment arms. 27 subjects (21.8%) in detemir group vs. 27 (18.5%) in NPH group; p= 0.5018.

7. Subjects that achieved Pre and Postprandial Targets (as defined per protocol) after 26 Weeks of Treatment: 16 subjects (12.9 %) in detemir group vs. 15 (10.3%) in NPH group; p=0.5681.

8. Relationship between BMI (kg/m2) and Daily Detemir Dose after 26 Weeks of Treatment: The Spearman's rank correlation coefficient that described the relationship between these two variables was 0.43801 (p < 0.0001), denoting a statistically significant relationship between BMI and daily detemir dose at the end of the trial.

9. Quality of life and treatment satisfaction:

There was no statistically significant difference in the change of quality of life from baseline measured by the SF 36 scale after 26 weeks of treatment (Mean 3.29 (SE 1.64) for physical health in the detemir group and 0.45 (1.51) for the NPH group; p=0.2048. Corresponding figures for Mental health were 2.05 (1.63) in detemir group vs. –2.14 (1.53) in NPH group; p=0.0627). Overall treatment satisfaction was better in the detemir group with a mean difference (Detemir-NPH) in the score change from baseline of 1.98 [0.33;3.63] CI 95%; p=0.0190. There were no significant differences between groups in perceived frequency of hypo or hyperglycaemia.

10. Insulin doses: Though mean starting dose of both basal insulins was very similar (insulin NPH 22.8 ± 7.8 IU (0.3 ± 0.1 IU/kg) vs. 23.6 ± 8.6 U (0.3 ± 0.1 U/kg) for insulin detemir) at the end of the trial, dose of insulin detemir (47.5 ± 21.3 U or 0.6 ± 0.2 U/kg) was significantly higher (p=0.0026) than dose of NPH insulin (39.3 ± 16 IU or 0.5 ± 0.2 IU/kg).

SAFETY RESULTS

1. Statistical Analysis of Treatment Emergent Hypoglycaemic Episodes:

	HR	(95% CI)	p-value
Major	NA	(NA; NA)	NA
Minor	1.66	(1.42; 1.95)	< 0.0001
Other	0.62	(0.25; 1.56)	0.3126
All	1.61	(1.37; 1.88)	<0.0001

NA: not applicable. HR (Hazard Ratio): Ratio of incidence rates (NPH/Detemir); p-value: test for homogeneity of risk ratios among treatment groups. The probability of having an hypoglycemic episode during the treatment period was significantly higher in the NPH group (HR 1.61 [1.37;1.88] 95% CI) Due to the low incidence of major episodes in both treatment arms no formal analyses were performed for this subgroup.

2.Incidence of hypoglycemic episodes during the treatment:

There were a total of 737 episodes: Detemir (256, 34.74%), NPH (481, 65.26%) Odds ratio: 0.45 [0.31, 0.65]. Incidence of hypoglycemic episodes was significantly higher in NPH group.

3.Treatment Emergent Nocturnal Hypoglycaemic Episodes:

Hazard ratio (ratio of incidence rates NPH/Detemir) was 2.41 [1.68; 3.47], p < 0.0001 for minor hypoglycemic episodes and 2.34 [1.64; 3.33], p <0.0001 for all hypoglycemic episodes. There was only one major nocturnal hypoglycemic episode (subject in the NPH group). Thus, the probability of having a nocturnal hypoglycaemic episode during the treatment period was significantly higher in the NPH group.

4.Incidence of nocturnal hypoglycaemic Episodes during the treatment:

There was a total of 153 nocturnal episodes during the study period. 46 (30.1%) in the Detemir group vs.107 (69.9%) in the NPH group; Odds ratio (Detemir/NPH): 0.6 [0.45, 0.97]. Thus, incidence of nocturnal hypoglycemic episodes was significantly higher in the NPH group.

5. Lipids after 26 Weeks of Treatment:

There was only a statistically significant difference between both treatment arms after 26 weeks of treatment in the total cholesterol values (2.02 (SE 0.03) g/L in detemir group vs. 1.93 (0.03) in NPH group; p =0.0282) and LDL cholesterol (1.19 (0.03) g/L in detemir group vs. 1.11 (0.02) in NPH group; p=0.041). Nevertheless, this difference

was not clinically relevant.

6. Summary of Treatment Emergent Adverse Events (TEAE):

Incidence of AE was similar in both groups (91 episodes in detemir group and 73 in NPH), being most of them mild or moderate in severity with only 3 severe adverse events in detemir group and none in NPH group. Relation to basal insulin was unlikely in most cases (1 event with a possible relation in every group and 2 with a probable relation in detemir group). There were only 6 serious adverse events in the detemir group and 4 in the NPH group, being the relation to trial product unlikely in all cases (as judged by investigator).

7. Laboratory safety

No clinically significant changes from baseline in haematology and biochemistry assessments were detected.

8. Summary of Change in Vital Signs from Baseline:

After 26 weeks of treatment there was a decrease in diastolic (-2.3 mm Hg (SD 9.8) and systolic blood pressure (-3.2 mm Hg (16.2) and pulse –0.1 b.p.m. (11.4) in the detemir group. Corresponding figures for NPH group were –1.5 mm Hg (10.2), -1.6 mm Hg (18.4) and –0.2 b.p.m. (10.9) respectively, without clinically significant differences between groups. (b.p.m: beats per minute).

CONCLUSIONS:

Treatment with insulin detemir, when used as basal component of a basal-bolus regimen in type 2 overweight or obese diabetic subjects, was associated with a significantly lower weight gain after 12 and 26 weeks of treatment compared to NPH. This result could not be explained by a different rate of metformin treated patients because at baseline both groups were comparable (even with a higher rate of metformin intake in the NPH group).This objective was achieved with a similar metabolic control (in terms of HbA1c levels, fasting plasma glucose, pre and postprandial glucose targets) and with a similar incidence of adverse events between both groups. Intra-subject variability of fasting plasma glucose was significantly lower in the detemir group. Insulin detemir regimen was also associated with a lower risk and incidence of hypoglycemic events (both global and nocturnal). Dose of insulin detemir was significantly higher than NPH dose at the end of the trial. Treatment satisfaction (measured by the DTSQ) was better in the detemir group.

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

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List of Abbreviations

AE	=	Adverse Event
ALAT	=	Alanine Aminotransferase
ALP	=	Alkaline Phosphatase
ANOVA	=	Analysis of Variance
B.P.M.	=	Beats per minute
BMI	=	Body Mass Index
C	=	Celsius
CDC	=	Clinical Development Centre
CRD	=	Clinical Research Department
CRF	=	Case Report Form
CRO	=	Contract Research Organisation
CTA	=	Clinical Trial Application
CV	=	Curriculum Vitae
EDPG	=	European Diabetes Policy Group
EME	=	External Medical Expert
dl	=	Decilitre
F	=	Fahrenheit
FDA	=	Food and Drug Administration
FPFV	=	First Patient First Visit
FPG	=	Fasting Plasma Glucose
GCP	=	Good Clinical Practice
HbA1c	=	Glycosylated Haemoglobin
hCG	=	human Chorionic Gonadotrophin
HDL	=	High Density Lipoprotein
HQ	=	Headquarters
IB	=	Investigators Brochure
ICH	=	International Conference on Harmonisation
ICTR	=	Integrated Clinical Trial Report
ID	=	Identification
IEC	=	Independent Ethics Committee
IRB	=	Institutional Review Board
ITT	=	Intent-To-Treat
IUD	=	Intra Uterine Device
IU/ml	=	International Units per ml
IVRS	=	Interactive Voice Response System
kg	=	Kilogram
l	=	Litre
LDH	=	Lactate Dehydrogenase
LDL	=	Low Density Lipoprotein
LPFV	=	Last Patient First Visit
LPLV	=	Last Patient Last Visit
MAO	=	Mono Amine Oxidase

mg	=	Milligram
ml	=	Millilitre
mmol	=	Millimol
NGSP	=	National Glycohaemoglobin Standardization Program
NN304	=	insulin detemir (INN name), LysB29(Nå- tetradecanoyl) des(B30) human insulin
NPH	=	Neutral Protamine Hagedorn
OAD	=	Oral Antidiabetic Drug
PG	=	Plasma Glucose
PP	=	Per-protocol Population
SAE	=	Serious Adverse Event
SAP	=	Statistical Analysis Plan
SAS	=	Statistical Analysis System
SE	=	Standard error
SD	=	Standard deviation
SMFPG	=	Self Monitoring Fasting Plasma Glucose
SMPG	=	Self Measured Plasma Glucose
SPC	=	Summary of Product Characteristics
SU	=	Sulphonylureas
TZD	=	Thiazolidinediones
UKPDS	=	UK Prospective Diabetes Study
U/ml	=	Units per ml

1 Ethics and Regulatory Approval(s)

The protocol, the two protocol amendments, the consent form, and the subject information sheet were reviewed and approved by the Independent Ethics Committee (IEC) "Comité Autonómico de Ensayos Clínicos de Andalucía". The Address of this IEC is provided in Appendix III.

The trial was performed in accordance with the "Declaration of Helsinki"[1] and its amendments in force at the initiation of the trial. The subjects were informed of the risks and benefits of the trial. The subjects were informed that they could withdraw from the trial at any time for any reason. Consent was obtained in writing prior to any trial-related activities and the Investigators retained the consent forms; these consent forms were available to Novo Nordisk for inspection (The subject information sheet and consent form are shown in Appendix I.).

The subjects were covered by the Sponsor's insurance according to local legal requirements.

2 Investigator(s) and Trial Administrative Structure

2.1 Trial Site(s)

The trial was conducted at the following 44 sites in Spain: **Active sites** (that enrolled patients): [redacted]. **Inactive sites** (did not enroll patients): [redacted].

All the investigators and their affiliations, as well as the trial staff at each trial site, are listed in Appendix IV. Abridged curricula vitae of the investigators are also in Appendix IV. The principal investigators were responsible for the conduct of the trial in accordance with the protocol, including the amendments, and current guidelines for good clinical practice (GCP)[2].

The coordinating investigator was [redacted] and his affiliation was: [redacted].

The names of the author of the report and responsible biostatistician are also provided in this listing (Appendix IV) as well as the signature of the sponsor's responsible medical officer.

2.2 Sponsor

The trial was sponsored and monitored by Novo Nordisk Pharma S.A. (Spain). The clinical research associates for this trial were [redacted], [redacted], [redacted] and [redacted]. Clinical trial supplies were provided by Novo Nordisk Pharma S.A. (Spain). C/ Caleruega 102, 28033 Madrid. Medical Director: [redacted].

Novo Nordisk prepared the protocol, the case report forms (CRFs) and performed data management (Novo Nordisk GmbH Austria).

2.3 Central Laboratory Facilities

The following central laboratory was used: [redacted]. Tel: [redacted]. The laboratory was responsible for analyzing different laboratory tests (pregnancy tests, haematology and biochemistry, lipids, fasting insulin concentration, fasting plasma glucose, Glycosuria and HbA1c) and for sending the data electronically to Data Management, Novo Nordisk GmbH Austria.

2.4 Contract Research Organization (CRO)

The following C.R.O. was used for the statistical analysis and the preparation of the Integrated Clinical Trial Report: [redacted]. Tel: [redacted]. Contact persons: [redacted] (Biostatistician) and [redacted] (Medical writer).

3 Introduction

3.1 Disease Background

Treatment of subjects with type 2 diabetes includes lifestyle adjustment, oral antidiabetic drugs and insulin treatment. The overall goal is to achieve satisfactory glycaemic control and thereby reduce the development and progression of microvascular and macrovascular complications seen in the long term in subjects with type 2 diabetes.

The UK Prospective Diabetes Study (UKPDS) showed that intensive glucose control and reduced HbA1c levels substantially reduce the long-term frequency of microvascular changes in subjects with type 2 diabetes. UKPDS also showed that the main disadvantages of intensive treatment are weight gain and an increased risk of hypoglycaemia, specially in connection with insulin treatment[3].

Subjects with type 2 diabetes treated with OAD monotherapy generally attain better glycaemic control than subjects treated with diet alone[4]. However, due to the progressive deterioration of diabetes control a majority of subjects with type 2 diabetes will, in the long term, need multiple therapies to attain the glycaemic targets set by the European Diabetes Policy Group (EDPG)[5].

Worldwide, the number of people with diabetes will increase from currently > 150 million to 300 million by the year 2025. Diabetes is present now in >7% of the U.S. population, primarily because of the 60% increase in adult obesity[6].

Insulin detemir has been associated with a lower within-subject variability of fasting blood glucose and reduced weight change compared to insulin NPH in subjects with type 2 diabetes[7]. In subjects with type 1 diabetes insulin detemir used in basal-bolus therapy has been associated with a lower risk of nocturnal hypoglycaemia and less weight gain in comparison to NPH insulin[8].

The basal-bolus regimen of insulin detemir plus the rapid insulin analogue insulin aspart, is an effective and well tolerated insulin regimen in people with type 2 diabetes, resulting in glycaemic control comparable to that of NPH + regular human insulin, but with some advantages such as less weight gain and a lower day-to-day within-person variation in fasting plasma glucose[9]. In subjects with type 1 diabetes the combination of insulin detemir and insulin aspart has shown an improved glycaemic control with lower risk of hypoglycaemia and no concomitant body weight increase in comparison with NPH insulin plus regular human insulin[10].

3.2 Trial Rationale

Overweight or obesity as a risk factor for type 2 diabetes has long been established and weight loss and prevention of weight gain remain a key tool in treating subjects with obesity and diabetes[5]. It has been shown by the Diabetes Prevention Program that weight loss can prevent the initiation of diabetes in subjects with impaired glucose tolerance[11]. A decrease in body weight of only 5% reduces the incidence of diabetes by 58 %. In type 2 diabetes subjects, a 60 % weight loss obtained by laparoscopic Roux-en-Y gastric bypass resulted in a normalisation of fasting plasma glucose and HbA1c in 83% of subjects[12].

Type 2 diabetes has been shown to be a progressive condition[13] with a need for more and more intensified therapy, due to a progressive loss of beta-cell function[4]. As a result, most subjects reach a point in their natural history where treatment with exogenous insulin is mandatory. Insulin typically leads to weight gain in type 2 diabetes, ranging from a mean of 4 kg in one study which used premixed human insulin[14] to 8.7 kg in another, using twice daily NPH insulin[15]. This weight gain remains one of the most important barriers to start insulin therapy in subjects with type 2 diabetes.

Recent studies have shown that insulin detemir, a basal insulin analogue, may be an insulin therapy of interest in treating subjects with overweight/obesity and diabetes. In studies using insulin detemir in type 1 diabetes, there has been shown a clear weight loss or more predictable FPG compared to NPH insulin in both 6 and 12 month trials[16-18, 8]. Similarly, in a trial in type 2 diabetes, the weight gain observed with insulin detemir was 0.7 kg less ($p=0.02$) than with NPH[7].

As the vast majority of subjects with type 2 diabetes are obese or overweight, the possibility of treating them with an insulin preparation not leading to changes in body weight or reaching some weight loss is extremely important.

Insulin detemir may therefore be an attractive therapeutic option in the treatment of subjects with both overweight/obesity and type 2 diabetes, but to date any clinical advantage has not been demonstrated in these subjects.

Metformin is an OAD frequently used in combination with insulin in overweight and obese subjects with type 2 diabetes. This is the main reason why it has been the only OAD accepted as a concomitant antidiabetic medication added to the insulin regimen in the trial population. In order to avoid a possible interference of this drug in the evaluation of the principal end-point of the trial

(change in weight), the randomization process took into account if the subject was taking or not metformin (stratification process) in order to have a similar proportion of subjects treated with that OAD in both groups of therapy (insulin detemir + insulin aspart vs. insulin NPH + insulin aspart). The subjects under treatment with metformin included in the trial must have been treated with stable doses of this drug in the last 2 months, and continued with the same dose during all the trial, as stated in the exclusion criteria.

4 Trial Objectives

As stated in the protocol and amendments (Appendix I), the objectives of the trial were as follows:

Primary Objective:
The primary objective of the trial was to compare the weight change during 26 weeks of treatment with insulin detemir versus NPH insulin in obese or overweight type 2 diabetic subjects.

Secondary Objectives:
A comparison of the following efficacy and safety variables between both treatments groups (insulin detemir versus NPH insulin):

- **Efficacy variables:**
  - HbA1c at the start and after 12 and 26 weeks of treatment.
  - Fasting plasma glucose at the start and after 12 and 26 weeks of treatment.
  - 7-point glucose profiles during the 26 weeks of treatment
  - Intra-variability of detemir and NPH insulin during 26 weeks of treatment.
  - Proportion of subjects reaching glycaemic control (HbA1c $\leq$ 7.0%) at the end of the trial
  - Proportion of subjects reaching pre and postprandial targets according to titration guidelines at the end of the trial.
  - Relationship between BMI and required daily dose of insulin detemir
- **Safety variables:**
  - Incidence of hypoglycaemia in the 26 weeks of treatment with insulin detemir versus NPH
  - Lipid profile at the start and after 26 weeks of treatment
  - Incidence of Adverse events during the trial
  - Safety profile as measured by laboratory safety parameters (haematology, biochemistry, glycosuria) and physical examination/vital signs before and at the end of treatment
  - Insulin resistance measured by the HOMA-IR at the start and at the end of the trial

5 Investigational Plan and Methodology

5.1 Trial Design Overview and Rationale

5.1.1 Trial Design

This study was a phase 3b, multi-centre, open-labelled, randomized, two-group parallel, treat-to-target clinical trial comparing insulin detemir and NPH in intensive insulin regimens in subjects with type 2 diabetes who were obese or overweight. Subjects requiring basal insulin therapy and with HbA1c ≥ 7.5% and ≤ 11% and a BMI ≥ 25 kg/m2 and ≤ 40 kg/m2 were recruited in this study. Trial diagram is shown in Figure 5-1.

Subjects were randomized to receive either:

• Insulin detemir once daily plus multiple prandial insulin analogue injections with insulin aspart during 26 weeks or

• NPH insulin administered once daily plus multiple prandial insulin analogue injections with insulin aspart during 26 weeks.

5.1.2 Trial Rationale

An open-labelled trial design was chosen because insulin detemir and NPH insulin are easily distinguishable from each other by visual inspection. Blinding would have required a double-dummy technique which could have been hazardous to subjects and might have affected compliance.

The primary endpoint was the weight change. The subjects must be weighted at every visit to the centre. HbA1c, a secondary endpoint and the rest of haematology and biochemistry parameters were analyzed by a central laboratory in order to limit the probability of introducing bias.

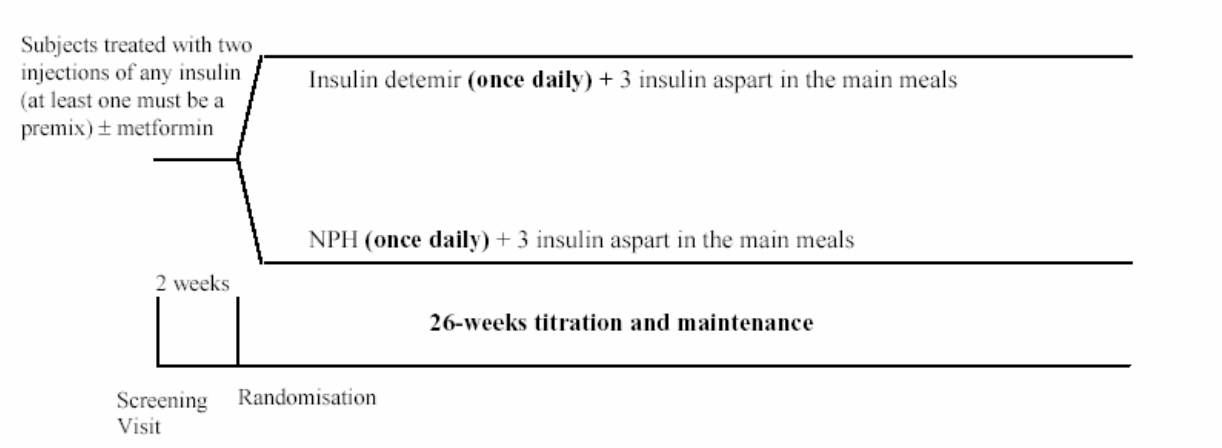
NPH insulin was chosen as comparator since it is still the most widely used basal insulin for the glycaemic control in subjects with type 2 diabetes treated with a basal-bolus insulin regimen. Clinical trials have confirmed a delayed but sustained blood glucose lowering effect with insulin detemir in both healthy subjects, and subjects with type 1 or type 2 diabetes. A less pronounced peak of action has been observed with insulin detemir than with currently available basal insulin

preparations such as NPH insulin. The results indicate that a similar metabolic effect can be achieved with a 3-4 fold higher molar dose of insulin detemir[16,19-21]. In addition, lower within-subject variation has been observed compared with NPH insulin[16,18] and treatment with insulin detemir has also been associated with a lower risk of hypoglycaemia and less body weight gain compared with NPH insulin[16,18]. At equivalent dosing levels, insulin detemir has a longer duration of action than NPH insulin[19]. No safety concerns have been raised during the pre-clinical and clinical phase 1, 2 and 3 trials.

The trial included a screening visit to assess the eligibility of the subjects, a randomization visit within two weeks of the screening visit, followed by a 26 week treatment period. In order to achieve glycaemic control as soon as possible after initiation of treatment, frequent contact between subjects and investigators including telephone calls and regular visits were scheduled and a specific insulin titration guideline was followed as this was a treat-to-target trial. There was no active post-treatment follow-up period. There were no interim analyses.

5.1.3 Trial Diagram

Figure 5-1. Trial Diagram.



5.2 Variables for Evaluation

The purpose of the trial was to determine whether there was a difference between insulin detemir regimen and NPH regimen for the following variables

5.2.1 Efficacy:

- ***Weight***

The subject was weighted at every visit to the centre. It was the primary endpoint. Body weight was measured without overcoat and shoes and recorded in kilograms (kg) with one decimal. Each centre must use the same scale during all the trial.

- ***HbA1c***

Blood samples were drawn at visit 1, 2, 5 and 7 for measurement of HbA1c. The analyses was performed by a Central Laboratory.

- ***Fasting Plasma Glucose (laboratory)***

At visits 2, 5 and 7 (end of study) a sample was collected to measure fasting plasma glucose by a central laboratory.

- ***7-Point Glucose profile***

Subjects were asked to perform 7-point plasma glucose profiles on a typical day, 4-7 days prior to each visit, and record the results in the supplied diary. Plasma glucose levels were measured at the following time points:

• Before each meal (breakfast, lunch, and dinner)
• 90 minutes after the start of each meal (breakfast, lunch, and dinner)
• at 3 am in the morning

Plasma glucose was measured by the subjects using blood glucose meters, which were provided by Novo Nordisk, along with test strips and calibration solutions. The subjects received instruction on the use of the blood glucose meter, including regular calibration according to the manufacturer's instruction. Subjects were also provided with written instructions.

The standard glucose meter used test strips calibrated to plasma values. This means that all glucose measurements performed with drawn capillary blood were displayed as plasma glucose values. The targets for the titration of the insulin treatment in Appendix C of the protocol are given as plasma

glucose values. In addition, subjects were advised to perform self-measurement of plasma glucose whenever symptoms of hypoglycaemia were suspected, and, if possible, before any intervention took place (i.e. food intake).

Subjects were instructed how to record the results of the self-measured plasma glucose values in the provided diaries. The record of each measurement should include the date, time and the plasma glucose value. The Investigator transcribed the results to the CRF at the following visit. Occasional review by the Investigator of the subject's glucose values stored in the memory of the glucose meter was advised to assure adequacy of the diary records.

- ***Within-subject variation of fasting plasma glucose***

Prior to visits 2, 5 and 7, subjects had to measure **fasting plasma glucose** and record the results in their diary, following this schedule:

• Between visits 1 and 2, subjects had to measure SMFPG in the morning three times in three different days (in different days in which they performed the 7-point profile).

• Between telephone contact T7 and visit 5, and during four weeks prior to visit 7, subjects had to measure SMFPG in the morning two times a week (in different days in which they performed the 7-point profile).

The intra-subject variation was measured as the coefficient of variation (in %) of the last six fasting BG measures performed by the subjects 4 weeks prior to visits 2, 5 and 7.

For each visit, the six measures were:

• For visit 2: three measures performed following the above schedule + one taken from the 7-point profile + two measures taken from subjects records and performed prior to visit 1 (within a period of 4 weeks before visit 2).

• For visit 5: four measures performed following the above schedule + two performed prior to telephone contact T7 for titration purposes (all must be performed within a period of 4 weeks prior to visit 5)

• For visit 7: six measures performed following the above schedule

- ***Self monitoring fasting plasma glucose for titration***

Prior to each telephone contact and prior to visits 3 and 4, subjects had to measure Self Monitoring Fasting Plasma Glucose before breakfast three times in three different days and record the results in

the diary. These data were provided to the Investigator in the telephone call or in the visit to the centre to titrate the insulin dose.

- ***Treatment Satisfaction***

Though this analysis was not initially planned in the protocol, it was included in the SAP and finally performed because data of two quality of life and treatment satisfaction questionnaires were available. Efficacy endpoint was the percentage change in the questionnaire scores between baseline and week 26. The Medical Outcomes Study 36-Item Short-Form Health Survey SF-36v2 and the WHO-DTSQ were used to measure Treatment Satisfaction. The SF-36 questionnaire was used to measure generic aspects of health, whilst WHO-DTSQ was used as a disease-specific questionnaire for diabetes. These questionnaires have been translated and validated according to stringent methodology to ensure cross-cultural equivalence.

Subjects were asked to complete the questionnaire at Visits 2, 5 and 7. The two questionnaires were completed at the visit and returned in a sealed envelope to the site personnel.

5.2.2 Safety:

- ***Adverse Events***

Adverse events were recorded at every visit/contact, except for visit 1, in accordance with the procedures described in Section 11(Adverse Events) of the protocol. See section 5.8.1 of this report for more details.

- ***Hypoglycaemic Episodes***

Hypoglycemic episodes were recorded by the subject in the diary from visit 2 to the end of trial. The recording included: date, time of hypoglycemic episode, time of last insulin dose prior to episode, time of last main meal prior to episode, whether the episode was symptomatic, whether the subject was able to treat him/herself (the answer to the question: subject able to treat him/herself?. should be No if food, glucagon or i.v. glucose had to be administered to the subject by another person, because of severe CNS dysfunction associated with the hypoglycemic episode) and the blood glucose level before treating the episode (if available). Additionally, in visit 2 the subject was asked about the number of hypoglycemic episodes he/she had suffered in last 4 weeks, with specification, if possible, of the category (following the below classification). Hypoglycemic episodes were classified in the database according to the following definitions: **major** if the subject

was not able to treat the episode him/herself, **minor** if the subject was able to treat the episode him/herself and plasma glucose (PG) measure was < 3.1 mmol/l (56 mg/dl) and **symptoms only** if the subject was able to treat the episode him/herself and the PG was not available or ≥ 3.1 mmol/l.

- ***Lipid profile at the start and after 26 weeks of treatment***

Fasting blood samples for total cholesterol, HDL-cholesterol, triglycerides and free fatty acids were taken at randomization and visit 7 (end of trial). LDL cholesterol was estimated from quantitative measurements of total and HDL-cholesterol and triglycerides using the empirical relationship of Friedewald et al.[22] Calculation of LDL cholesterol was performed by the central laboratory.

- ***Insulin resistance measured by the HOMA-IR***

Insulin resistance was calculated using the formula of the homeostasis model assessment insulin resistance (HOMA-IR) as described by Matthews et al[23]: (fasting insulin [μU/ml] X fasting glucose [mmol/l])/22.5

- ***Physical examination***

A general physical examination was carried out at visit 1 and at the end of the trial (visit 7) including: cardiovascular system, respiratory system, gastrointestinal system, central and peripheral nervous system, musculoskeletal system and skin, according to local procedure. Any clinically significant deterioration since visit 1 should be regarded as an Adverse Event (Section 11 of the protocol).

- ***Vital signs***

Vital signs were measured at every visit. Blood pressure and pulse were measured after resting in a sitting/supine position for five minutes.

- ***Laboratory Assessments***

Hematology and biochemistry were analyzed by a central laboratory. Details were described in the trial specific laboratory manual together with procedures for obtaining blood samples and handling conditions. The manual was supplied by the central laboratory.

- ***Haematology***

  Blood samples for hematology (hemoglobin, leucocytes, differential count if leucocytes abnormal and Thrombocytes) were taken at visits 1 and 7.

- ***Biochemistry***

Blood samples for biochemistry were taken at visits 1 and 7. Analyses performed were creatinine, sodium, potassium, total protein, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), and lactate dehydrogenase (LDH).

- ***Pregnancy test***

Women of childbearing potential had blood sample taken for serum pregnancy test (human Chorionic Gonadotrophin (hCG)) at visit 1. Pregnancy urine test was performed at any time during the trial if a menstrual period was missed or if deemed necessary by the Investigator or required by national law. The central laboratory provided the pregnancy kits for urine testing performed at the site.

- ***Glycosuria***

Glycosuria was collected from a urine sample and measured at baseline and at the end of the study (visits 2 and 7) by the central laboratory.

- ***Fasting insulin concentration***

Fasting insulin concentration was measured at baseline and at the end of the study (visits 2 and 7) by the central laboratory.

- ***Funduscopy or Fundusphotography***

A fundoscopy/fundusphotography was performed at visit 1 in accordance with local practice. An examination performed within the period from eight weeks prior to visit 1 or performed in the period between visits 1 and 2 was acceptable as visit 1 data. The dates of fundoscopy/fundusphotography were recorded in the CRF and were source data verifiable.

5.2.3 Other Assessments

- ***Diabetes History***

The date of diagnosis of type 2 diabetes and of diabetic complications: retinopathy, neuropathy, nephropathy and macroangiopathy including peripheral vascular disease was recorded in the CRF at visit 1.

- ***Demographic data***

Date of birth, gender and race were recorded at visit 1.

- ***Height***

Height (without shoes) was measured at visit 1. Height was measured in meters and recorded with two decimals.

- ***Current therapy with insulin and metformin (if applicable)***

At the selection visit, data about the type (brand name preferable), total daily dose and start date of current therapy with insulin was recorded in the CRF. In this visit, it was also recorded the brand name, total daily dose and start date of metformin therapy (if applicable).

- ***Insulin and metformin (if applicable) dose***

From visit 2 to visit 7, subjects recorded their insulin dose on one of the three days where SMPG or 7-point profile was performed prior to each visit/contact. Furthermore, during the telephone contacts, subjects recorded in the diary the insulin dose prescribed by the Investigator or designated person. The investigator also recorded in the CRF from visit 2 to visit 7 the brand name and current dose of metformin (if applicable).

- ***Subject compliance***

Formal subject compliance with trial products was not assessed due to the variable doses used. At each visit, the Investigator emphasised the necessity to adhere to trial procedures in order to encourage subject compliance. In addition, subject compliance was monitored by means of the trial specific subject's diary and careful monitoring of the drug accountability.

5.3 Trial Population

The population in the present trial constituted those subjects with type 2 diabetes overweight or obese who were not in satisfactory control according to accepted guidelines[5]. They were expected to benefit from a treatment with an intensive insulin regimen that could reduce the weight gain and with the use of a treat-to-target concept that may help to achieve a satisfactory glycaemic control.

5.3.1 Sample Size

It was planned to screen 313 subjects in order to randomise 272 patients to have 230 evaluable subjects. See section 6.1 for more details of sample size calculation.

5.3.2 Selection Criteria

Subject selection was based on the inclusion and exclusion criteria listed below.

Inclusion Criteria:

1. Informed consent obtained before any trial-related activities. (Trial-related activities were any procedure that would not have been performed during normal management of the subject.)
2. Female or male, age ≥18
3. Subjects with type 2 diabetes who have been treated with 2 doses of insulin (one of them must be a premix) for at least 3 months prior to inclusion
4. HbA1c ≥7.5 and ≤ 11% based on analysis from central laboratory
5. BMI ≥ 25 kg/m^2 and ≤ 40 kg/m^2
6. Able and willing to perform self-monitoring of blood glucose.
7. Willing to accept multidose insulin therapy.
8. Able to self-inject all required doses of insulin.

Exclusion Criteria:

1. Treatment with any OAD in the last 6 months, except metformin (subjects currently treated with metformin within the interval of 1000 - 2550 mg daily could be included in the trial. The dose should have remained unchanged for a period of 2 months prior to randomization and should be expected to remain unchanged throughout the trial period).
2. Any disease or condition (such as renal, hepatic or cardiac) that, according to the judgement of the Investigator, made the subject unsuitable for participation in the trial.
3. Total daily insulin dose ≥ 2 IU/kg.
4. Anticipated change in concomitant medication known to interfere with glucose metabolism, such as systemic steroids, non-selective beta-blockers or mono amine oxidase (MAO) inhibitors.
5. Proliferative retinopathy or maculopathy that had required acute treatment within the last six months.
6. Uncontrolled hypertension (treated or untreated) as judged by the Investigator
7. Known or suspected allergy to trial product(s) or related products.

8. Previous participation in this trial. Participation was defined as screened.
9. Pregnant, breast-feeding or the intention of becoming pregnant or not using adequate contraceptive measures. Adequate contraceptive measures were sterilisation, intrauterine device (IUD), oral contraceptives or consistent use of barrier methods.
10. Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-Operation.
11. Any condition that the Investigator felt would interfere with trial participation or evaluation of results.
12. Receipt of any investigational drug within 1 month prior to this trial.
13. Patients currently in treatment of obesity (including any drug or pre-planned surgery).

5.3.3 Withdrawal Criteria

The subject could withdraw at will at any time. The subject could be withdrawn from the trial at the discretion of the Investigator or the Sponsor if judged non-compliant with trial procedures or due to a safety concern.

As stated at the protocol and added (5) in Amendment 1, a subject must be withdrawn if any of the following applied:

1) Pregnancy or intention of becoming pregnant
2) Any disease or new condition which the Investigator felt would interfere with the trial.
3) Not in acceptable metabolic control when maximum effects of the treatment regimens were seen, according to the discretion of the Investigator.
4) Initiation of concomitant medication known to interfere with glucose metabolism such as systemic steroids, non-selective beta-blockers and MAO inhibitors.
5) Start of any treatment of obesity (including any drug or surgery procedure)

5.4 Treatments

5.4.1 Treatment Regimen

Throughout the 26 week treatment period, all subjects were treated with a basal insulin once daily in combination with multiple prandial insulin injections with insulin aspart. Insulin detemir or NPH insulin were used as basal insulin. The injection was given according to randomization in the evening for both NPH insulin and insulin detemir. *Evening* was defined from one hour before the last main meal until bedtime (as guidance a main meal was defined as a meal containing more than 20% of the total daily calorie intake). The insulin dose should be taken at approximately the same time each day. The starting dose of basal insulin should be 40% of the total dose of insulin that the patient was receiving the day before randomization. Subjects were dosed according to individual requirements during the trial period as described in the Table 5.1

Subjects were titrated individually with the aim of reaching and maintaining the before breakfast plasma glucose target of ≤110 mg/dl (≤ 6.11 mmol/l) without significant hypoglycaemia. The starting dose of mealtime insulin at randomization visit should be 60% of the total dose of insulin that the patient was receiving the day before randomization. The dose of aspart insulin was individually titrated to reach the postprandial glucose target of ≤180 mg/dl (≤10.0 mmol/l) without significant hypoglycaemia. The algorithms are described in detail in Appendix C of the protocol.

Table 5.1 Algorithm for titration of basal insulin dose

Average PG before breakfast used for titration	Increase in basal insulin dose (IU/Units)
≤ 110 mg/dl (≤ 6.11 mmol/l) Target	No adjustment
111 – 130 mg/dl (6.17 – 7.22 mmol/l)	+ 2
131 – 145 mg/dl (7.28 – 8.06 mmol/l)	+ 2
146 – 165 mg/dl (8.11 – 9.17 mmol/l)	+ 4
166 – 180 mg/dl (9.22 – 10.00 mmol/l)	+ 6
> 180 mg/dl (> 10.00 mmol/l)	+ 8

PG before breakfast	Dose reduction of insulin detemir/NPH insulin
One or more values < 56 mg/dl (3.1 mmol/l) without obvious explanation	Reduce insulin detemir/NPH insulin dose by **4 units** (for those on a basal dose > 40 units, a dose reduction of 10% is suggested).
One or more values between 56-72 mg/dl (3.1- 4.0 mmol/l) without obvious explanation	Reduce insulin detemir/NPH insulin dose by **2 units** (for those on a basal dose > 40 units, a dose reduction of 5% is suggested).

Insulin injections were given subcutaneously preferably in the thigh. As absorption differs in the different areas, with the fastest rate of absorption in the abdomen, the injection area chosen should remain unchanged throughout the trial, even if a single dose was delivered as more than one injection. Subjects were instructed to rotate the site of injection within the area chosen to prevent lipohypertrophy.

5.4.2 Trial Products

As basal insulin, the following were supplied:

- Insulin detemir FlexPen® 100 U/ml solution for injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S.
- Isophane (NPH) Insulin FlexPen® 100 IU/ml suspension for injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S.
- Insulin aspart was supplied as mealtime insulin in FlexPen® 100 U/ml solution for injection in a pre-filled disposable pen device, 3 ml, Novo Nordisk A/S.

Details of the preparations including batch numbers are shown in Table 5–2.

Table 5-2. Trial products.

Product name	Item code	Batch No.	Filled Butch No.	Re-Test date
FlexPen Detemir 100IU/ml, 3ml	5-9677-08	RP50873	-	2007-02-19
FlexPen Protaphan 100IU/ml, 3ml	5-9657-05	RP50931	-	2007-05-12
FlexPen Insulin Aspart 100IU/ml, 3ml NN2000	5-9670-20	RP50736	-	2007-04-20

All insulin preparations were stored at 2-8 °C until use and were not allowed to freeze. No trial products were used after its expiry date.

All auxiliaries needed for participation in this trial were also supplied by Novo Nordisk Pharma S.A. The following equipment was supplied:

- Standard blood glucose meters, lancets, test strips and control solutions. The subjects received instruction in the use of the blood glucose meter, including regular calibration in accordance with manufacturer's instructions.
- Subject diaries and subject ID cards.
- NovoFine 30G needles
- Containers for used needles
- Thermo bags

5.4.3 Assignment Procedures

A randomized (1:1), open-labelled, 2-arm parallel group design was chosen. A stratification method was used to ensure that there was a similar proportion of subjects treated with metformin in both groups of treatment (detemir + insulin aspart vs. NPH + insulin aspart). It consisted in two different randomization lists: one for subjects treated at the screening visit with metformin and one for subjects not treated with metformin.

The treatment was open-labelled. The randomization took place at Visit 2 just prior to initiation of treatment. Each investigator was provided with sufficient sealed codes, one for each subject. One randomization number was printed on each sealed code (visible) and the treatment for the subject was sealed. At the randomization visit the investigator assigned the lowest available randomization number at the site and revealed the treatment for the subject number by scratching off the protective surface of the sealed code.

Subject initials, date and Investigator's signature were stated on the sealed code before the treatment was uncovered. The randomization list was generated by Clinical Supplies Operations (Local Clinical Supplies Coordination), Novo Nordisk A/S and kept under locked condition until database release. The sealed codes were provided by Clinical Supplies Operations (Local Clinical Supplies Coordination), Novo Nordisk A/S.

The Investigator transferred information about trial product from sealed codes into the CRF.

The randomization list is shown in Appendix VI.

5.4.4 Blinding

Not applicable for this trial. An open-labelled trial design was chosen because insulin detemir and NPH insulin are easily distinguishable from each other by visual inspection. Blinding would have required a double-dummy technique which could have been hazardous to subjects and might have affected compliance.

5.4.5 Treatment Compliance

At each visit, the Investigator emphasised the necessity to adhere to trial procedures in order to encourage subject compliance. In addition, subject compliance was monitored by means of the trial specific subject's diary and careful monitoring of the drug accountability. Formal subject compliance with trial products was not assessed due to the variable doses used.

5.4.6 Concomitant and Previous Treatment

Concomitant medication was defined as any medication other than the trial products that was taken during the trial, including the screening and run-in periods.

Details of all concomitant medication were recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication were recorded at each visit. If the change influenced the subject's eligibility to continue in the trial, the Sponsor was informed. The information collected for each concomitant medication included start date, stop date or continuing, and indication.

Exclusion criteria No. 1 stated that subjects treated with metformin in the 2 months prior to visit 1 (screening) with unchanged doses of 1000 - 2550 mg daily, could be included in the trial. This dose must have remained unchanged throughout the trial period, except for safety reasons. According to this statement, all subjects treated with metformin at screening, must have followed his/her metformin treatment with the same dose. This dose was recorded in the diary/CRF during all the trial period. Subjects were not provided with metformin by Novo Nordisk A/S.

Concomitant medication and treatments disallowed in this trial are listed under exclusion criteria in Section 5.3.2 and under withdrawal criteria in Section 5.3.3.

5.5 Trial Flow

5.5.1 Overview

Table 5-3 Trial Flow-Chart

FLOW CHART OF THE TRIAL														
Visit Number	Visit 1	Visit 2	Tel. contacts			Visit 3	Tel. contacts			Visit 4	Tel. contact	Visit 5	Visit 6	Visit 7
			T1	T2	T3		T4	T5	T6		T7			
Weeks in relation to Visit 2	< -2	0	1 wk ±2 days	2 wks ±2 days	3 wks ±2 days	4 wks ±2 days	5 wks ±2 days	6 wks ±2 days	7 wks ±2 days	8 wks ±2 days	10 wks ±4 days	12 wks ±4 days	18 wks ±4 days	26 wks ±7 days
Informed consent	X													
Inclusion & exclusion criteria	X													
Withdrawal criteria						X				X		X	X	
Randomization		X												
Demographics & diabetes history	X													
Phys. examination	X													X
Vital signs	X	X				X				X		X	X	X
Height	X													
Body weight	X	X				X				X		X	X	X
Fundoscopy / Fundusphotography[1]	X													
Current treatment														
Insulin therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Metformin therapy (if applicable)	X	X				X				X		X	X	X
Central laboratory														
Pregnancy test[2]	X	X[2]				X[2]				X[2]		X[2]	X[2]	X[2]
Haematology & Biochemistry	X													X
Lipids		X												X
Fasting insulin concentration		X												X
Fasting plasma glucose		X										X		X
Glycosuria		X												X
HbA_{1c}	X	X										X		X
Self monitoring plasma glucose determinations														
7-point SMPG profile[3]		X				X				X		X	X	X
SMFPG[4] (for titration)			X	X	X	X	X	X	X	X	X			
SMFPG[5] (for intra-subject variability)		X										X		X
Safety														
Hypoglycaemic		X	X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART OF THE TRIAL														
Visit Number	Visit 1	Visit 2	Tel. contacts			Visit 3	Tel. contacts			Visit 4	Tel. contact	Visit 5	Visit 6	Visit 7
			T1	T2	T3		T4	T5	T6		T7			
Weeks in relation to Visit 2	< -2	0	1 wk ±2 days	2 wks ±2 days	3 wks ±2 days	4 wks ±2 days	5 wks ±2 days	6 wks ±2 days	7 wks ±2 days	8 wks ±2 days	10 wks ±4 days	12 wks ±4 days	18 wks ±4 days	26 wks ±7 days
episodes[6]														
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant illness	X													
Concomitant medication	X	X				X				X		X	X	X
Other														
QoL questionnaire (SF-36 + WHO-DTSQ)		X										X		X
Titration data														
Insulin dose titration			X	X	X	X	X	X	X	X	X	X	X	
Fax/mail titration data to Novo Nordisk[7]						X				X		X	X	X
Patient diary														
Dispense/collect diary	X	X				X				X		X	X	X
Record diary info		X				X				X		X	X	X
Trial supplies														
Glucose meter dispense & instruct.	X													
Instruction in use of pen device		X												
Dispense medication		X				X				X		X	X	
Drug accountability		X				X				X		X	X	X
End of trial form														X

[1] An examination performed within the period from eight weeks prior to Visit 1 to the date of Visit 2 is acceptable as Visit 1 data.
[2] Only females of childbearing potential will undergo this test. A serum test will be performed at Visit 1, and a pregnancy urine test will be performed any time during the trial if a menstrual period is missed.
[3] To be performed on a typical day, 4-7 days prior to the visit (not on the same day as SMFPG)
[4] Prior to each telephone contact and prior to visits 3 and 4, subjects will have to measure Self Monitoring Fasting Plasma Glucose before breakfast three times in three different days and record the results in their diary. These data should be provided to the investigator in the telephone call or in the visit to the centre to titrate the insulin dose.
[5] Between visits 1 and 2, patients will have to measure Self Monitoring Fasting Plasma Glucose (SMFPG) in the morning three times (not on the same day as the 7-point profile).
Between visits T7 and 5, and during four weeks prior to visit 7, patients will have to measure Self Monitoring Fasting Plasma Glucose (SMFPG) in the morning two times a week (not on the same day as the 7-point profile).
[6] Hypoglycaemic episodes will be recorded by the subject in the diary from visit 2 to the end of trial.
Additionally, in visit 2 the patient will be asked about the number of Hypoglycaemic episodes he/she has suffered in last 4 weeks, with specification, if possible, of the category (following classification of section 8.3.5)
[7] A template with data of SMPG performed by the patient and dose of insulin must be sent by fax/mail to Novo Nordisk Pharma S.A. for follow-up of titration process.

See protocol for a detailed description of activities performed in every visit.

5.5.2 Protocol Amendments and General Procedural Deviations

Protocol Amendments

There were two protocol amendments. The rationale for **amendment 1** (22-06-2005) was that it was not very clear that the patients currently in treatment of obesity were allowed to enter the trial (after amendment a new exclusion criteria for patients currently in treatment for obesity was added); a new withdrawal criterion was also added: if a patient started a treatment for obesity, he/she would have to be withdrawn from the trial. On the other hand, exclusion criteria No 1 stated that patients in treatment with any OAD, except metformin, were excluded. It was also not very clear if a patient that took in the past this treatment was allowed to be included. A period of 6 months was then set up as wash-out period for treatment with OADs.

Changes were also made in the insulin titration guideline in order to get that all patients could start the treatment with similar distribution of basal and mealtime insulin doses. After this amendment the starting dose of basal insulin should be 40% of the total dose of insulin that the patient was receiving the day before randomization and the starting dose of mealtime insulin should be 60% of the total dose of insulin that the patient was receiving the day before randomization. The calendar to start the recruitment was also changed (without affecting the LPLV because recruitment period was reduced from 6 to 4 months) and more centres were included in the trial. Information about the central Lab was also given.

After **amendment 2** (23-11-2005) the number of centres in the study was increased and the recruitment period was extended in order to reach the recruitment target. Changes of personnel of NovoNordisk and Primary Investigators were also reported.

General Procedural Deviations

The main general procedural deviation detected during the trial was that not all the investigators followed the titration guideline given in Appendix C of the protocol and titration of insulin doses were mainly guided by the investigator practice, in these cases.

5.6 Efficacy Assessment

5.6.1 Efficacy variables

- Weight
- HbA1c
- Fasting Plasma Glucose (central laboratory)
- 7-Point plasma glucose profiles
- Self-monitoring fasting plasma glucose (for intrasubject variability)

5.6.2 Sampling

See Section 5.2.1 for a description of the sampling and methods used for efficacy variables.

5.7 Quality of Life Assessments

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)[24] and the WHO-DTSQ were used as Quality of Life questionnaires.

5.8 Safety Assessments

5.8.1 Adverse Events

Adverse Event Definitions

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following was not recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

• Pre-planned procedure, unless the condition for which the procedure was planned had worsened from the first trial related activity after the subject had signed the informed consent.

• Pre-existing conditions found as a result of screening procedures

Clinical Laboratory Adverse Event:

A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):

A serious AE was an experience that at any dose resulted in any of the following:

• Death

• A life-threatening* experience

• In-patient hospitalisation or prolongation of existing hospitalisation

• A persistent or significant disability/incapacity

• A congenital anomaly/birth defect

• Important medical events that may not result in death, be life-threatening*, or require hospitalisation were considered as SAE when, based upon appropriate medical judgement, they might jeopardise the subject and might require medical or surgical intervention to prevent one of the outcomes listed in this definition.

*The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

Non-Serious Adverse Event:

A non-serious AE was any AE which did not fulfil the definition of a serious Adverse Event.

Assessment Definitions

Severity

• Mild: Transient symptoms, no interference with the subject's daily activities

• Moderate: Marked symptoms, moderate interference with the subject's daily activities

• Severe: Considerable interference with the subject's daily activities, unacceptable

***Relation to trial product*:**

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship was conceivable and could not be dismissed
- Unlikely: The event was most likely related to an aetiology other than the trial product.

***Outcome*:**

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent.
- Recovering: The condition was improving and the subject was expected to recover from the event. This term should only be used when the subject had completed the trial.
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

Recording of Adverse Events

All events meeting the definition of an Adverse Event were collected and reported from the first trial related activity after the subject had signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol. At each contact with the site (visit or telephone, excluding safety visits, where the subject was not seeing the Investigator or his staff (i.e. visits to the laboratory), the subject was asked about Adverse Events, ie "Have you experienced any problems since the last contact?" The Investigator recorded the diagnosis, if available. If no diagnosis was available, the Investigator recorded each sign and symptom as individual Adverse Events. All Adverse Events, observed by the Investigator or reported by the subject, were recorded by the Investigator and evaluated.

Hypoglycaemic episodes were only reported as Adverse Events if they fulfilled the definition of a serious Adverse Event.

The Adverse Events were recorded by the Investigator on the standard Adverse Event Form. If more than one sign or symptom was to be reported, a separate Adverse Event Form for each sign and symptom was used. For serious Adverse Events, the Serious Adverse Event Supplementary pages were also completed.

The Investigator must report initial information on all serious Adverse Events to Novo Nordisk within 24 hours of obtaining knowledge about the event. The information was provided by fax or telephone or electronically to the contact persons mentioned in Attachment I of the protocol.
The Investigator must complete and forward electronically/fax/courier copies of the Adverse Event Form and the Serious Adverse Event Supplementary Pages to Novo Nordisk within 5 calendar days of obtaining knowledge about the serious Adverse Event.
The Investigator must inform the Regulatory Authorities and IECs/IRBs in accordance with the local requirements in force and ICH guideline for GCP. The Monitor must be informed accordingly.

Description and Rating of Adverse Events
For each adverse event, the investigator recorded the following parameters on the adverse event Form: description of event, onset and outcome date, severity, relation to trial product, changes to Trial product, outcome and whether or not the event was serious.

Coding of Adverse Events
All the adverse events were coded using MedDRA 8.1. Non-serious and serious adverse events were coded by Data Management Novo Nordisk GmbH Austria.

Treatment and Follow-up of Adverse Events
Any adverse event that occurred during the trial was treated by established standards of care. During and following a subject's participation in a clinical trial, the Investigator/institution should ensure that adequate medical care was provided to the subject for any Adverse Events, including clinically significant laboratory values related to the trial. The Investigator/institution should inform the subject when medical care was needed for Adverse Event(s) of which the Investigator becomes aware.
The follow up information only included new (updated and/or additional) information that reflected the situation at the time of the investigator's signature. There was no active post-treatment follow-up period in this trial.
All non-serious Adverse Events classified as severe or possibly/probably related to the trial product were followed until the subject had recovered and all queries had been resolved. For cases of chronic conditions or if the subject died from another event, follow-up until the outcome category

was recovered was not required, as these cases could be closed with an outcome of "recovering" or "not recovered".

All other non-serious Adverse Events were followed until the outcome of the event was "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever came first, and until all queries related to these AEs had been resolved. If the subject died from another event, follow-up until the outcome category was "recovered" was not required, as these cases could be closed with an outcome of "recovering" or "not recovered"

The Investigator must forward follow-up information on non-serious Adverse Events on the Adverse Event Follow-up Form. The Investigator must forward follow-up information on serious Adverse Events to Novo Nordisk within 5 calendar days of obtaining the follow-up information. All serious Adverse Events were followed until the outcome of the event was "recovered", "recovered with sequelae" or "fatal" and until all queries had been resolved. For cases of chronic conditions and cancer or if the subject died from another event, follow-up until the outcome categories were "recovered", "recovered with sequelae" or "fatal" was not required, as these cases could be closed with an outcome of "recovering" or "not recovered". The investigator must forward follow-up information on serious Adverse Events using the Adverse Event Follow-up Form and/or the Serious Adverse Event Supplementary Pages Follow-up Form.

5.8.2 Hypoglycaemic episodes

Hypoglycaemic episodes were recorded by the subject in the diary from visit 2 to the end of trial. See section 5.2.2. for more details. Hypoglycaemic episodes occurring during the trial were only defined as Adverse Events if they fulfilled the definition for a serious Adverse Event in Section 5.8.1 (Definitions). If a hypoglycaemic episode fulfilled the definition, it was handled as stated in the corresponding sections (Collection, Recording and Reporting of Adverse Events and Follow-up of Adverse Events). The entries in the subject's diary were transcribed to the Hypoglycaemic Episode Form of the CRF at the following visit to the clinic.

5.8.3 Clinical Laboratory Tests

Haematology and biochemistry were analyzed by a central laboratory. Details were described in the trial specific laboratory manual together with procedures for obtaining blood samples and handling conditions.

Haematology

Blood samples for haematology (haemoglobin, leucocytes, differential count if leucocytes abnormal and Thrombocytes) were taken at visits 1 and 7.

Biochemistry

Blood samples for biochemistry were taken at visits 1 and 7. Analyses performed were creatinine, sodium, potassium, total protein, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALAT), and lactate dehydrogenase (LDH).

Lipids

Fasting blood samples for total cholesterol, HDL-cholesterol, triglycerides and free fatty acids were taken at randomization and visit 7 (end of trial).

Pregnancy Test

Women of childbearing potential had blood sample taken for serum pregnancy test (human Chorionic Gonadotrophin (hCG)) at visit 1. Pregnancy urine test was performed at any time during the trial if a menstrual period was missed or if deemed necessary by the Investigator or required by national law. The central laboratory provided the pregnancy kits for urine testing performed at the site.

Glycosuria

Glycosuria was collected from a urine sample and measured at baseline and at the end of the study (visits 2 and 7) by the central laboratory.

Fasting insulin concentration

Fasting insulin concentration was measured at baseline and at the end of the study (visits 2 and 7) by the central laboratory.

Insulin resistance

Insulin resistance was calculated using the formula of the homeostasis model assessment insulin resistance (HOMA-IR) as described by Matthews et al[23]: (fasting insulin [μU/ml] x fasting glucose [mmol/l])/22.5.

5.8.4 Other Safety Parameters

The following additional safety parameters were recorded during the trial:

Physical Examination

A general physical examination was carried out at visit 1 and at the end of the trial (visit 7) including: cardiovascular system, respiratory system, gastrointestinal system, central and peripheral nervous system, musculoskeletal system and skin, according to local procedure. Any clinically significant deterioration since visit 1 should be regarded as an Adverse Event.

Vital Signs

Vital signs were measured at every visit. Blood pressure and pulse were measured after resting in a sitting/supine position for five minutes.

Fundoscopy/Fundusphotography

A fundoscopy/fundusphotography was performed at visit 1 in accordance with local practice. An examination performed within the period from eight weeks prior to visit 1 or performed in the period between visits 1 and 2 was acceptable as visit 1 data. The dates of fundoscopy/fundusphotography were recorded in the CRF and were source data verifiable.

5.9 Data Quality Assurance

The trial was conducted in accordance with Good Clinical Practice.

During the course of the trial, the Monitor visited the trial site at approximately 6-8 week intervals but more often during the first three months of the trial (approximately every 2-4 weeks) and was available for discussions by telephone. The purpose of these visits was to ensure that the CRFs were completed correctly, the protocol was adhered to, and to monitor drug accountability and to collect completed CRF pages.

The Monitor was given direct access to source documents (original documents, data and records). Direct access included permission to examine, analyze, verify and reproduce any record(s) and report(s) that were important to evaluation of the clinical trial. For screening failure subjects, the Screening Failure Form, the Affirmation Statement Form and any Adverse Event Forms for serious Adverse Events and any other CRF pages containing data were collected. Only data from the screening failure form were entered into the database.

In case of withdrawal of a randomized subject, the subject should be called in for a final visit where procedures according to visit 7 should be performed and the pages covering visit 7 in the CRF had to be completed together with the End of Trial Form, the Affirmation Statement Form, the Drug Accountability Form and the CRF Accountability Form. If the subject was not able to attend, the End of Trial Form, the Affirmation Statement Form, the Drug Accountability Form and the CRF Accountability Form must be completed.

The following data could be recorded directly on the CRFs and was considered source data:

- Ethnic origin
- Sex
- Physical examination
- Height
- Vital signs

For all other data in the CRFs it must be possible to verify these against source documents. The subject's diaries were collected after each visit and kept as source data by the Investigator. The diary data were transcribed to the CRF and the monitor ensured the CRFs were collected.

6 Statistical Methodology

Statistical analysis was responsibility of the C.R.O. [redacted] ([redacted]). The statistical analysis was based on the Statistical Analysis Plan (SAP) written by Data Management, Novo Nordisk GmbH (Austria). It was approved, according to the current version of the internal Novo Nordisk procedure for preparation of the SAP, before the database release meeting.

All tests were two-sided. P-values below or equal to 0.05 were considered as statistically significant. Summary statistics and 95% confidence intervals (CI) were presented based on the estimates from the statistical model that was used.

Analyses were based on the ITT analysis set. It should be noted that the number of subjects in the ITT analysis set varied depending on the analysis. The reason for this is that a different number of subjects contributed with data for that particular analysis. Furthermore, different endpoints may have different restrictions for inclusion of data in the analysis.

All primary and secondary efficacy and safety analysis were based on the ITT analysis set. For supportive evidence, analysis on the primary efficacy variable was also performed on the PP analysis set.

In addition, if the number of subjects in the ITT and PP analysis set differed by more than 10%, the efficacy analyses and the analyses of hypoglycaemic episodes should be repeated for the PP analysis set. This was not the case in this trial and, therefore, these analyses were only performed for the ITT population.

6.1 Sample Size Calculations

Sample size calculations of this trial were based on weight change after 26 weeks of treatment. It was presumed that insulin detemir had a lower increase of weight than NPH insulin. In previous phase III trials with insulin detemir and NPH insulin the weighted standard deviation was 4 kg and the expected difference was 1.5 Kg. A sample size of 272 subjects in total, 230 evaluable subjects, randomized 1:1, would (with a drop-out rate of 15%) yield 136 subjects in insulin detemir group and 136 in the NPH insulin group for evaluation of weight change. This gave 80% of

power to detect a difference in weight change, after 26 weeks of treatment, of 1.5 kg, assuming that the standard deviation was 4.0 using a two-sided test with a 0.05 significance level. To randomise 272 subjects, a total of approximately 313 subjects should be screened (15% of screening failure rate).

6.2 Analysis Groups

Two analysis sets were defined in the protocol, the modified intention-to-treat (from now on referred to only as the intention-to-treat) and the per protocol analysis set. The definitions were as follows:

- Intention-to-treat (ITT) analysis set consisting of all randomized subjects exposed to at least one dose of trial product
- Per protocol (PP) analysis set consisting of all exposed subjects who completed the trial without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

A Randomized subject lost to follow up and where no information was available after the randomization visit was handled as unexposed.

Subjects fulfilling any of the following criteria were excluded from the PP analysis set:

- Violating any of the inclusion criteria
- Violating the exclusion criteria
- Violating the randomization
- Drop outs

Each deviation that led to exclusion of a subject from the PP analysis set was decided and documented before data was released for statistical analysis. This document is appended to the minutes of the data base release meeting. As explained in the protocol a review of all relevant data took place. The review was performed without revealing which treatment the subject was assigned to. The main reason for excluding a subject was included in the selected listings.

The primary analyses were also performed on the PP analysis set to verify the robustness of the conclusion based on the results from the ITT analysis set. Since the number of subjects in the ITT

and PP analysis sets did not differ by more than 10%, the secondary analyses were not repeated based on the PP analysis set (see Statistical Analysis Plan in Appendix VII).

6.3 Subject Disposition

The subject disposition was presented for each treatment group in terms of number of subjects and percentage (%):

- screened
- randomized
- exposed (in the ITT analysis set)
- withdrawn and the reason for withdrawal (AE, Ineffective therapy, Non-compliance, Other)
- completed
- in the PP analysis set.

Information on screening failures and withdrawals was included in the selected listings.

6.4 Baseline Comparability of Treatment Groups

Demographics and baseline characteristics were summarised using descriptive statistics for each treatment group and in total. No formal comparison between treatment groups was performed.

Baseline characteristics and demographics were recorded at screening (Visit 1) and randomization (Visit 2). If an item was recorded on both visits and if not otherwise specified, the value from the randomization visit was used when presenting the study population. Age and duration of diabetes were calculated based on the date when the informed consent was signed.

Demographics consisted of age, sex and ethnic origin. The following were reported as baseline characteristics: body weight, height, BMI, duration of diabetes, diabetic complications, physical examination, vital signs, fasting plasma glucose (FPG), funduscopy/fundusphotography, HbA_{1c}, haematology, biochemistry, glycosuria, fasting insulin, HCG serum, HOMA-IR, urine test and baseline insulin treatment.

Baseline insulin treatment was summarised as:

- Total and daily insulin doses (units and units/kg). A more detailed analysis (bolus and basal insulin) was not performed taking into account the wide variety of insulins used before randomization.
- Number of subjects receiving Metformin treatment.

The abnormal findings recorded at the physical examinations were included in the selected listings and the percentage with abnormal values was tabulated. Concomitant illnesses were coded using the medical dictionary for regulatory activities (MedDRA). The illnesses were included in the selected listings and summarised in a table based on the system organ class and preferred term.

Diabetes complications (retinopathy, neuropathy, nephropathy and macroangiopathy, including peripheral vascular disease) were presented in a separate table including the number of subjects and percentage (%) for each complication. The diabetes complications were captured both on the concomitant illness page and on a special case report form CRF whereof the latter was used for this table.

6.5 Trial Product Exposure

The first and last date of trial product was recorded on the last visit. If the subject was withdrawn and the last date of trial product was missing, the withdrawal date was used instead.
All subjects randomized to insulin Detemir or NHP were treated on OD basal regimen. Subjects should be withdrawn from the trial if they were not in acceptable metabolic control as judged by the investigator. The number and percent subjects exposed per treatment week was summarised for each treatment group and in total. These numbers corresponded to the population at risk in the analysis of the hypoglycaemic episodes.

Insulin doses were summarised using descriptive statistics - mean, SD, median, minimum and maximum-. Summaries were made in units and units per kilo body weight for basal and bolus insulins separately as well as dose ratios between the two.

The following was tabulated for each treatment group by visit:

- Total daily insulin dose (U for insulin Detemir and aspart, and international units IU for insulin NHP)
- Total daily dose per body weight (kg). The dose per kilo was calculated using the body weight at the corresponding visit. If the weight was missing for that visit the last non-missing weight was used.
- Daily dose ratios (% based on units and units/kg) basal vs. bolus

The distribution of the daily basal dose for each treatment group over time was graphically presented using box plots. Daily basal dose for each treatment group was compared at the end of trial.

Medications were coded using a drug dictionary. Medications which were ongoing at, or started after first date of trial product, were referred to as concomitant medications. These were included in the selected listings and summarised in a table based on the coded terms for each treatment group and in total.

6.6 Efficacy Analysis

6.6.1 Efficacy Endpoints

- The primary endpoint was Weight Change after 12 and 26 weeks of treatment.
- HbA_{1c} after 12 and 26 weeks of treatment.
- FPG after 12 and 26 weeks of treatment.
- 7-point plasma glucose profiles during the 26 weeks of treatment.
- Intra-variability of SMFPG after 26 weeks of treatment.
- Proportion of subjects reaching glycaemic control (HbA1c $\leq$ 7.0%) from baseline to 26 weeks.

- Proportion of subjects reaching targets for pre and postprandial glucose control (according to titration guidelines) from baseline to 26 weeks.

- To quantify the relationship between BMI and required dose of insulin Detemir.

- Treatment Satisfaction: percentage change in the questionnaire scores between baseline and week 26.

6.6.2 Efficacy Analysis

- **Weight Change after 12 and 26 weeks of treatment**

The primary objective of this trial was to compare insulin Detemir regimen with that of insulin NPH after 12 and 26 weeks of treatment as measured by weight in subjects with type 2 diabetes on a basal-bolus regimen with insulin aspart as bolus insulin.

Let $x_{Detemir}$ and x_{NPH} denote the mean weight after use of insulin Detemir and insulin NPH, respectively.

The aim of the analysis was to test whether the mean weight of the subjects between both treatments were statistically different from each other. Therefore the null-hypothesis and its alternative were:

H_0: $x_{Detemir} = x_{NPH}$
H_1: $x_{Detemir} \neq x_{NPH}$

The hypothesis was tested by fitting one-way analysis of covariance model (ANCOVA) to the primary endpoint with treatment as fixed effect and weight at baseline as a covariate. Differences in weight changes were attributable not only to differences among the treatments but also to the initial differences in baseline weight. To control this source of variation, the effect of the baseline weight was removed from the weight change by using the regression method. Then the F test could be performed on the adjusted weight changes. The ANCOVA assumed a linear relationship between the covariate and the weight change within both treatment group and there was no interaction between the covariate and treatments.

The primary analysis was performed on the ITT population. A normality test was performed to confirm normality assumption. A two-sided 95% confidence interval for the difference in the least square means (insulin Detemir- insulin NPH) and p-value was calculated based on the above model.

For supportive evidence analysis on the primary efficacy variable for the PP analysis set was also performed.

Presentation of Primary Endpoint

The results of the between group comparison was described by the mean difference in weight measurements, the corresponding 95% CI and p-value adjusted for the appropriate factors and covariates.

For each treatment group the following was presented:

- number of subjects included in the analysis
- mean baseline weight and standard deviation (SD)
- the estimated mean from the model and the standard error (SE) for weight after 26 weeks of treatment
- The estimated mean change in weight and SE.

Mean weight for each treatment were plotted versus time. Summary tables were made for weight at each visit for each treatment group and in total. The graphics and the summary tables were based on the raw means, LOCF (missing weight values at the end of the trial were extrapolated by LOCF approach from the closer data of missing after Visit 2).

Individual weight values were included in the selected listings.

- **HbA1c**

The aim of the analysis was to compare the glycaemic control of insulin Detemir with that of insulin NPH as measured by HbA_{1c} after 26 weeks of treatment.

Mean HbA_{1c} after 26 weeks of treatment was compared between the groups by fitting an ANCOVA, similar to that used for the primary efficacy endpoint, with treatment as fixed factor and

baseline HbA_{1c} as covariate. A 95% two-sided confidence interval was constructed for the difference between the means from the two treatment groups in comparison.

The same restrictions that were imposed on HbA_{1c} for the primary efficacy endpoint were applied and LOCF was used.

- **Fasting Plasma Glucose (g/L)**

The secondary endpoint, FPG, was analyzed at Visit 7, using an ANCOVA model with treatment as fixed effect and the corresponding baseline values as a covariate. A 95% two-sided confidence interval was constructed for the difference between the means from the two treatment groups in comparison.

- **Within-Subject Variation of Self-Measured Fasting Plasma Glucose**

The within-subject variation was measured as the CV (%) of the last six fasting BG measures performed by the subjects 4 weeks prior to Visits 2, 5 and 7.

The within-subject variation of values was compared between the two treatment groups using variance-component models.
The within-subject variation for each treatment was estimated by fitting a mixed effect model with subject as a random effect, treatment as fixed factor. The Restricted Maximum Likelihood (REML) estimation method was used to produce the variance components.
The test was carried out as a likelihood ratio test where the above model with a separate residual variance component for each treatment group was compared to a model where a common residual variance was fitted by computing -2 times the difference between their residual log likelihoods (-2RLL). Then this statistic was compared to the Chi square distribution with one degree of freedom ($\chi^2(1)$).

- **7-Point Plasma Glucose Profiles (mg/dL)**

The 7-point SMPG profiles were compared after 26 weeks of treatment.

The repeated measures ANOVA with treatment, time and treatment-by-time as fixed effects were used to compare the group means on PG (dependent variable) across repeated measurements of time. The time-point in the 7-point profile was referred to as the within-subjects factor, whereas a treatment was referred to as the between-subjects factor.

The between group comparison was made by investigating the mean PG change across the time-points and between Detemir and NPH. Furthermore, the treatment by time interaction which assess if the pattern of differences between mean plasma glucose rates for treatment groups change at each time-point was tested.

The covariance structure was modelled as 'unstructured' for each subject whereas independence was assumed across subjects. Models were compared using the likelihood ratio test.

- **HbA1c ≤ 7.0%**

The proportion of subjects that achieved HbA_{1c} below or equal to 7% was compared between the two groups using Fisher's exact test.

Furthermore, the proportion of subjects that achieved $HbA_{1c} \leq 7.0\%$ without having any symptomatic hypoglycaemia with a plasma glucose value <4.0 mmol/L or any single plasma glucose value <3.1 mmol/L in the last four weeks of treatment was investigated. The hypoglycaemic episode needed to fulfil the definition of a symptomatic episode that was made in the protocol and occur during the last month that the subject was on trial product. The proportions were compared using Fisher's exact test.

- **Pre and postprandial targets according to titration**

The proportion of subjects reaching pre and postprandial targets according to titration after 26 weeks of treatment was compared between treatment groups with a Fisher's Exact Test.

- **Relationship between BMI and required daily dose of insulin Detemir**

The relationship between change in BMI and change in daily dose was investigated in exploratory analyses. Furthermore, descriptive statistics and shift tables were made on the change in mean BMI after 26 weeks for each treatment group.

To measure the relationship between BMI and required daily dose of insulin Detemir, a nonparametric test (measure of association based on the rank of the data values, Spearmen rank-order correlation) was used because variables did not fit with normal distribution.

As this secondary point was applicable only to the Detemir group no formal comparison was made for the daily dose change and the change in BMI.

- **Treatment Satisfaction**

Efficacy endpoint was the percentage change in the questionnaire scores between baseline and week 26. The Medical Outcomes Study 36-Item Short-Form Health Survey SF-36v2 and the WHO-DTSQ were used to measure Treatment Satisfaction. The SF-36 questionnaire was used to measure generic aspects of health, whilst WHO-DTSQ was used as a disease-specific questionnaire for diabetes. These questionnaires have been translated and validated according to stringent methodology to ensure cross-cultural equivalence.
Subjects were asked to complete the questionnaire at Visits 2, 5 and 7. The two questionnaires were completed at the visit and returned in a sealed envelope to the site personnel.

SF-36v2

The SF-36 is a multi-purpose, short-form health survey with 36 items. The taxonomy has three levels: items, eight scales that aggregate 2-10 items each and two summary measures that aggregate scales. Each item has an ordinal response of 3 (scored on a scale of 1-3), 5 (scale of 1-5) or 6 (scale of 1-6) units. All but one of the 36 items (item 2) are used to score the eight scales and no item is used in more than one scale. The scale score of ten items (1, 6, 7, 8, 9a, 9e, 9d, 9h, 11b and 11d) are recoded prior computation to ensure that a higher item value indicate better health on all SF-36 items.

The items are summarised among the following scales (number of items and corresponding item number on SF-36). All scales except for PF and GH should cover the subjects' experience during the past four weeks of treatment.

- Physical Functioning (PF) (10, items 3a-3j)
- Role-Physical (RP) (4, items 4a-4d)
- Bodily Pain (BP) (2, items 7-8). The "Very mild", "Mild", "Moderate" and "Severe" responses in item 7 are recalibrated to achieve a better linear fit with the bodily point evaluation concept measured by the BP scale. Item 8 is recalibrated on the basis of the response to item 7.
- General Health (GH) (5, items 1, 11a-11d). The "Very Good" and "Good" responses in item 1 are recalibrated to achieve a better linear fit with the general health evaluation concept.
- Vitality (VT) (4, items 9a, 9g, 9e, 9i)
- Social Functioning (SF) (2, items 6, 10)
- Role-Emotional (RE) (3, items 5a-5c)
- Mental Health (MH) (5, items 9b-9d, 9f, 9h).

A raw scale score as the simple algebraic sum of the items responses in the scale was calculated. A scale score was calculated if a subject answered at least half of the items in a scale (or half plus one in the case of scales with an odd number of items). The missing values were replaced by the subject's scale mean. Scales where more missing values were seen than accepted were set to missing.

The following summary measures aggregated the eight scales:

- Physical Health (PHS) (4, scales PF, RP, BP, GH)
- Mental Health (MHS) (4, scales VT, SF, RE, MH).

The summary measures and the scale scores were transformed to a scale from 0 to 100, with higher scores indicating better treatment satisfaction. Scores between these values represent the percentage of the total possible score achieved. The summary score was calculated if all scales scores were non-missing.

WHO-DTSQ

The DTSQ contains 8 items scored on a 7-point Likert scale from 0 to 6. Each item should cover the subjects' experience during the past two weeks of treatment.

- Overall Treatment Satisfaction

Six items 1, 4, 5, 6, 7 and 8 are summed to produce a total treatment satisfaction score (range 0-36). Higher scores indicate better treatment satisfaction.

Two separate items measure the perceived imposition caused by hyperglycaemia and hypoglycaemia:

- 'Perceived frequency of hyperglycaemia'

Item 2 rated: 6 ('most of the time') to 0 ('none of the time'). Lower scores indicate blood glucose levels closer to the ideal.

- 'Perceived frequency of hypoglycaemia'

Item 3 rated: 6 ('most of the time') to 0 ('none of the time'). Lower scores indicate blood glucose levels closer to the ideal.

On subscales including five or more items one missing value was accepted and was replaced by that subject's subscale mean. Subscales where missing values were not accepted or where more missing values were seen than accepted were set to missing. The total score was calculated if all subscales scores were non-missing.

The change in SF-36 and DTSQ scores to week 26 was analyzed by fitting an ANCOVA model with treatment as fixed factor and the baseline score as a covariate.

6.6.3 Handling of Missing Data and Withdrawals

Missing observations were considered missing at random in the analysis.

Imputation of data was used in the following cases:

- When the treatment start or stop date was missing, incomplete dates were converted to complete dates by imputation of "January" if the month was missing or "1" if the date in the month was missing.

- Missing measurements at the end of the trial (after 26 weeks) were extrapolated by Last Observation Carried Forward (LOCF) from the closer data of missing after basal visit (V2). In case of missing baseline measurements (randomization, Visit 2), the corresponding measurements from the screening (Visit 1) were used.

6.6.4 Multiple Endpoints

No adjustment for multiplicity was needed, as the primary and secondary analyses were clearly identified as such, in advance of performing the analyses.

6.6.5 Interim Analyses

No interim analyses were performed.

6.7 Safety Analysis

6.7.1 Safety Endpoints

- **Hypoglycaemic Episodes**

Secondary endpoint was the incidence of hypoglycaemic episodes after 26 weeks. All episodes were categorised as either: major, minor or other. The category "other" was not defined in the protocol but included episodes that have missing values on data preventing episodes from being categorised. Episodes were defined as nocturnal if they occurred between 11:00 pm (included) and 6:00 am (excluded).

- **Lipid profile**

Secondary endpoint was the change of lipid scores between baseline and week 26.

- **Insulin resistance measured by the HOMA-IR**

Secondary endpoint was the insulin resistance change between baseline and week 26 measured by HOMA-IR index.

- **Adverse events**

Secondary endpoint was the incidence of Adverse Events after 26 weeks.

- **Laboratory Safety**

Blood samples for central analysis of haematology and biochemistry were taken at Visit 1 and 7 (-2 and 26 weeks after randomization) and on Visit 2 and 7 for lipids (0 and 26 weeks after

randomization). Haematology included haemoglobin, leucocytes, differential count if leucocytes abnormal and Thrombocytes. Biochemistry included creatinine, sodium, potassium, total protein, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALAT) and lactate dehydrogenase (LDH). Glycosuria was collected from a urine sample and measured at baseline and at the end of the study (Visits 2 and 7) by the central laboratory.

Laboratory values were compared to the relevant reference range and flagged as being below or above the range. Any clinical laboratory abnormalities regarded as clinically significant should be reported and handled as AE.

- **Physical Examination**

A general physical examination was carried out at Visits 1 and 7 including: cardiovascular system, respiratory system, gastrointestinal system, central and peripheral nervous system, musculoskeletal system and skin, according to local procedure. Any clinically significant deterioration since Visit 1 should be regarded as an Adverse Event.

- **Vital Signs**

Vital signs were measured at every Visit. Blood pressure and pulse were measured after resting in a sitting/supine position for five minutes.

- **Funduscopy or Fundusphotography**

Funduscopy or fundusphotography was performed at Visit 1.

6.7.2 Safety Analysis

- **Hypoglycaemic Episodes**

The incidence of hypoglycaemia occurring was compared between the groups after 26 weeks of treatment by estimating the relative risk of having a hypoglycaemic episode in the insulin Detemir group compared to the insulin NHP group.

The following categories of hypoglycaemic episodes were analyzed separately for 24h episodes and nocturnal episodes:

- all episodes
- Minor episodes.

Only a limited number of major hypoglycaemic episodes occurred during the treatment period. Therefore no statistical analysis was performed on this endpoint.

The incidence of hypoglycaemic episodes was divided into major and minor episodes, where minor episodes and symptoms only episodes were analyzed together. The incidence of hypoglycaemic episodes was compared between the groups by estimating the relative risk of having a hypoglycaemic episode in the insulin NPH group compared to the insulin Detemir group. The treatment emergent hypoglycaemic episodes were analyzed as recurrent events using a semiparametric proportional means model. This model was an extended Cox regression model with treatment as covariate. Also the relative risk was estimated based on time to the first episode by using an ordinary Cox regression model.

- **Lipid profile**

Lipid profile was analyzed at Visit 7, using an ANCOVA model with treatment as fixed effect and the corresponding baseline values as a covariate. A 95% two-sided confidence interval was constructed for the difference between the means from the two treatment groups in comparison.

- **Insulin resistance measured by the HOMA-IR**

The change in HOMA-IR score from baseline to Visit 7 was analyzed using an ANCOVA model with treatment as fixed effect and the corresponding baseline values as a covariate. A 95% two-sided confidence interval was constructed for the difference between the means from the two treatment groups in comparison.

- **Adverse Events**

AEs and SAEs emerging during the treatment period were summarised and presented. The incidence of AEs was compared between the groups by means of descriptive statistics. No formal statistical analysis was performed.

- **Laboratory Safety**

The laboratory safety parameters were compared between the groups by means of descriptive statistics. Only if suggested by the summaries, supplementary analyses were performed.

- **Vital Signs, Funduscopy or Fundusphotography**

Descriptive statistics for vital signs (change from baseline to final visit) and funduscopy/fundusphotography were presented. Subjects with only baseline data recorded were excluded from the summary statistics and the graphics aiming to illustrate change over time. No formal comparison was performed.

6.8 Changes to the Statistical Analysis Plan

The following deviations from the protocol were introduced in the SAP:

- It was suggested that centre should be included in the model as random effect. Since the number of centres was high and a limited number of patients were included at most centres, the centre effect was not investigated in any analysis.
- It was also suggested that metformin and diuretic treatment should be included in the model as fixed effects. These variables would be included in the model when substantial correlation with the treatment group (Detemir vs. NPH) is observed and a large reduction in the error SS may be achieved if these two factors are not ignored. Actually the randomization process had taken into account if the subject is taking or not metformin (stratification process) in order to have a similar proportion of subjects treated with that OAD in both groups of therapy (insulin Detemir + insulin aspart vs. insulin NPH + insulin aspart).
- No Quality of Life endpoints and analysis were suggested in the Protocol. A formal analysis of SF-36 and DTSQ endpoints was performed.

6.9 Software

SAS V 9.1 was the software used to perform the statistical analysis.

7 Subjects

7.1 Subject Disposition

A total of 277 patients were included (randomized) in this trial, 126 in the detemir group and 151 in the NPH. There were 68 screening failures. Reasons for screening failures are listed in Selected Listing 1. 258 patients (93.1%) completed the study. There were 19 subjects withdrawn from the study. Primary reasons were Non-compliance with protocol and "Other" reasons as listed below. Individual reasons for withdrawal are listed in Selected Listing 2. 2 subjects in the NPH group and 1 subject in the detemir group were withdrawn due to adverse events. Finally, 125 subjects were included in the ITT population for the detemir group and 146 in the NPH group. Corresponding figures for the PP population were 115 subjects in detemir group and 136 in NPH.

Table 7-1. Subject Disposition.

	Detemir N (%)	NPH N (%)	All N (%)
Screened			345
Randomized	126(45.5)	151(54.5)	277(100)
Withdrawals	7 (5.6)	12(7.9)	19(6.9)
Adverse Event	1 (0.8)	2(1.3)	3(1.1)
Ineffective therapy	0 (0.0)	2(1.3)	2(0.7)
Non-compliance with protocol	3 (2.4)	3(2.0)	6(2.2)
Other	3 (2.4)	5(3.3)	8(2.9)
Completers	119(94.4)	139(92.1)	258(93.1)
ITT analysis set (Exposed)	125(99.2)	146(96.7)	271(97.8)
PP analysis set	115(91.3)	136(90.1)	251(90.6)

7.2 Protocol Deviations and Violations

7.2.1 Important protocol deviations and violations

A total of 20 subjects of the ITT population were excluded from the PP analysis set. Individual reasons for exclusion from this population are listed in Selected Listing 4.

Patients who entered the study even though they did not satisfy the inclusion criteria

There were 4 patients ([redacted], [redacted], [redacted] and [redacted]) that did not satisfy one of the inclusion criteria.

Patients who entered the study even though they did not satisfy the exclusion criteria

There were 3 patients ([redacted], [redacted], [redacted]) that did not met one of the exclusion criteria

Patients who received the wrong treatment

There was a patient assigned to insulin detemir at randomization who was treated with insulin NPH for two weeks during hospitalisation for an adverse event. This patient was excluded from ITT population for the Statistical analysis.

7.2.2 Minor protocol deviations and violations

The following minor procedural deviations occurred at some time during the trial. None of these deviations were considered as having any major impact on the outcome of the trial:

• The time windows between visits were exceeded in a number of cases.

• Some measurements were not performed at some visits, as specified in the protocol.

7.3 Demographic and Other Baseline Characteristics

The following table summarises the main baseline characteristics of patients assigned to both arms of treatment (insulin detemir and insulin NPH). Individual subject characteristics are listed in Selected Listing 3. Both populations were fairly comparable in these variables. Other baseline characteristics (Lipid profile, laboratory values, diabetic complications, concomitant illness, vital signs, physical examination at baseline, Funduscopy results) are listed in EOT Tables section 2.

Table 7-2 Demographic and other baseline characteristics

	Detemir	NPH	All
ITT analysis set (N)	125 (100.0)	146 (100.0)	271 (100.0)
Sex (N (%))			
Male	47 (37.6)	63 (43.2)	110 (40.6)
Female	78 (62.4)	83 (56.8)	161 (59.4)
Ethnic Origin (N (%))			
Asian/Pacific Islander	0 (0.0)	1 (0.7)	1 (0.4)
Hispanic	1 (0.8)	0 (0.0)	1 (0.4)
White	124 (99.2)	145 (99.3)	269 (99.3)
Age (years)			
Mean (SD)	62.06(9.25)	61.79 (8.26)	61.92(8.72)
Median	62.00	62.00	62.00
Weight (kg)			
Mean (SD)	79.45 (11.9)	82.23(12.2)	80.94 (12.1)
Median	78.10	83.20	80.50
Height (m)			
Mean (SD)	1.59 (0.09)	1.60 (0.08)	1.59 (0.08)
Median	1.58	1.61	1.60
BMI (kg/m^2)			
Mean (SD)	31.61(4.25)	32.02(4.17)	31.83(4.20)
Median	31.74	31.79	31.75
Duration of diabetes (years)			
Mean (SD)	16.18(8.69)	16.40(7.43)	16.30(8.02)
Median	15.00	16.00	16.00
FPG (g/L)			
Mean (SD)	1.94(0.63)	1.82(0.65)	1.87(0.64)
Median	1.98	1.79	1.88
HbA1c (%)			
Mean (SD)	8.85(0.87)	8.78(0.96)	8.81(0.92)
Median	8.90	8.65	8.80

The last available value before randomization is presented for Weight, HbA1c and FPG

Baseline Physical Examination, Vital Signs, Clinical Laboratory Tests and Diabetic Complications

Overall, there were no noteworthy differences between the two treatment groups with respect to baseline physical examination, vital signs, clinical laboratory tests or diabetic complications, though a formal comparison was not performed.

Physical Examination

The proportion of abnormal findings at the baseline physical examination was similar in the two treatment groups (see EOT Table 2.3). Abnormal findings were infrequent. Most abnormal findings in both groups were related to the skin (5.6% of subjects in the insulin detemir group and 5.5% of subjects in the NPH insulin group) or musculoskeletal system (4% in detemir group and 6.2% in NPH). Individual abnormal findings are listed in Selected Listing 5.

Vital Signs

No major differences were observed between the two treatment groups at baseline with respect to blood pressure or pulse. Mean blood pressure of the trial population was 142/78 mmHg and mean pulse was 80 b.p.m. (EOT Table 2.2).

Clinical Laboratory Test/ Funduscopy-Fundusphotography

The clinical laboratory test values and results of Funduscopy-Fundusphotography were very similar in the two treatment groups at baseline (EOT Tables 2.4 to 2.9).

Diabetic Complications

Diabetic complications were not uncommon due to the mean duration of diabetes (16 years) of the subjects included in this trial. 43.1% of subjects in NPH group had diabetic retinopathy vs. 35.2% in the detemir group (difference not statistically significant; p=0.182). Corresponding figures for neuropathy, nephropathy and macroangiopathy were 12.8, 13.6 and 14.4% in the detemir group and 13.7, 8.9 and 17.1% in the NPH group respectively (EOT Table 2.10).

Concomitant Medication and Illness

A variety of concomitant illnesses were reported at baseline in both treatment groups. Vascular disorders (mostly Hypertension), Metabolism and nutrition disorders (dyslipidemia) and eye disorders (diabetic retinopathy) were among the most frequent group of illnesses reported (EOT Table 2.11 and Selected Listing 7).

Most of the subjects in both treatment groups used a variety of concomitant medications during the trial (Selected Listing 9). The most frequent concomitant medications used in both treatment groups (at baseline and during the trial) were acetylsalicylic acid (39.1% of the subjects) and statins or antihypertensive drugs (see EOT Table 3.16 and Selected Listing 9). None of the concomitant medications reported for either treatment group were considered likely to affect the outcome of the efficacy analyses.

Pre-trial Insulin and Metformin Regimen and Dosing

Due to the large variety of insulin preparations (including human insulin and insulin analogues as separate injections and pre-mixed preparations) and injection regimens used before the start of the trial, only a brief description is given in terms of total daily insulin in U and U/kg in both groups of treatment. 50.4% of the patients assigned to detemir were treated at baseline also with metformin vs. 57.55% of the subjects in the NPH group (See EOT Tables 2.12 to 2.14). The mean pre-trial daily dose of basal insulin per kg body weight and metformin (in those treated with that OAD) prior to randomization was similar in both treatment groups;

8 Extent of Exposure

8.1 Exposure to Trial Drug

The extent of exposure to insulin detemir was similar to that of NPH insulin. Approximately 97% of subjects in both treatment groups were exposed to trial products for more than 18 weeks; Mean duration of exposure was similar in both groups (177 ± 27.5 days in detemir group and 178 ± 24.5 days in the NPH group); see EOT Table 3.14 and 3.15.

8.2 Insulin Doses

According to protocol the starting dose of basal insulin (detemir or NPH) should be 40% of the total dose of insulin that the patient was receiving the day before randomization. Mean starting dose of both basal insulins was very similar: insulin NPH 22.8 ± 7.8 UI (0.3 ± 0.1 UI/kg) vs. 23.6 ± 8.6 U (0.3 ± 0.1 U/kg) for insulin detemir. All subjects were then individually titrated according to pre-specified plasma glucose targets. The mean daily basal insulin dose per kg body weight at the end of trial was significantly higher (p=0.0026) in the detemir group (47.5 ± 21.3 U or 0.6 ± 0.2 U/kg) than in the NPH insulin group (39.3 ± 16 IU or 0.5 ± 0.2 IU/kg) .See Figure 8–1 and 8-2 and EOT Table 3.6 to 3.9.

Figure 8-1. Mean Daily Basal Insulin Dose (U or IU) over Time

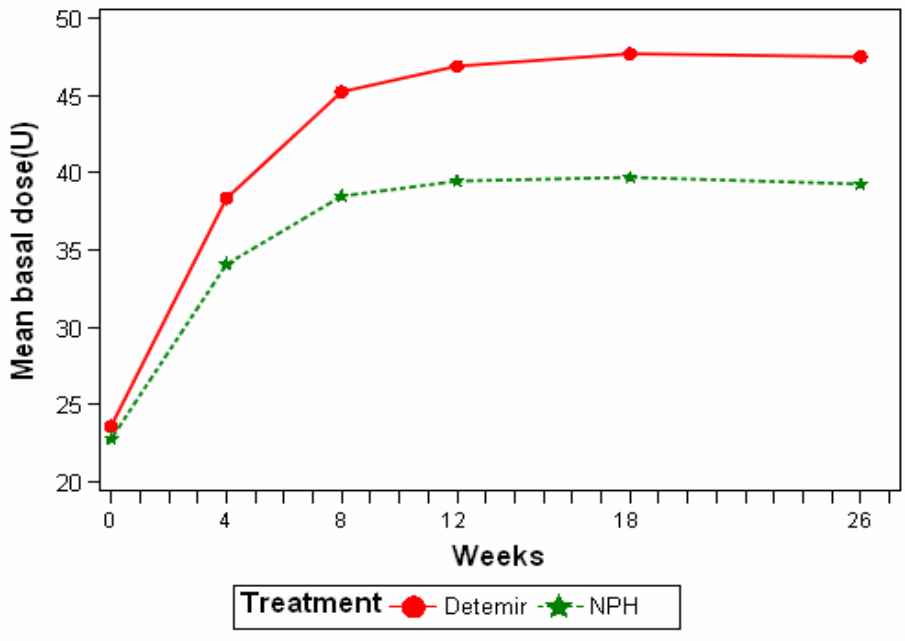
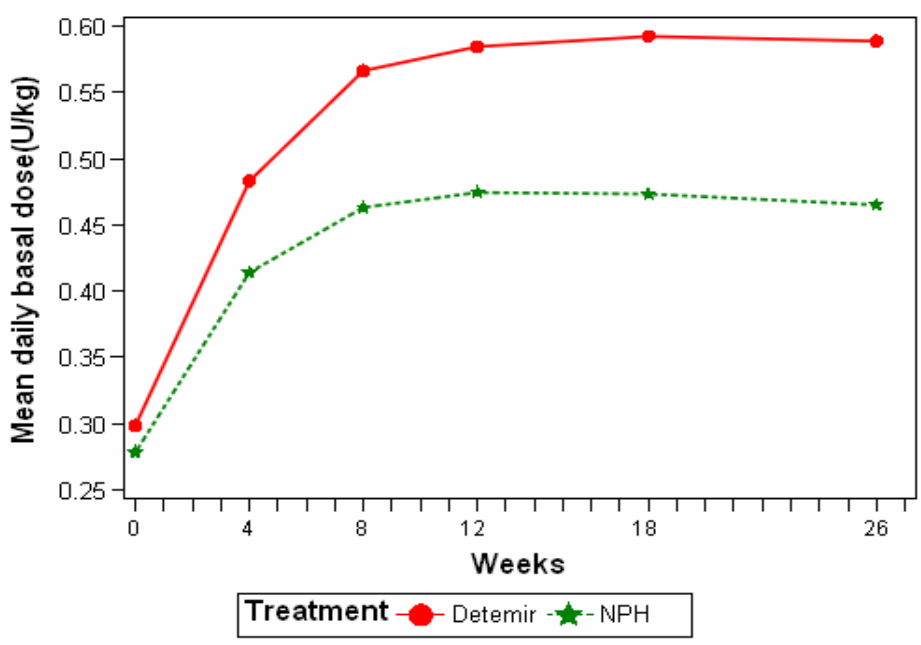
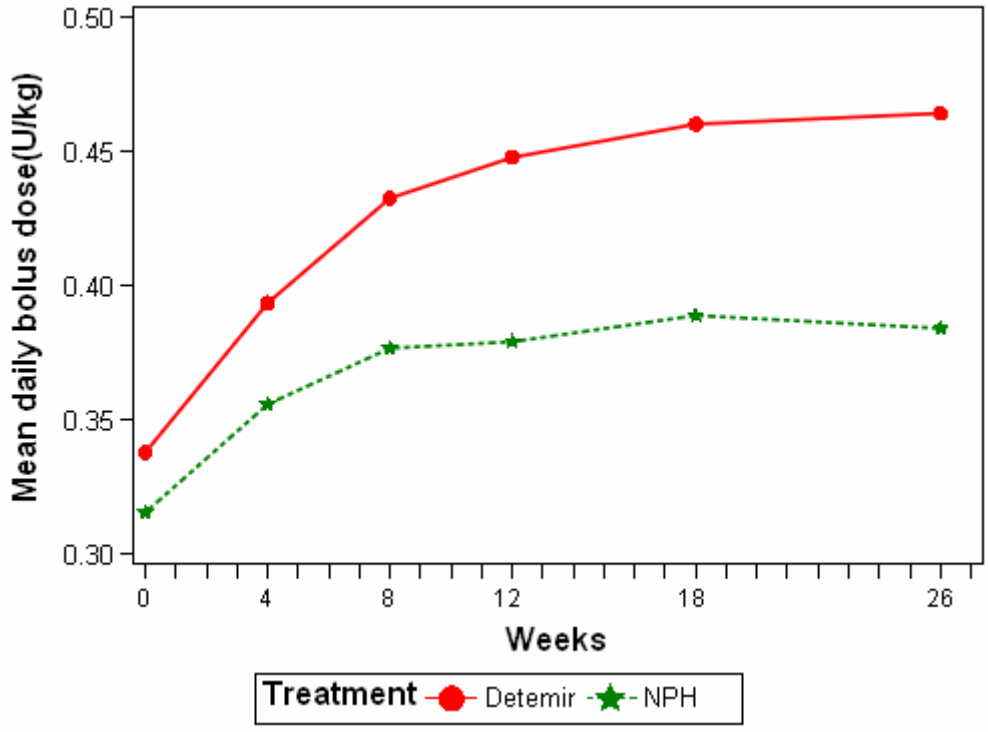


Figure 8-2. Mean Daily Basal Insulin Dose by Body Weight (U/kg) over Time



The mean daily bolus insulin dose per kg body weight was also slightly higher during the trial in the detemir group as shown in Figure 8-3 (see also EOT Figure 1.3 and EOT Tables 3.10 and 3.11)

Figure 8-3. Mean Daily Bolus Insulin Dose (U/kg) by kg Body Weight over Time



In accordance with these data total daily insulin doses were also higher during the trial in the detemir group: 1.05 ± 0.4 U/kg vs. 0.8 ± 0.3 IU/kg in NPH group (see also EOT Tables 3.1 to 3.3)

8.3 Compliance to Trial Drug

Compliance to the trial products was not collected as part of this trial.

9 Efficacy Evaluation

9.1 Data Sets Analyzed

All the primary and secondary efficacy analyses were based on the ITT analysis set. Since the number of subjects in the ITT and PP analysis sets did not differ by more than 10%, only the primary efficacy analyses were repeated based on the PP analysis set (see Section 6.2). The PP analyses were considered as supportive evidence.

9.2 Primary Efficacy Analysis

The primary objective of the trial was to compare the weight change during 26 weeks of treatment with insulin detemir versus NPH insulin in obese or overweight type 2 diabetic subjects. After 12 and 26 weeks of treatment, subjects in the NPH group experienced a significantly higher weight gain than those assigned to detemir as shown in Tables 9-1 and 9-2 (see also EOT Table 4.5) and Figures 9-1 and 9-2.

Table 9-1. Weight (kg) change after 12 Weeks of Treatment

Detemir		NPH		Detemir - NPH		
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
125	-0.02 (0.221)	146	1.09 (0.204)	-1.11	(-1.710 , -0.520)	0.0003

The analysis is one-way ANCOVA on Weight after 12 and 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline Weight value. Mean and SE are estimated from the model; CI: Confidence interval; p-value: test for fixed effect.

Table 9-2. Weight (kg) change after 26 Weeks of Treatment

Detemir		NPH		Detemir - NPH		
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
125	0.42 (0.283)	146	1.94 (0.262)	-1.52	(-2.82 , -0.758)	0.0001

The analysis is one-way ANCOVA on Weight after 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline Weight value. Mean and SE are estimated from the model; CI: Confidence interval; p-value: test for fixed effect.

Similar results were obtained in the PP set analyses (see EOT Tables 4.3 and 4.4).

Figure 9-1 Mean Body Weight (kg) over Time

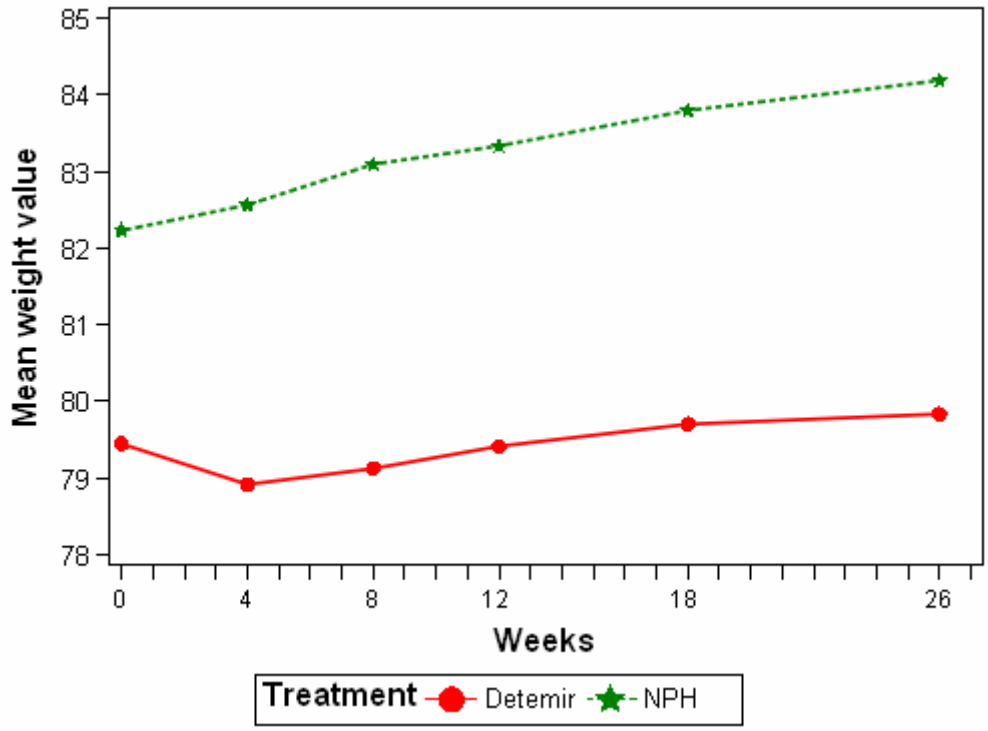
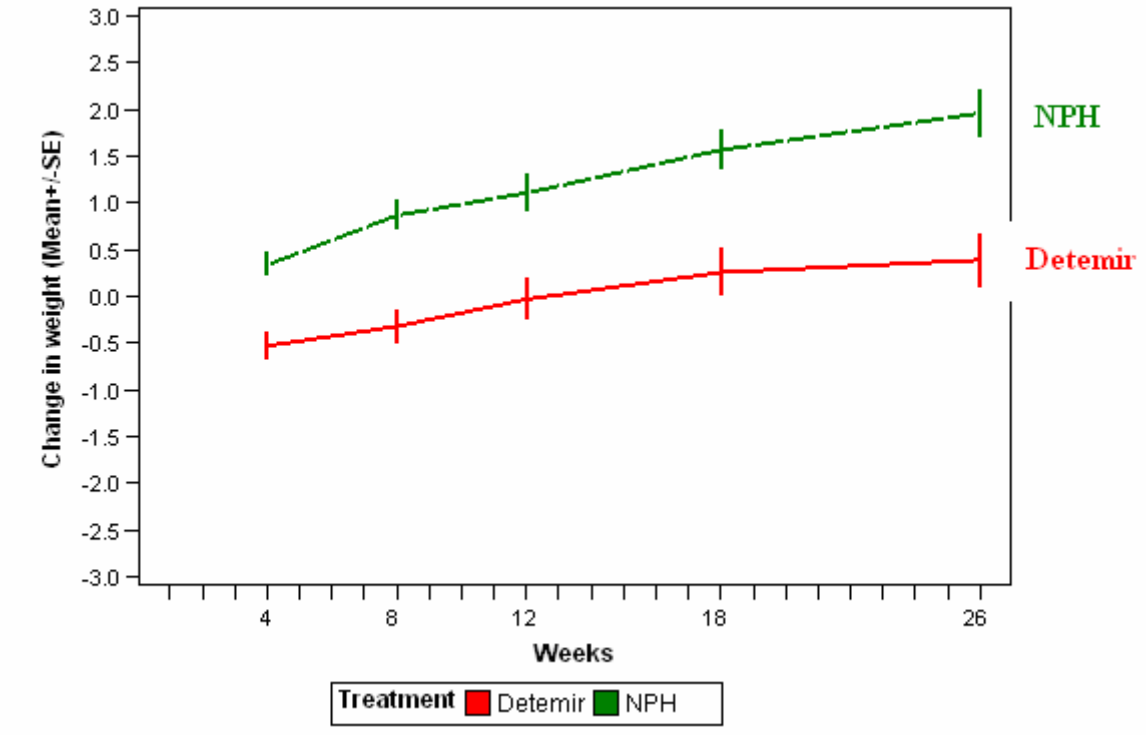


Figure 9-2 Change in Body Weight (kg) from Baseline over Time (Mean±SE)



When Change in BMI was compared between both treatment arms similar results were obtained, as shown in Table 9-3

Table 9-3. BMI (kg/m2) Change after 26 Weeks of Treatment

	Detemir		NPH		Detemir - NPH	
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
123	0.165 (0.110)	143	0.767 (0.102)	-0.60234	(-0.898255, -0.306393)	<0.0001

The analysis is one-way ANCOVA on BMI after 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline BMI value. Mean and SE are estimated from the model; CI: Confidence interval; p-value: test for fixed effect.

9.3 Secondary Efficacy Analyses

9.3.1 HbA1c after 12 and 26 weeks of treatment

A similar metabolic control was achieved in both groups of treatment measured through HbA1c values as shown in Tables 9-4, 9-5 and 9.6 (see also EOT Table 4.9 and EOT Figure 2.11).

Table 9-4. HbA1C after 12 Weeks of Treatment (%)

	Detemir		NPH		Detemir - NPH	
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
122	8.01 (0.077)	145	7.92 (0.071)	0.0086940	(-0.119566, 0.293446)	0.4079

The analysis is a one-way ANCOVA on HbA1C after 12 and 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline HbA1C value. Mean and SE are estimated from the model;

Table 9-5. HbA1C after 26 Weeks of treatment (%)

	Detemir		NPH		Detemir - NPH	
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
122	7.80 (0.089)	145	7.82 (0.082)	-0.02	(-0.260824, 0.216818)	0.8562

The analysis is a one-way ANCOVA on HbA1C after 12 and 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline HbA1C value. Mean and SE are estimated from the model; CI: Confidence interval; p-value: test for fixed effect.

Table 9-6. Change in HbA1C from baseline after 26 Weeks of treatment

	Detemir		NPH		Detemir - NPH	
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
122	1.01 (0.089)	145	0.99 (0.082)	0.02	(-0.216818, 0.260824,)	0.4446

The analysis is a one-way ANCOVA on HbA1C after 12 and 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline HbA1C value. Mean and SE are estimated from the model;

9.3.2 Fasting Plasma Glucose (FPG) after 12 and 26 weeks of treatment

No significant differences were found between both groups of treatment in terms of Fasting Plasma Glucose values at the end of trial, as shown in table 9-7 (see also EOT Tables 4.10, 4.11, 4.12 , 4.14, 4.15 and EOT Figure 2.12). In both treatment arms FPG values decreased from baseline to the end of trial.

Table 9-7. Statistical Analysis of Fasting Plasma Glucose (mg/dl) after 26 Weeks of Treatment

Detemir		NPH		Detemir - NPH		
N	Mean (SE)	N	Mean (SE)	Mean	95%CI	p-value
124	156.81 (4.63)	146	161.59 (4.26)	-4.78	(-17.1989, 7.6326)	0.4488

The analysis is a one-way ANCOVA on FPG after 26 weeks of treatment with treatment as fixed effect and covariate adjustment for baseline FPG value. Mean and SE are estimated from the model; CI: Confidence interval; p-value: test for fixed effect.

9.3.3 Within-Subject Variation of Self-Measured Fasting Plasma Glucose

A lower within-subject variability of self-measured FPG was found in the detemir group compared with NPH regimen as shown in Table 9-8.

Table 9-8. Within-Subject Variation of Self-Measured Fasting Plasma Glucose (mg/dL)

Treatment Group	N	Mean	SD	(CV%)	p-value
Detemir	1753	142.75	47.58	(33.33)	
NPH	2037	146.48	50.54	(34.50)	
					<0.0001

Six measurements of Self-measured plasma glucose taken at home in the morning two times a week within a period of 4 weeks before the actual Visit. CV: Coefficient of variation

Mean, SE (standard error), Estimated by the mixed model

Treatment Group	N	Mean	SE	(CV%)	p-value
Detemir	1753	143.75	2.54	()	
NPH	2037	147.12	2.35	()	
					<0.0001

The analysis is a mixed model including treatment as fixed effect and subject as a random effect. p-value: Likelihood ratio test for the model with a common residual variance component for each treatment group, against the alternative model with varying residual variance components.

9.3.4 7- point Self-Measured Plasma Glucose Profiles (mg/dl) after 26 weeks of treatment

No significant difference (p = 0.2527) was found in this parameter between both treatment groups as shown in Table 9-9 (see also EOT Table 4.17 and EOT Figure 2.13)

Table 9.9 7-point Self-Measured Plasma Glucose Profiles (mg/dL) after 26 Weeks of Treatment

	Detemir Mean (SE)	NPH Mean (SE)	Detemir - NPH Mean 95%CI	p-value
Determir vs NPH	162.46(3.28)	157.30(3.07)	5.16 (-3.701 , 14.012)	0.2527*
Time-point				<0.0001**
Before Breakfast	135.23(3.71)	138.63(3.48)	-3.97(-13.417 , 6.623)	
90 Min. after Breakfast	163.45(5.44)	170.37(5.08)	-6.92(-21.585 , 7.743)	
Before Lunch	138.39(4.68)	140.80(4.38)	-2.41(-15.033 ,10.208)	
90 Min. after Lunch	167.43(5.27)	160.04(4.95)	7.39(-6.848 ,21.624)	
Before Dinner	178.54(5.34)	161.06(5.00)	17.48(3.070 ,31.895)	
90 Min. after Dinner	195.22(6.11)	182.51(5.66)	12.71(-3.696 ,29.112)	
At 3:0 A.M.	158.93(5.06)	147.69(4.81)	11.24(-2.514 ,24.993)	
Treatment*time-point				0.0737***
Test for Reduction of Variance Structure				<0.0001****

The analysis is a two-way repeated measures ANOVA on SMPG after 26 weeks of treatment with treatment (between-subject factor), time (within-subject factor) and treatment-by-time interaction as fixed effects.
*p-value of between-subject main effect (difference in treatment);
**p-value of within-subject main effect (difference over time);
***p-value of time by treatment group interaction effect

****p-value for null model likelihood ratio, indicating that the unstructured covariance matrix is preferred to the diagonal one of the ordinary least-squares null model.

9.3.5 Pre and postprandial targets according to titration

The percentage of patients that, after 26 weeks of treatment, achieved the preprandial (≤110 mg/dl or 6.1 mmol/L) and postprandial targets (≤ 180 mg/dl or 10 mmol/L) as defined per protocol, was similar in both groups (12.9% with detemir vs. 10.3% with NPH; p=0.5681), as shown in table 9-10. See also EOT Table 4.21.

Table 9-10. Subjects that Achieved Pre and Postprandial Targets after 26 Weeks of Treatment

	Detemir N (%)	NPH N (%)	p-value
ITT population	124(100.00)	145 (100.00)	
Non Responders	108(87.10)	130 (89.66)	
Responders	16 (12.90)	15 (10.34)	0.5681

Target value of preprandial glucose (before breakfast): 110 mg/dl (≤ 6.11 mmol/l). Target value of postprandial glucose (90 minutes after each main meal): 180 mg/dl (≤ 10 mmol/l).

The analysis is a Fisher's Exact Test.
Responders are subjects that achieved pre and postprandial targets according to titration.

9.3.6 Subjects that achieved HbA1c ≤ 7%

The percentage of patients that achieved the target of HbA1c ≤ 7% (without having any symptomatic hypoglycaemia with a plasma glucose value < 4.0 mmol/L or any single plasma glucose value < 3.1 mmol/L in the last four weeks of treatment) at the end of the trial was similar in both groups: 21.8 % in the detemir group vs. 18.5% in the NPH group (p = 0.5). See also EOT Tables 4.22 and 4.23.

9.3.7 Relationship between BMI (kg/m2) and Daily Detemir Dose (Week 26)

There was a significant association between BMI and daily Detemir dose as shown below.

Table 9-11. Relationship between BMI (kg/m2) and Daily Detemir Dose (Week 26)

	Detemir
Visit 7 (26 weeks)	
N	121
Spearman correlation	0.43801
p-value	<0.0001

The analysis of association between BMI and Daily Dose of Detemir is based upon a Spearman rank-order correlation by lack of normality.

Figure 9-3. Scatter Plot BMI vs Daily dose Detemir (Week 26)

9.3.8 Treatment satisfaction and quality of life

Quality of life was analyzed by means of the SF-36 scale and compared between both insulin regimens after 12 and 26 weeks of treatment. No significant differences were found in any of the scales or subscales of this questionnaire (see EOT Tables 4.26, 4.27, 4.28, 4.29, 4.32 and EOT Figures 2.17 to 2.26).

With respect to treatment satisfaction (measured by the DTSQ) a significant difference favouring detemir was found after 26 weeks of treatment. Subjects in the detemir group showed a better treatment satisfaction than subjects of the NPH group. Nevertheless, perceived frequency of hyper and hypoglycemia was similar in both groups. See Table 9-12, EOT Table 4.30 and 4.33 and EOT Figures (2.27, 2.28 and 2.29)

Table 9-12. DTSQ Score after 26 Weeks of Treatment, ITT

Detemir		NPH		Detemir - NPH	
N	Mean (SE)	N	Mean (SE)	Mean 95% CI	p-value
Treatment Satisfaction					
104	30.0 (0.62)	125	28.0 (0.56)	1.98 (0.33, 3.63)	0.0190
Perceived frequency of hyperglycaemia					
111	2.31 (0.16)	134	2.57 (0.14)	-0.25 (-0.68, 0.17)	0.2366
Perceived frequency of hypoglycaemia					
112	1.76 (0.16)	133	2.07 (1.41)	-0.31 (-0.73, 0.10)	0.1407

The analysis is based upon an ANOVA model with treatment as fixed effect and baseline value as a covariate. Mean and SE are estimated from the model. CI: Confidence interval

9.4 Summary of Efficacy Results

Weight gain was significantly lower after 12 (mean difference -1.11 Kg [-1.71,-0.52] 95% IC; p=0.0003) and 26 (mean difference -1.52 Kg [-2.82,-0.76]; p=0.0001) weeks of treatment in the detemir group than in the NPH group (Both for ITT and PP populations). Metabolic control (measured through HbA1C, fasting plasma glucose levels, 7-point self measured plasma glucose profiles at the end of trial, percentage of patients with HbA1C ≤ 7% and % of patients that achieved pre and postprandial targets at the end of the study) was similar in both treatment groups. Within subject variation of self-measured fasting plasma glucose was significantly lower in the detemir group. Quality of life was also similar in both groups. Treatment satisfaction was better in detemir group after 26 weeks of treatment. Insulin doses were higher in the detemir group at the end of trial.

10 Safety Evaluation

10.1 Safety analysis

All subjects who were exposed to at least one dose of trial product (ITT) were included in the safety analyses: 125 subjects in the insulin detemir group and 146 subjects in the NPH insulin group.

10.2 Adverse Events

10.2.1 Overview of Adverse Events

The overall frequency and severity of treatment emergent adverse events are summarized in the Table 10–1. See also EOT Table 5.16 for TEAEs coded by System Organ Class.

Table 10-1. Summary of Treatment Emergent Adverse Events (TEAE)

	Detemir			NPH		
	N	(%)	E	N	(%)	E
ITT analysis set (N)	125			146		
All Adverse Events	58	(46.40)	91	45	(30.82)	73
Serious Adverse Events	4	(3.20)	6	4	(2.74)	4
Relation to Basal product						
Probable	2	(1.60)	2	0	(0)	0
Possible	1	(0.80)	1	1	(0.68)	1
Unlikely	51	(40.80)	78	44	(30.14)	67
Severity						
Mild	50	(40.00)	75	39	(26.71)	59
Moderate	10	(8.00)	13	12	(8.22)	14
Severe	2	(1.60)	3	0	(0)	0
Adverse Events Withdrawals	1	(0.80)	1	0	(0)	0

N: Number of subjects with adverse event
%: Proportion of subjects having adverse event
E: Number of adverse events

Most of adverse events had an unlikely relation to basal product (detemir or NPH) and were mild or moderate in severity. Incidence of Serious Adverse Events was similar in both groups of treatment (6 events in the detemir group and 4 in the NPH).

The most frequently reported adverse event was Nasopharyngitis (10.4% in detemir group and 8.2% in NPH group). For more details of other TEAEs with an incidence < 5% see EOT Tables 5.18, 5.19 and 5.20. Details for individual treatment emergent adverse events are listed by subject in Selected Listing 13.

10.2.2 Adverse Events by Relation to Trial Product

The Table 10-2 summarizes the relationship of the adverse events with the trial products as judged by the investigators. Only 1 adverse event was considered as possibly related with the basal product (insulin detemir or NPH) in both groups of treatment and 2 adverse events were considered as probably related with trial drug in the detemir group. These adverse events are listed in Table 10-3.

Table 10-2. Summary of TEAE Relation to Trial Drug as Judged by Investigator

		Detemir			NPH		
Trial products	**Relation**	**N**	**%**	**E**	**N**	**%**	**E**
Relation to any product	Missing	9	(7.2)	10	5	(3.4)	5
	POSSIBLE	1	(0.8)	1	1	(0.7)	1
	PROBABLE	2	(1.6)	2	1	(0.7)	1
	UNLIKELY	51	(40.8)	78	44	(30.1)	66
Relation to basal product	Missing	9	(7.2)	10	5	(3.4)	5
	POSSIBLE	1	(0.8)	1	1	(0.7)	1
	PROBABLE	2	(1.6)	2	.	.	.
	UNLIKELY	51	(40.8)	78	44	(30.1)	67
Relation to bolus product	Missing	9	(7.2)	10	5	(3.4)	5
	POSSIBLE	2	(1.6)	2	1	(0.7)	1
	PROBABLE	.	.	.	1	(0.7)	1
	UNLIKELY	52	(41.6)	79	44	(30.1)	66

Table 10-3. TEAEs Probably or Possibly Related to Trial Product by System Organ Class

		Detemir			NPH		
System Organ Class	**Adverse Event**	**N**	**%**	**E**	**N**	**%**	**E**
Cardiac disorders	Cardiac failure	.	.	.	1	(0.7)	1
General disorders and administration sit	Injection site erythema	1	(0.8)	1	.	.	.
Respiratory, thoracic and mediastinic disorders	Nasopharyngitis	1	(0.8)	1	.	.	.
Skin and subcutaneous tissue disorders	Pruritus	1	(0.8)	1	.	.	.

10.3 Deaths, Other Serious Adverse Events and Other Clinically Relevant Adverse Events

10.3.1 Deaths

No deaths were reported during the trial.

10.3.2 Other Serious Adverse Events

There were 6 Serious adverse events (SAEs) in 4 patients of the detemir group vs. 4 SAEs in 4 patients of the NPH group. Relation with basal insulin was considered unlikely in all of them.

Table 10-4. Summary of Treatment Emergent Serious Adverse Events (TESAE)

	Detemir			NPH		
	N	(%)	E	N	(%)	E
ITT analysis set (N)	125			146		
All Serious Adverse Events	4	(3.20)	6	4	(2.74)	4
Relation to Basal product						
Probable	0	(0.0)	0	0	(0.0)	0
Possible	0	(0.0)	0	0	(0.0)	0
Unlikely	4	(3.20)	6	4	(2.74)	4
Severity						
Mild	2	(1.60)	2	0	(0.0)	0
Moderate	1	(1.30)	1	4	(2.74)	4
Severe	2	(1.60)	3	0	(0.0)	0
Adverse Events Withdrawals	1	(1.30)	2	0	(0.0)	0

N: Number of subjects with adverse event
%: Proportion of subjects having serious adverse event
E: Number of adverse events

Table 10-5. Treatment Emergent Serious Adverse Events (TESAEs) by System Organ Class

		Detemir			NPH		
System Organ Class	**Adverse Event**	**N**	**%**	**E**	**N**	**%**	**E**
Cardiac disorders	Myocardial infarction	1	(0.8)	1	.	.	.
	Myocardial ischaemia	1	(0.8)	1	.	.	.
Eye disorders	Retinal detachment	.	.	.	1	(0.7)	1
Gastrointestinal disorders	Abdominal pain	1	(0.8)	1	.	.	.
General disorders and administration sit	Chest pain	1	(0.8)	1	.	.	.
Infections and infestations	Cellulitis	.	.	.	1	(0.7)	1
Musculoskeletal and connective tissue di	Ankle fracture	.	.	.	1	(0.7)	1
Nervous system disorders	Ischaemic stroke	1	(0.8)	1	.	.	.
Respiratory, thoracic and mediastinal di	Pulmonary embolism	1	(0.8)	1	.	.	.
Vascular disorders	Hypertensive crisis	.	.	.	1	(0.7)	1

SOC: System Organ Class; N: Number of subjects with adverse event; %: Proportion of subjects in analysis set having adverse event; E: Number of adverse events

Table 10-5 shows the system organ class classification of the Serious adverse events, being cardiac disorders the most frequent in the detemir group.

10.4 Hypoglycemic episodes

10.4.1 Overview of Hypoglycemia

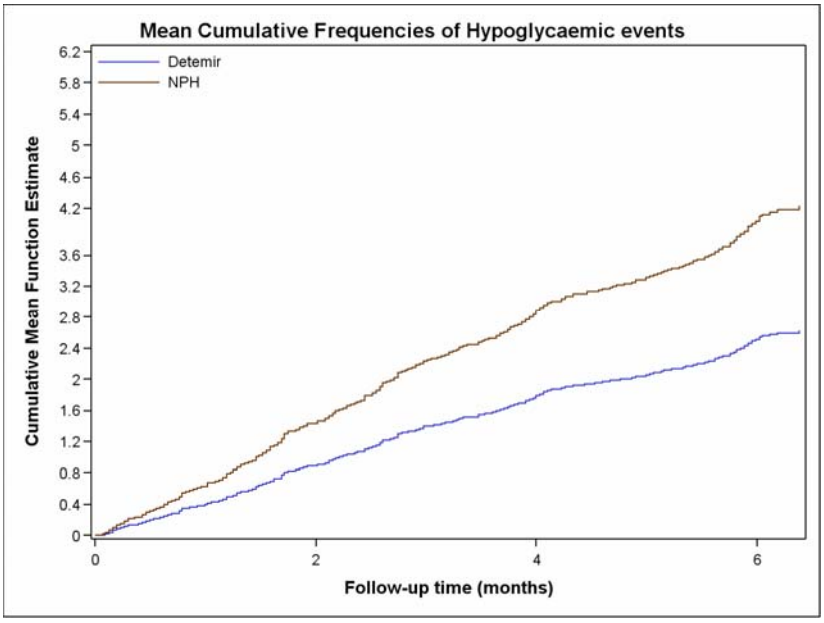
Table 10-6. Analysis of treatment emergent hypoglycemic episodes

	HR	(95% CI)	p-value
Major	NA	(NA; NA)	NA
Minor	1.66	(1.42; 1.95)	< 0.0001
Other	0.62	(0.25; 1.56)	0.3126
All	1.61	(1.377; 1.884)	<0.0001

The analysis is based on Cox regression model for recurrent events with treatment as fixed covariate. HR (Hazard Ratio): Ratio of incidence rates (NPH/Detemir); p-value: test for homogeneity of risk rations among treatment groups.

The probability of having an hypoglycaemic episode during the treatment period was significantly higher in the NPH group (HR: 1.61 [1.38;1.88] 95% IC; p <0.0001). This applied for all hypoglycemic episodes and for minor episodes. Incidence of major hypoglycemic events as defined per protocol was so low that did not permit a formal comparison between groups.

Figure 10-1. Mean Cumulative frequencies of hypoglycemic events



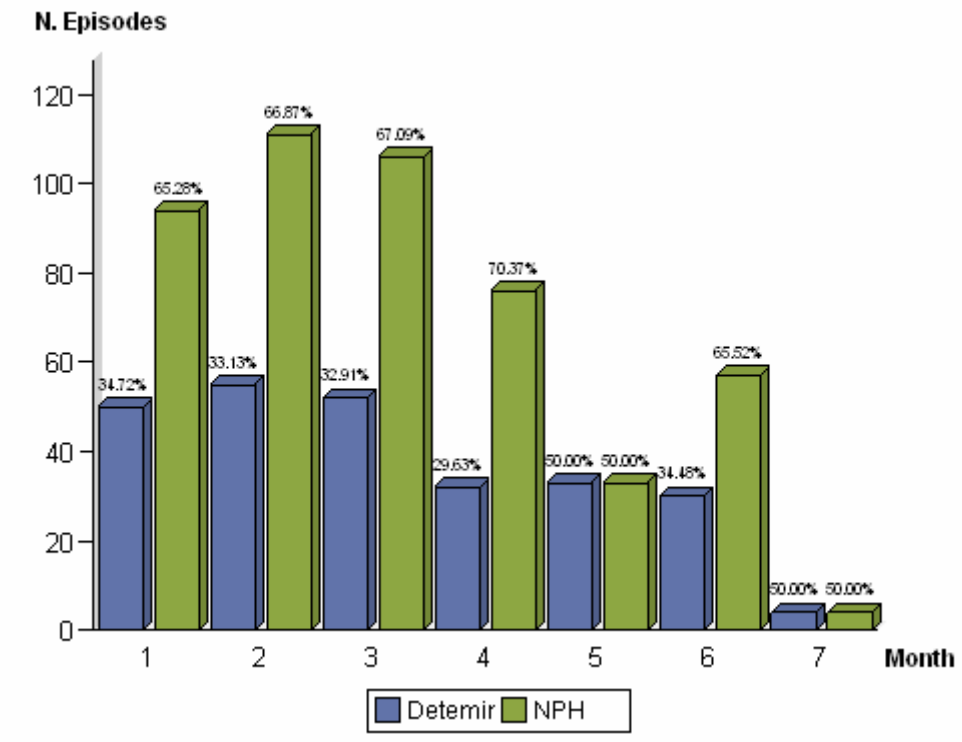
See also EOT Table 5.1.1. for details of the Cox regression model and EOT Figures 3.2 and 3.3

Table 10-7. Incidence of hypoglycaemic Episodes during the treatment

	Detemir		NPH		All	
	N	%		%	N	%
MAJOR	.	.	3	100.00	3	0.41
MINOR	243	34.03	471	65.97	714	96.88
OTHER	13	65.00	7	35.00	20	2.71
All	256	34.74	481	65.26	737	100.00

There were a total of 737 hypoglycemic episodes (most of them occurring during the first 3 months as shown in Figure 10-2): 256 in the Detemir group (34.74%) and 481 in the NPH group (65.26%); Odds ratio: 0.45 (0.31, 0.655). Thus, incidence of hypoglycemic episodes was significantly lower in the detemir group.

Figure 10-2. Time distribution of hypoglycemic episodes during trial period



10.4.2 Nocturnal hypoglycemic episodes

Table 10.8 Analysis of Treatment Emergent Nocturnal Hypoglycaemic Episodes

	HR	(95% CI)	p-value
Major (1)			
Minor	2.41	(1.685; 3.472)	< 0.0001
Other (2)			
All	2.336	(1.638; 3.331)	<0.0001

Hazard ratio: Ratio of incidence rates (NPH/Detemir); p-value: test for homogeneity of risk ratios among treatment groups.

(1) There was only one Major nocturnal hypoglycemic episode (patient under NPH treatment).

(2) There were 2 cases of Other nocturnal hypoglycemic episodes in patients under Detemir treatment.

There were 48 hypoglycemic episodes (18 in Detemir group and 30 in NPH) where the time of occurrence was not reported. They were not included in this analysis.

The Hazard Ratio was 2.33 [1.64;3.34] for all nocturnal episodes and 2.41 [1.68;3.47] for minor episodes indicating that the probability of having a nocturnal hypoglycemic episode during the treatment period was significantly higher in the NPH group.

See EOT Table 5.3.1 for more details of the Cox regression model and EOT Figures 3.5 and 3.6

Figure 10-3. Mean Cumulative frequencies of nocturnal hypoglycemic events

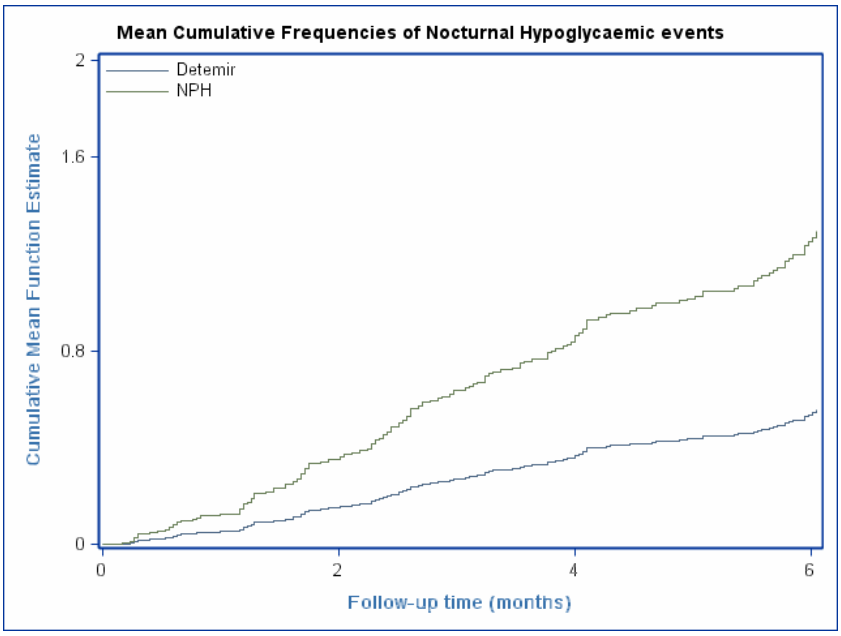
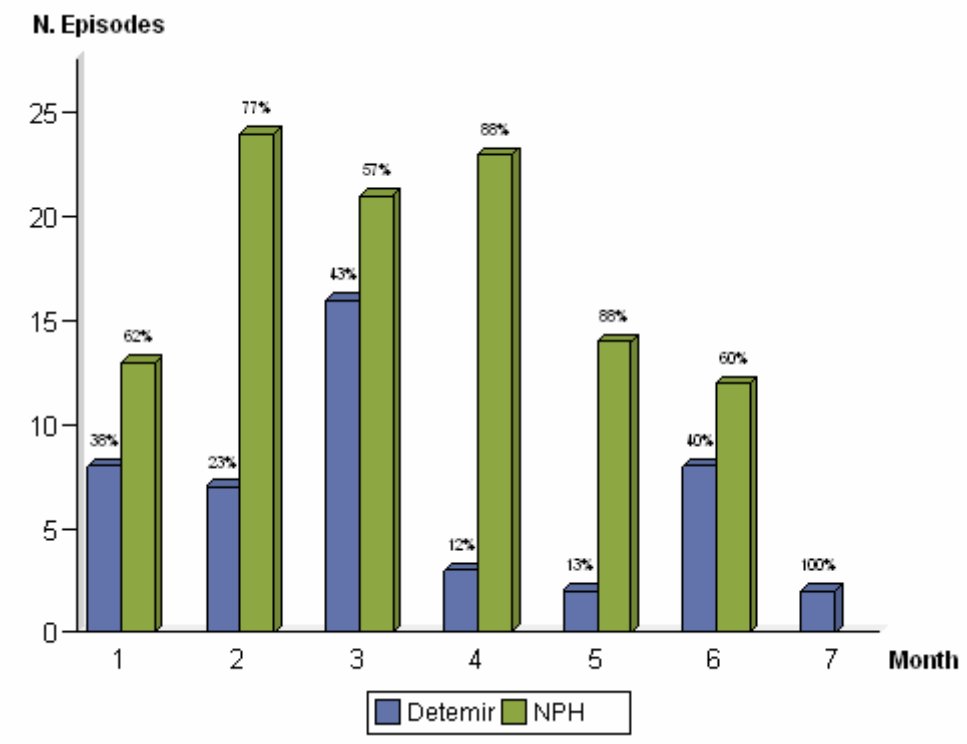


Table 10-9. Incidence of nocturnal hypoglycaemic Episodes during the treatment

	Detemir		NPH		All	
	N	%		%	N	%
MAJOR	.	.	1	100.00	1	0.65
MINOR	44	29.33	106	70.67	150	98.04
OTHER	2	100.00	.	.	2	1.31
All	46	30.07	107	69.93	153	100.00

There was a total of 153 nocturnal episodes: 46 in the Detemir group (30.07%), and 107 in the NPH group (69.93%); Odds ratio: 0.6 (0.455, 0.967). Thus, incidence of nocturnal hypoglycemic episodes was significantly lower in the detemir group.

Figure 10-4. Time distribution of nocturnal hypoglycemic episodes during trial period



10.5 Clinical Laboratory Tests

Shift tables for hematology, biochemistry and lipids are presented in EOT Tables 5.24, 5.25 and 5.26, respectively. No clinically relevant differences between treatment groups were observed in

any of the tests after 26 weeks. Reference ranges for each of the laboratory variables are presented in Selected Listing 19. Individual laboratory variables outside the reference ranges at any of the visits are listed in Selected Listings 20, 21 and 22.

10.5.1 Haematology

Individual changes in haematological variables from Visits 1 to 8 are summarised in EOT Table 5.24. There were no obvious differences between treatment groups for changes in any of the haematological variables. Few changes from normal to abnormal values were reported for any of the haematological variables in either treatment group. None of the changes observed were considered to be suggestive of a disease and/or organ toxicity, or were of a severity requiring active management, i.e., no clinical laboratory adverse events were reported as a result of any of these changes.

10.5.2 Biochemistry

Individual changes in biochemical variables from Visits 1 to 8 are summarised in EOT Table 5.25. There were no obvious differences between treatment groups for changes in any of the biochemical variables. Few changes from normal to abnormal values were reported for any of the biochemical variables in either treatment group. None of the changes observed were considered to be suggestive of a disease and/or organ toxicity, or were of a severity requiring active management, i.e., no clinical laboratory adverse events were reported as a result of any of these changes.

10.5.3 Lipids

Individual changes in lipid parameters from Visit 1 to 8 are summarised in EOT Table 5.26. At the end of the trial there was a statistically significant difference in total cholesterol levels and LDL levels between both treatment groups as shown in EOT Table 5.8 (2.02 ± 0.03 g/L in detemir group vs. 1.93 ± 0.03 g/L in NPH group, p = 0.028 for total cholesterol and 1.2 ± 0.03 g/l in the detemir group vs. 1.1 ± 0.02 g/l in the NPH group for LDL cholesterol; p = 0.041). However this difference was not clinically relevant. Few changes from normal to abnormal values were reported for any of the lipid variables in either treatment group. In general, the total cholesterol and triglycerides values were not high in both treatment groups. None of the changes observed were considered to be

suggestive of a disease and/or organ toxicity, or were of a severity requiring active management, i.e., no clinical laboratory adverse events were reported as a result of any of these changes.

10.5.4 Pregnancy Test

For fertile females, a pregnancy a serum test was performed at Visit 1, and a pregnancy urine test should be performed any time during the trial if a menstrual period was missed. All pregnancy tests performed during the trial were negative (EOT Table 5.27 and Appendix VIII).

10.6 Vital Signs, Physical Examination Findings and Other Safety Findings

10.6.1 Vital Signs

Summary of changes of vital signs from baseline are shown in EOT Table 5.29. Mean systolic and diastolic blood pressure decreased slightly in both treatment groups (mean change –2.3 mm Hg in diastolic blood pressure in detemir group vs. –1.47 mm Hg in NPH group and –3.17 mm Hg for systolic blood pressure in detemir group vs. –1.64 mm Hg in NPH group). Mean pulse decreased also minimally in both groups. None of the changes seen were considered to be of clinical relevance.

10.6.2 Physical Examination

Physical examination was performed at Visits 1 and 7. If any new findings or deterioration in previous findings were observed at Visit 7, these were recorded as adverse events and are therefore not presented separately.

10.6.3 HOMA-IR

Though insulin resistance was analyzed by means of this parameter (See EOT Tables 5.10 to 5.13) the results are not discussed due to the little value of this parameter in subjects treated with exogen insulin.

10.7 Summary of Safety Results

In general, 26 weeks of treatment with insulin detemir resulted in a safety profile similar to that of NPH insulin. Incidence of adverse events was similar in both groups. There were 6 serious adverse events (SAE) in 4 patients from the detemir group vs. 4 SAEs in 4 patients from the NPH group.

Relation to basal product was probable in 2 cases (both non SAEs) and possible in 1 case (non serious adverse event) of the detemir group vs. only one possible relationship with basal product in the NPH group (a non SAE). Most frequent treatment emergent adverse events where Respiratory thoracic and mediastinic disorders according to MedDRA system organ class codification.

The probability of having an hypoglycemic episode during the treatment was higher in the NPH group (Hazard ratio 1.61 [1.37;1.88] 95% CI; $p<0.0001$). This difference was mainly due to the increased risk of having a minor hypoglycemic episode in the NPH group (HR 1.66 [1.42;1.95]; $p<0.0001$). Incidence of hypoglycemic episodes was higher in the NPH group (481 (65.3%) vs. 256 (34.7%) in the detemir group. Odds ratio 0.45 (0.31,0.65). The probability of having a nocturnal hypoglycemic episodes was also higher in the NPH group: HR 2.34 [1.64;3.33]; $p<0.0001$, again due mainly to minor hypoglycemic events. Incidence of nocturnal hypoglycemic episodes was also lower in the detemir group: Odds ratio 0.6 [0.45;0.97].

There were no clinically significant changes in clinical laboratory parameters from baseline during the trial in both groups. Change in vital signs (systolic and diastolic blood pressure and pulse) from baseline was not clinically relevant.

11 Discussion

Data from the 1999-2000 US National Health and Nutrition Examination Survey[25], showed that two thirds of adults diagnosed with type 2 diabetes have a BMI ≥of 27 kg/m^2. Though insulin therapy has been shown to improve the blood glucose control[26] and prognosis in patients with type 2 diabetes, its initiation and intensification is often delayed due to concerns about hypoglycemia and weight gain[27-29]. Results from the UKPDS showed that those who received insulin treatment gained, on average, 5 kg from the start of the study.[30] Such weight gain may have negative implications in patients who are trying to adhere to an exercise and diet regimen. Thus, the benefits of insulin therapy may be potentially undermined by weight gain. Such weight gain, far from being only an esthetic problem, may have deleterious consequences. It has been estimated that for every 1 kg of weight gain after high school, the risk of coronary heart disease increases by 5.7% for women and 3.1% for men, with adverse changes in lipid profile and blood pressure[31,32]. Excessive weight gain has been also shown to be a significant factor in the reluctance of subjects with diabetes and health care professionals to initiate insulin therapy. This has been termed *psychological insulin resistance*[33]

Weight gain with insulin detemir (0.42 kg) in the present study was less than a third of that for NPH insulin (1.94 kg). A significant between-treatment difference in weight gain favouring insulin detemir has been previously described in clinical trials comparing insulin detemir with NPH insulin in people with type 1[8,34-38] or type 2[7,9,39] diabetes. Increase in BMI was also significantly higher in the NPH group (0.77 Kg/m^2) than in detemir group (0.17 Kg/m^2). In the present study, treatment with metformin was allowed as it is an OAD frequently used in combination with insulin in overweight and obese subjects with type 2 diabetes. This difference in weight change could not be attributed to this drug because at baseline the percentage of subjects treated with metformin was around 50% in the detemir group and 58% in the NPH group, remaining this percentage and metformin doses unchanged during the trial. Potential pharmacological explanations for this weight-sparing effect of insulin detemir have been suggested[40,41] though not clearly demonstrated. The patients included in this study were all obese or overweight (as the vast majority of subjects with type 2 diabetes) and the possibility of treating them with an insulin preparation not leading to clinically significant changes in body weight could be highly important.

Metabolic control was similar in both groups, changing HbA1c from 8.9% at baseline to 7.8% at the end of the study in detemir group and from 8.8 to 7.8% in the NPH group. Fasting plasma glucose also improved in both treatment arms (from 194 mg/dl at baseline to 157 mg/dl at the end of the study in the detemir group and from 182 mg/dl to 162 mg/dl in NPH group) being the difference after 26 weeks of treatment not statistically significant. Percentage of patients that achieved a good glycemic control (Hba1c < 7%) was also similar in both groups (22% in detemir vs. 18% in NPH; ns) and percentage of patients that achieved the pre and postprandial targets specified in the protocol at the end of the study was not statistically different either (13% in the detemir group vs. 10% in the NPH group). Consistent with earlier findings in other trials comparing insulin detemir with NPH,[7,16,17] within-subject variability in self-measured Fasting plasma glucose levels was significantly lower in the detemir group. Unpredictable fluctuations in blood glucose levels represent a major obstacle for obtaining safe plasma glucose targets. For NPH insulin this higher variability in FPG levels has been attributed to incomplete re-suspension prior to injection, and variable rates of insulin release from insulin crystals in the subcutaneous tissue at the injection site[42,43]. The lower within-subject variability in FPG levels observed with insulin detemir may be related to the fact that insulin detemir is a soluble preparation with a unique mechanism of protraction. More reproducible and predictive levels of fasting plasma glucose could make titration for FPG targets safer and more achievable.

Though metabolic control (measured by HbA1c levels) and other glycemic targets were similar in both groups, the risk for overall and nocturnal hypoglycemia was reduced with detemir treatment (Hazard ratio 0.62 and 0.43 respectively). Major hypoglycaemic episodes (defined as those episodes where the patient was not able to treat him/herself) occurred too infrequently for statistical analysis (no episodes with insulin detemir and three with NPH). This lower risk of hypoglycemia associated to the use of insulin detemir has also been reported previously in other trials.[9,37,38,39] While some of these trials[9,37,38] showed only a reduction in risk of nocturnal hypoglycemia other[39] showed a reduction of overall and nocturnal hypoglycemias. The use of a mealtime insulin added to the basal insulin in the first mentioned trials and only a basal insulin in the last one has been cited as a possible explanation for this difference. In this sense the mealtime insulin could have increased the risk of hypoglycemic episodes during the day. Nevertheless in our study a basal-bolus regimen,

with detemir and NPH as basal insulins and aspart as mealtime insulin, was used and the risk for hypoglycemia was reduced in the detemir group not only for nocturnal episodes but also for overall hypoglycemia, making that explanation not very plausible and reinforcing the idea that insulin detemir has itself a lower propensity to cause hypoglycemia. This lower incidence of hypoglycemic events with insulin detemir has been related to its more consistent blood glucose response.[44]

Safety profile with respect to adverse events was similar between both arms of treatment, being most of them mild or moderate in severity and with an unlikely relation to basal insulin (detemir or NPH). There were only 6 serious adverse events in the detemir group and 4 in the NPH group and their relation to basal insulin was considered unlikely by the investigators in all cases. All these results are in accordance with a recently published systematic review of six randomized controlled trials (with a duration of at least 24 weeks) in adults with type 2 diabetes mellitus comparing long-acting insulin analogues (insulin glargine and detemir) to NPH insulin. In these trials, 578 patients were randomized to insulin detemir. Metabolic control, measured by HbA1c, and adverse effects did not differ between treatment groups. While no statistically significant difference for severe hypoglycaemia rates was shown in any of the trials, the rate of symptomatic, overall and nocturnal hypoglycaemia was statistically significantly lower in patients treated with insulin detemir[45].

Quality of life and treatment satisfaction were also analyzed in this trial. Overall treatment satisfaction after 26 weeks of treatment was significantly better in the detemir group, while perceived frequency of hyper and hypoglycemia and quality of life were not different between groups. Though the main objective in the treatment of type 2 diabetic subjects is the normalization of blood glucose levels and the control of cardiovascular risk factors, it is very important to bear in mind the patient treatment satisfaction due to its close relationship to treatment compliance. The adequate management of diabetes should consider not only factors related to drug efficacy or safety but also patient-related factors such as treatment satisfaction. Treatment satisfaction has been shown to have influence on patient compliance[46,47] and cost of care.[48] Thus, an improvement in patient treatment satisfaction could have a positive repercussion on those important parameters in a chronic disease like diabetes.

At the end of trial, dose of insulin detemir (mean 47.5 ± 21.3 U) was significantly higher than dose of NPH (39.3 ± 16 IU), starting from similar doses at randomization (mean 23.6 ± 8.6 U for detemir vs. 22.8 ± 7.8 IU for NPH). This dose discrepancy has been also detected in previous trials,

comparing insulin NPH vs. detemir,[18,39] in which a higher molar dose of insulin detemir was needed to obtain similar blood glucose compared with NPH. In our study metabolic control was similar at the end of the trial in both treatment arms and a possible explanation for this difference in insulin doses could be a lesser potency of insulin detemir. According to this, both insulins should not be probably considered equipotent when changing from one to the other.

The present study was not blinded due to reasons previously explained (see section 5.4.4) and therefore the conclusions must be interpreted with some caution.

12 Overall Conclusions

Treatment with insulin detemir, when used as basal component of a basal-bolus regimen in type 2 overweight or obese diabetic subjects, was associated with a significantly lower weight gain after 12 and 26 weeks of treatment compared to NPH. This result could not be explained by a different rate of metformin treated patients because at baseline both groups were comparable (even with a higher rate of metformin intake in the NPH group).This objective was achieved with a similar metabolic control (in terms of HbA1c levels, fasting plasma glucose, pre and postprandial glucose targets) and with a similar incidence of adverse events between both groups. Insulin detemir regimen showed a lower within subject variability of self-measured fasting plasma glucose. Insulin doses were higher in the detemir group at the end of the trial. Treatment with detemir regimen was also associated with a lower risk and incidence of hypoglycemic events (both global and nocturnal). Treatment satisfaction was better in the detemir group.

References

[1] World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002.

[2] International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. 01-May-1996.

[3] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group**.** *Lancet.* 1998; 352:837-853.

[4] Turner RC, Cull CA, Frighi V et al. Glycaemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. Progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999; 281, 21: 2005-2012.

[5] European Diabetes Policy Group. A Desktop Guide to Type 2 Diabetes Mellitus. *Diabetic Medicine.* 1999;16:716-730.

[6] Bloomgarden ZT. Treatment of Type 2 Diabetes. The American Association of Clinical Endocrinologists Meeting. *Diabetes Care.* 2002;25;9:1644-1649.

[7] Haak T, Tiengo A, Draeger E, et al. 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 Metabo. 2005;7:56-64.

[8] De Leeuw I, Vague P, Selam JL et al. Lower risk of nocturnal hypoglycaemia and favourable weight development in type 1 diabetic subjects after 12 months treatment with insulin detemir vs. NPH insulin. *Diabetologia.* 2002; 45 (suppl. 2); A257

[9] Rasloga K, Bogoev M, Raz I, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract*. 2004;66:193-201.

[10] Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy with Type 1 diabetes. *Diabetologia.* 2004;47:622-629.

[11] Knowler WC, Barrett-Connor E, Fowler SE et al. Diabetes Prevention Program Research Group**.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin**.** *N Engl J Med*. 2002;346:393-403.

[12] Schauer PR, Burguera B, Ikramuddin S et al. Effect of laparoscopic Roux-In Y Gastric Bypass on Type 2 Diabetes Mellitus. Annals of Surgery. 2003; 238:467-485.

[13] UKPDS16. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes.* 1995;44:1249-58.

[14] Riddle MC, Schneider J. Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. Glimepiride Combination Group. *Diabetes Care*. 1998; 21: 1052-1057.

[15] Henry RR, Gumbiner B, Ditzler T et al. Intensive conventional insulin therapy for type 2 diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care.* 1993;16:21-31.

[16] Vague P, Selam JL, Skeie S et al. Insulin Detemir Is Associated With More Predictable Glycemic Control and Reduced Risk of Hypoglycemia Than NPH Insulin in Patients With Type 1 Diabetes on a Basal-Bolus Regimen With Premeal Insulin Aspart. *Diabetes Care.* 2003;26:590-596.

[17] Russell-Jones D, Bolinder J, Simpson R. Lower and more predictable fasting blood glucose and reduced risk of nocturnal hypoglycaemia with once daily insulin detemir vs. NPH in subjects with type 1 diabetes. *Diabetologia.* 2002;45 (suppl. 2): A51.

[18] Hermansen K, Madsbad S, Perrild H et al. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin. *Diabetes Care.* 2001;24:296-301.

[19] Pieber T R, Plank J, Görzer E et al. Duration of action, pharmacodynamic profile and between-subject variability of insulin detemir in subjects with type 1 diabetes. *Diabetologia* 2002; 45 (Suppl. 2): A257.

[20] Roberts A, Bayer T, Munksgaard E et al. Efficacy and safety of 6-month treatment with insulin detemir in type 1 diabetic patients on a basal-bolus regimen. *Diabetologia* 2001; 44 (Suppl. 1): A207

[21] Schmitz O, Gray R S, Kristensen A et al. Dose relationship between insulin detemir and NPH: A multi-centre, open, two-period, trial in type 2 diabetic patients. *Diabetologia* 2001; 44 (Suppl. 1): A207

[22] Friedewald WT, Levy RI, Friedrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972; 18:499-502.

[23] Matthews D, Hosker J, Rudenski A, et al. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28: 412-9.

[24] Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83

[25] National task force on the prevention and treatment of obesity overweight, obesity, and health risk (NAASO). Arch Intern Med. 2000;160:898-904.

[26] Wright A, Burden ACF, Paisey RB, et al. the U.K. Diabetes Study Group: Sulphonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care.2002;25:330–336.

[27] McCrimmon RJ, Frier BM: Hypoglycemia, the most feared complication of insulin therapy. Diabet Metab. 1994;20:503–512.

[28] Korytkowski M: When oral agents fail: practical barriers to starting insulin. Int Jobes. 2002; 26:S18 –S24.

[29] Heinemann L: Overcoming obstacles: new management options. Eur J Endocrinol. 2004;151:T023–T027.

[30] UK Prospective Diabetes Study Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-865.

[31] Anderson JW, Konz EC. Obesity and disease management: effects of weight loss on comorbid conditions. Obes Res. 2001;9(suppl 4): 326S-334S.

[32] Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22:331-339.

[33] Polonsky WH, Fisher L, Guzman S, et al. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. Diabetes Care. 2005;28(10):2543-5.

[34] Standl E, Lang H, Roberts A: The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther. 2004; 6:579 –588.

[35] De Leeuw I, Selam J-S, Skeie S, et al. Insulin detemir-based used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obesity and Metabolism 2005;7:73– 83.

[36] Home P, Bartley P, Russell-Jones D, et al. Study to Evaluate the Administration of Insulin Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group: Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care 2004;27:1081–1087.

[37] Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal bolus regimen. Clin Ther. 2004;26:724 –736.

[38] Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia. 2004;47:622– 629.

[39] Hermansen K, Davies M, Derezinski T, et al., on behalf of the levemir treat to target study group. 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. 2006;29:1269–1274.

[40] Fritsche A, Haring H: At last, a weight neutral insulin? Int J Obes Relat Metab Disord. 2004;28 (Suppl. 2):S41–S46.

[41] Hordern SV, Wright JE, Umpleby AM, et al. Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp. Diabetologia. 2005;48:420–426.

[42] Jehle PM, Micheler C, Jehle DR, et al. Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. Lancet. 1999;354:1604-1607.

[43] Binder C, Lauritzen T, Faber O, et al. Insulin pharmacokinetics. Diabetes Care 1984;7:188-199.

[44] Heise T, Nosek L, Ronn BB et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in subjects with type 1 diabetes. Diabetes. 2004; 53: 1614–1620.

[45] Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005613. DOI: 10.1002/14651858.CD005613.pub3.

[46] Albrecht G, Hoogstraten J. Satisfaction as determination of compliance. Community Dent Oral Epidemiol. 1998;26:139–146.

[47] Atkinson MJ, Kumar R, Cappelleri JC, et al. Hierarchical construct validity of the treatment Satisfaction Questionnaire for Medication (TSQM Version ll) among outpatient pharmacy consumers. Value Health. 2005;8:S9–S24.

[48] Hogan P, Dall T, Nikolov P, American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2002. Diabetes Care. 2003;26:917–932.