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.