2 Synopsis

Trial registration ID-number NCT01232491	**UTN** – N/A **IND number –** 51,789 **EudraCT number –** 2009-014894-42

Title of trial

A 26-week randomised, controlled, open label, multicentre, multinational, treat- to-target trial investigating the impact of dietary intervention on weight change and the relationship between weight change and baseline body mass index (BMI) in subjects with type 2 diabetes inadequately controlled on oral antidiabetic drugs (OADs) initiating insulin therapy with insulin detemir in combination with metformin. Levemir® DIET™

Investigators

There were 110 principal investigators.

[redacted], MD, PhD, was appointed signatory investigator:

[redacted]

Trial sites

The trial was conducted at 110 sites in 9 countries: Argentina (5 sites), Germany (7 sites), Poland (4 sites), Serbia (4 sites), Slovakia (3 sites), Slovenia (2 sites), Spain (4 sites), Turkey (5 sites) and USA (76 sites). In addition, 9 sites (4 in USA, 3 in Russia, 1 in Germany and 1 in Slovenia) were approved, but did not enroll any subjects.

Publications

None

Trial period	**Development phase**
Initiation date: 29 October 2010 Completion date: 14 November 2011	Phase 4

Objectives

Primary objective:

- To investigate if treat-to-target treatment with insulin detemir once-daily (OD) combined with metformin accompanied with dietary intervention is superior to treat-to-target treatment with insulin detemir OD combined with metformin without dietary intervention with respect to weight change after 26 weeks of treatment in subjects with type 2 diabetes inadequately controlled on metformin treatment with or without other OADs.

Secondary objectives:

- To investigate the association between weight change at 26 weeks and baseline BMI
- To assess and compare efficacy after 26 weeks of treatment
- To assess and compare safety and tolerability after 26 weeks of treatment

Other objectives

- To evaluate food intake and physical activity level

Methodology

The trial was a 26-week randomised, controlled, stratified, open-labelled, two-armed parallel group, multicentre, multinational treat-to-target trial comparing the impact of dietary intervention on weight change as well as the efficacy and safety of initiating treatment with insulin detemir in combination with metformin in subjects with type 2 diabetes mellitus inadequately controlled on OADs.

Subjects attended a screening visit (Visit 1) in order to assess their eligibility, followed by a randomisation visit

(Visit 2) approximately 2 weeks later. At Visit 2, all OAD treatments were to be discontinued except for metformin.

After discontinuation of all OADs other than metformin, the subjects were randomised to one of two parallel treatment groups consisting of either insulin detemir OD with metformin and dietary intervention (Diet group) or insulin detemir with metformin without dietary intervention (Control group). Subjects were randomised in a 1:1 fashion (Diet:Control). Subjects were stratified according to BMI categories; 25.0–29.9 kg/m^2, 30.0–34.9 kg/m^2, 35.0–39.9 kg/m^2, and 40.0–45.0 kg/m^2.

All subjects were titrated according to an insulin dose titration guideline. The treatment period lasted for 26 weeks during which weekly clinic visits or phone contacts with the investigator ensured the enforced titration targeting pre-breakfast self-monitored plasma glucose (SMPG) of 4.0–5.0 mmol/L (71–90 mg/dL). During the trial, subjects in the Diet group received dietary consultation with a certified dietician according to local standard at 6 occasions (3 face-to-face meetings and 3 phone contacts). Subjects in the Control group did not receive dietary consultation except for basic dietary advice at baseline.

Number of subjects planned and analysed

Based on the sample size calculation, the planned number of subjects to be randomised was approximately 600. The actual numbers of subjects included in the trial are shown below.

	Dietician N (%)	Control N (%)	Total N (%)
Screened			1132
Screening Failures			521
Withdrawn before Randomisation			0
Randomised	306 (100.0)	305 (100.0)	611 (100.0)
Exposed	305 (99.7)	301 (98.7)	606 (99.2)
Withdrawn at/after Randomisation	60 (19.6)	63 (20.7)	123 (20.1)
Adverse Event	13 (4.2)	8 (2.6)	21 (3.4)
Ineffective Therapy	1 (0.3)	5 (1.6)	6 (1.0)
Non-Compliance With Protocol	13 (4.2)	11 (3.6)	24 (3.9)
Withdrawal Criteria	12 (3.9)	21 (6.9)	33 (5.4)
Other	21 (6.9)	18 (5.9)	39 (6.4)
Completed	246 (80.4)	242 (79.3)	488 (79.9)
Full Analysis Set	306 (100.0)	305 (100.0)	611 (100.0)
PP Analysis Set	243 (79.4)	235 (77.0)	478 (78.2)
Safety Analysis Set	305 (99.7)	301 (98.7)	606 (99.2)

Abbreviations: N = number of subjects; % = proportion of randomised subjects; PP = per protocol

Diagnosis and main criteria for inclusion

Inclusion criteria: Insulin-naïve male or female subjects aged ≥ 18 years, with type 2 diabetes mellitus (diagnosed clinically) ≥ 6 months, HbA_{1c} 7.0–9.0% (both inclusive) by central laboratory analysis, BMI 25.0–45.0 kg/m^2 and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogues (sulphonylurea or glinide), DPP-4 inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to Visit 1 were included in the trial.

Exclusion criteria: Subjects on treatment with thiazoledinediones (TZDs) or glucagon-like peptide-1 analogue (GLP-1) receptor agonists within 3 months prior to Visit 1, anticipated change in concomitant medication known to interfere significantly with glucose metabolism or weight, previous participation in this trial, known or suspected allergy to any of the trial products or related products and any clinically significant disease or disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion could have interfered with the results of the trial were excluded from the trial.

Investigational medicinal product, dose and mode of administration, batch number

Insulin detemir (Levemir®) 100 U/mL, 3 mL FlexPen® for subcutaneous administration. Insulin detemir was to be injected once daily with the evening meal (dinner) or at bedtime. Insulin injections were given subcutaneously preferably in the thigh. Insulin doses were titrated weekly by the investigator based upon the subject's SMPG levels and an insulin titration guideline. No minimum or maximum insulin dose was specified. Batch Numbers: YP51478 and YP51419.

Duration of treatment

The total duration of treatment for each subject was approximately 28 weeks including the screening visit.

Reference therapy, dose and mode of administration, batch number

Metformin was not considered a trial product and was not supplied by Novo Nordisk A/S.

Criteria for evaluation – efficacy

- Body measurements
  - Body weight
  - Height
  - BMI
  - Waist circumferences
- Glucose metabolism
  - HbA_{1c}
  - Fasting plasma glucose (FPG)
- SMPG
  - Pre-breakfast SMPG
  - 9-point SMPG profile
- Insulin dose
- Caloric intake and physical activity

Criteria for evaluation – safety

- Adverse events (AEs)
- Hypoglycaemic episodes
- Physical examination
- Vital signs
- Eye examination
- Electrocardiogram (ECG)
- Laboratory safety variables

Statistical methods

Analysis sets

The following analysis sets were defined:

- Full analysis set (FAS): included all randomised subjects. In exceptional cases, subjects from the FAS could be excluded. In such cases, the reason was to be justified and documented. The statistical evaluation of the FAS was to follow the intention-to-treat (ITT) principle and subjects were to contribute to the evaluation 'as randomised'.
- Per protocol (PP) analysis set: included subjects without any major protocol violations that could have affected the primary endpoint. Moreover, subjects must have been exposed to insulin detemir for the full treatment period and must have had a valid assessment necessary for deriving the primary endpoint. Subjects in the PP analysis set were to contribute to the evaluation 'as treated'.
- Safety analysis set: included all subjects receiving at least one dose of insulin detemir. Subjects in the safety set were to contribute to the evaluation 'as treated'.

Analyses of all efficacy endpoints were based on the FAS. All other endpoints related to safety were based on the safety analysis set. The robustness of the results for the primary endpoint was explored by additional analysis on the PP analysis set.

Primary efficacy analysis
Change from baseline in weight after 26 weeks of treatment was analysed using a normal linear regression model with treatment, strata, use of insulin secretagogue at screening, sex and region as factors, and age and weight at baseline as covariates. Treatment was a factor with two levels (dietary intervention/no dietary intervention), strata was defined according to the BMI groups at baseline (25.0–29.9, 30.0–34.9, 35.0–39.9, 40.0–45.0 kg/m^2), use of insulin secretagogue at screening was a factor with two levels (yes/no) and region was a factor with 3 levels: North America (USA), South America (Argentina) and Europe (Germany, Poland, Russia, Serbia, Slovakia, Slovenia, Spain, Turkey). The model was fitted to all the data simultaneously (both groups) and from this model, the relevant treatment differences (dietary intervention versus no dietary intervention) was estimated. Superiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the estimated treatment difference (dietary intervention versus no dietary intervention) was below 0 kg.

Secondary confirmatory analyses
None of the secondary endpoints in this trial were considered confirmatory.

Secondary supportive efficacy analyses
- Change from baseline in BMI after 26 weeks of treatment was analysed using a normal linear regression model with treatment, strata, treatment by strata interaction, sex, use of insulin secretagogue at screening and region as factors and age and BMI at baseline as covariate. Changes and treatment differences within each stratum were estimated.
- Responders for weight change from baseline to end-of-trial was analysed by applying a logistic regression model using treatment, strata, sex, use of insulin secretagogue at screening and region as factors, and weight and age at baseline as covariates.
- Change in HbA_{1c} from baseline to 26 weeks was analysed using a normal linear regression model with treatment, strata, use of insulin secretagogue at screening and region as factors, and baseline HbA_{1c} as covariate.
- Change in FPG from baseline to 26 weeks of treatment was analysed using a normal linear regression model with treatment, strata, use of insulin secretagogue at screening and region as factors and baseline FPG as covariate.
- 9-point profile (SMPG): A mixed effect model was fitted to the 9-point SMPG profile data. The model included treatment, time, interaction between treatment and time, strata, use of insulin secretagogue at screening and region as fixed factors and subject as random effect. From the model mean profile by treatment and relevant treatment differences were estimated and explored. Mean of the 9-point SMPG profile and prandial PG increment were analysed using a normal linear regression model with treatment, strata, use of insulin secretagogue at screening and region as factors, and the relevant baseline value as covariate.
- The HbA_{1c} responder endpoints (proportion of subjects reaching the HbA_{1c} targets <7% or ≤6.5% at end-of-trial with or without hypoglycaemia) were analysed separately based on a logistic regression model using treatment, strata, use of insulin secretagogue at screening and region as factors, and baseline HbA_{1c} as covariate.

- Responder for HbA_{1c} and weight change (change in weight <+0.5 kg or change in weight <3%) from baseline to end-of-trial were based on a logistic regression model using treatment, strata, sex and use of insulin secretagogue at screening and region as factors and age, baseline HbA_{1c} and baseline weight as covariates
- Insulin dose was summarised descriptively according to treatment groups as dose in units and units/kg.
- Change from baseline in waist circumference after 26 weeks of treatment was analysed using a normal linear regression model with treatment, strata, use of insulin secretagogue at screening, sex and region as factors and age, and baseline waist circumference as covariate.
- Caloric intake at baseline and end-of-trial and change from baseline to end of trial, overal, and by BMI subgroup were summarised descriptively. Caloric intake by macro-nutrient composition was summarised and listed and the proportion of subjects who reduced their caloric intake with <15% was summarised in the dietary intervention arm only. Change in physical activity level from baseline to end-of-trial was summarised descriptively.

Safety Analyses

- A treatment emergent adverse event (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. AEs were coded using the most recent version (version 14.1) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of AEs was based on descriptive statistics. AEs and hypoglycaemic episodes are also presented as the rate of the events per 100 subject years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent if the onset of the episode was on or after the first day of exposure to randomised treatment and no later than 1 day after the last day of randomised treatment. A hypoglycaemic episode with time of onset between 00:01 and 05:59 a.m. (both included) was considered nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following 5 categories based on plasma glucose (PG) measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Furthermore, minor hypoglycaemic episodes were defined as episodes with symptoms consistent with hypoglycaemia with confirmation by blood glucose (BG) values <2.8 mmol/L (50 mg/dL) or PG <3.1 mmol/L (56 mg/dL) which was handled by the subject him/herself, or any asymptomatic BG value <2.8 mmol/L (50 mg/dL) or PG value <3.1 mmol/L (56 mg/dL) which was handled by the subject him/herself. The number of treatment emergent hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, strata, use of insulin secretagogue at screening and region as factors and duration of diagnosed diabetes as covariate. Severe or minor and nocturnal hypoglycaemic episodes were analysed separately.
- Change from baseline in lipid endpoints was analysed separately using a normal linear regression model with treatment, strata, use of insulin secretagogue at screening and region as factors and baseline value as covariate. Some of the endpoints were log-transformed before they were analysed.
- Laboratory safety parameters, physical examination, ECG, fundoscopy / fundusphotography and vital signs were evaluated based on descriptive statistics.

Demography of trial population

The demographics and baseline characteristics in the two groups were similar with only marginal differences between the groups. The population consisted of male and female subjects with type 2 diabetes mellitus, with a mean age of 58.2 and 56.5 years (Diet and Control) and a mean duration of diabetes of 8.6 and 8.5 years (Diet and Control) and with a mean HbA_{1c} of 8.0% and 7.9% (Diet and Control). Body weight was 96.4 kg in the Diet group and 97.0 kg in the Control group and the BMI was similar in the two groups (34.4 kg/m^2 and 34.3 kg/m^2, respectively). Approximately 25% of subjects in each group were stratified into the four BMI strata. The majority of the subjects (~89%) that reported their race were White. Slightly more male subjects were enrolled than females; 50.2% in the Diet group and 52.5% in the Control group. The pre-trial antidiabetic treatment regimens were evenly distributed in the two groups. The majority of the subjects in both groups were treated with metformin in combination with insulin secretagogues (47.9% and 48.2%; Diet and Control) while 37.7% in the Diet group and 34.9% in the Control group were on metformin monotherapy.

	Dietician	Control
Number of Subjects	305	301
Age (years)		
N	305	301
Mean (SD)	58.2 (9.7)	56.5 (10.0)
Median	58.7	56.8
Min ; Max	25.9 ; 86.6	22.5 ; 83.2
Body Weight (kg)		
N	305	301
Mean (SD)	96.4 (18.2)	97.0 (20.4)
Median	95.4	95.0
Min ; Max	58.1 ; 154.2	56.6 ; 153.9
BMI (kg/m^2)		
N	305	301
Mean (SD)	34.4 (5.4)	34.3 (5.6)
Median	33.9	33.9
Min ; Max	25.1 ; 44.9	25.0 ; 45.0
BMI grp - Screening, N (%)		
N	305 (100.0)	301 (100.0)
25.0-29.9 kg/m2 - Preobese	80 (26.2)	78 (25.9)
30.0-34.9 kg/m2 - Obese class I	81 (26.6)	80 (26.6)
35.0-39.9 kg/m2 - Obese class II	78 (25.6)	77 (25.6)
40.0-45.0 kg/m2 - Obese class III	66 (21.6)	66 (21.9)
Duration of Diabetes (year)		
N	303	301
Mean (SD)	8.6 (5.8)	8.5 (6.0)
Median	7.5	7.4
Min ; Max	0.6 ; 36.4	0.6 ; 31.6
HbA1c (%)		
N	305	301
Mean (SD)	8.0 (0.7)	7.9 (0.6)
Median	7.9	7.9
Min ; Max	6.7 ; 11.8	6.7 ; 10.0
FPG (mmol/L)		
N	305	298
Mean (SD)	9.3 (2.3)	9.2 (2.0)
Median	9.0	9.0
Min ; Max	3.9 ; 19.5	4.5 ; 15.0

Abbreviations: BMI = body mass index; N = number of subjects; SD = standard deviation

Efficacy results

After 26 weeks of treatment with insulin detemir OD combined with metformin and dietary intervention or insulin detemir OD combined with metformin but without dietary intervention, the following can be concluded:

Primary endpoint (weight change from baseline to end-of-trial)

- **Weight change:** On average, both groups lost weight from baseline to end-of-trial, but superiority of dietary intervention compared to no dietary intervention in terms of weight change from baseline to end-of-trial could not be confirmed. The estimated mean change in body weight was -1.05 kg in the Diet group and -0.56 kg in the Control group. The estimated difference (Control-Diet) was 0.49 $[-0.15; 1.13]_{95\%CI}$; the difference was not statistically significant (p=0.132). In both groups, subjects in the highest BMI strata had a greater observed weight change (reduction) compared to subjects in the lowest BMI strata.

Secondary efficacy endpoints (supportive endpoints)

- **Change in BMI from baseline to end-of-trial:** In both groups, a reduction in BMI from baseline to end-of-trial was measured; the estimated mean change in the Diet group was -0.37 kg/m^2 and -0.20 kg/m^2 in the Control

group. The estimated mean difference (Control-Diet) was 0.17 [-0.05; 0.39]$_{95\%CI}$; the difference was not statistically significant (p=0.137).

- **Responders for weight change from baseline to end-of-trial:** The majority of subjects in both groups had no weight gain (<+0.5 kg); 65.0% in the Diet group and 61.0% in the Control group. The estimated odds ratio (Control/Diet) was 0.85 [0.61; 1.20]$_{95\%CI}$; no statistically significant difference was shown between the groups (p=0.358). The majority of subjects in both groups had a minimal weight gain (weight gain <3%); 85.3% in the Diet group and 86.2% in the Control group. The estimated odds ratio (Control/Diet) was 1.17 [0.73; 1.88]$_{95\%CI}$; no statistically significant differences were shown between the groups (p=0.521).
- **Change in HbA1c from baseline to end-of-trial:** Long-term glycaemic control as measured by HbA_{1c} was improved in both groups. The estimated mean change in HbA_{1c} was -0.93 %-point with Diet and -0.80 %-points with Control. The estimated difference (Control-Diet) was 0.13 [-0.00; 0.26]$_{95\%CI}$; the difference was not statistically significant (p=0.053). After 26 weeks of treatment, the observed mean HbA_{1c} was 7.0 %-points with Diet and 7.1 %-points with Control.
- **Change in FPG from baseline to end-of-trial:** FPG decreased during the trial in both groups. The estimated mean change in FPG was -3.00 mmol/L with Diet and -2.93 mmol/L with Control. The estimated mean difference (Control-Diet) was 0.07 [-0.25; 0.39]$_{95\%CI}$; the difference was not statistically significant (p=0.674). After 26 weeks of treatment, the observed mean FPG levels were 6.2 mmol/L and 6.3 mmol/L with Diet and Control, respectively.
- **9-point SMPG profiles:** The estimated overall mean of the 9-point SMPG profile and the estimated mean increment across all meals showed no statistically significant differences between the Diet and Control groups after 26 weeks treatment.
- **Responders for HbA_{1c} at end-of-trial:**
  - The proportion of subjects who achieved the HbA_{1c} target of <7.0% at end-of-trial was 52.3% with Diet and 46.9% with Control. The estimated odds ratio (Control/Diet) was 0.74 [0.52; 1.05]$_{95\%CI}$; no statistically significant differences were shown between the groups (p=0.091). The proportion of subjects who achieved the stricter HbA_{1c} target of ≤6.5% was 34.0% with Diet and 28.9% with Control. The estimated odds ratio (Control/Diet) was 0.72 [0.50; 1.05]$_{95\%CI}$; no statistically significant differences were shown between the groups (p=0.090).
  - In all, 4.9% of subjects in the Diet group and 3.3% of subjects in the Control group achieved the HbA_{1c} target <7% without documented (symptomatic and asymptomatic) or severe hypoglycaemia during the treatment period. The estimated odds ratio (Control/Diet) was 0.64 [0.28; 1.46]$_{95\%CI}$; no statistically significant differences were shown between the groups (p=0.289). In all, 9.4% (Diet) and 7.1% (Control) of subject exposed for at least 20 weeks achieved this target during the last 12 weeks of treatment. The estimated odds ratio (Control/Diet) was 0.71 [0.37; 1.37]$_{95\%CI}$; no statistically significant differences were shown between the groups (p=0.309).
  - A higher percentages of subjects in the Diet group achieved the HbA_{1c} target <7% without minor or severe hypoglycaemia during the treatment period; 26.5% of subjects in the Diet group compared to 18.7% of subjects in the Control group. The estimated odds ratio (Control/Diet) was 0.61 [0.41; 0.90]$_{95\%CI}$; the difference was statistically significant (p=0.014). The percentages of subjects exposed for at least 20 weeks who achieved this target during the last 12 weeks of treatment was 30.6% in the Diet group and 23.8% in the Control group. The estimated odds ratio (Control/Diet) of achieving this target was 0.69 [0.46; 1.04]$_{95\%CI}$; the difference was not statistically significant (p=0.078).
- **Responders for HbA_{1c} and weight change from baseline to end-of-trial:** The proportion of subjects who achieved the HbA_{1c} target of <7.0% at end-of-trial without weight gain (<+0.5 kg) was 38.2% with Diet and 28.5% with Control. The estimated odds ratio (Control/Diet) was 0.59 [0.41; 0.85]$_{95\%CI}$; the difference was statistically significant (p=0.005). The proportion of subjects who achieved the HbA_{1c} target of <7.0% at

end-of-trial with minimal weight gain (<3%) was 46.4% with Diet and 41.3% with Control. The estimated odds ratio (Control/Diet) was 0.74 $[0.52; 1.05]_{95\%CI}$; the difference was not statistically significant (p=0.090).

- **Insulin dose:** See safety results
- **Change in waist circumference from baseline to end-of- trial:** A small decrease in waist circumference was measured in both groups at end-of-trial. The estimated mean changes from baseline to end-of-trial were -1.79 cm with Diet and -1.02 cm with Control. The estimated mean difference (Control-Diet) was 0.77 $[-0.05; 1.59]_{95\%CI}$; the difference was not statistically significant (p=0.064).
- **Caloric intake and physical activity:** The caloric intake was reduced in both groups during the trial; from 8064 kJ to 7510 kJ in the Diet group and from 8669 kJ to 7881 kJ in the Control group. No differences were seen between the groups with respect to caloric intake (%) from fat, protein and carbohydrate. Approximately 50% of subjects in both groups kept the same physical activity level throughout the trial, whereas approximately 17% of subjects in each group reduced their physical activity level and approximately 23% increased their physical activity level from baseline to end-of-trial.

Safety results

After 26 weeks of treatment with insulin detemir OD combined with metformin and dietary intervention or insulin detemir OD combined with metformin without dietary intervention, the following can be concluded:

- **AEs:** A similar percentage of subjects reported AEs in the Diet and Control groups (59.0% and 64.8%, respectively). The rate of all AEs was lower in the Diet group than in the Control group (387.9 and 437.1 events per 100 PYE, respectively). The rate of severe AEs was slightly higher for the Diet group than the Control group (16.3 and 11.3 events per 100 PYE, respectively). The most frequent AEs in both groups were nasopharyngitis, headache and injection site reaction. The rate of AEs possibly or probably related to trial product was 44.5 and 38.4 events per 100 PYE for Diet and Control, respectively; the most frequent AE in both groups was injection site reaction.
- **Deaths, serious adverse events (SAEs) and other significant AEs:** Two (2) deaths were reported in the trial; 1 in the Diet group ('metastases to central nervous system') and 1 in the Control group ('congestive cardiomyopathy'). A total of 17 (5.6%) and 19 (6.3%) subjects reported SAEs in the Diet and Control groups, respectively. The rate of SAEs per 100 PYE was 16.3 in the Diet group and 16.6 in the Control group. None of the preferred terms reported as SAEs occurred in more than one subject, except for 2 cases of 'acute myocardial infarction' and 2 cases of 'dyspnoea' in the Control group. In all, 5 SAEs were considered possibly or probably related to trial product (2 in the Diet group; both hypoglycaemia and 3 in the Control group; 'congestive cardiomyopathy', 'myocardial infarction' and 'dyspnoea'). In all, 13 (4.3%) subjects in the Diet group and 8 (2.7%) subjects in the Control group withdrew due to an AE. Five (5) of the AEs leading to withdrawal were reported as SAEs; 3 in the Diet group and 2 in the Control group. In both groups, the majority of AEs that led to withdrawal was injection site reactions.
- **Hypoglycaemic episodes:** The rate of all hypoglycaemic episodes per subject exposure year was 25.47 episodes with Diet and 23.30 episodes with Control; the estimated rate ratio (Control/Diet) of all hypoglycaemic episodes was 0.96 $[0.79; 1.17]_{95\%CI.}$ The rate of all nocturnal hypoglycaemic episodes was 5.59 and 5.51 episodes for Diet and Control, respectively; the estimated rate ratio (Control/Diet) of nocturnal hypoglycaemic episodes was 1.08 $[0.75; 1.56]_{95\%CI.}$ Severe hypoglycaemia was reported by 1 subject in each group (2 episodes by the subject in the Diet group and 1 episode by the subject in the Control group). One of the episodes in the Diet group and the episode in the Control group were reported as nocturnal severe hypoglycaemia.
- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: Overall, no clinically relevant changes from baseline to end-of-trial were seen in either group. No clinically relevant differences between the groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination or laboratory values.
- **Insulin dose:** No difference in mean daily basal insulin dose was seen between the groups. The mean insulin dose increased in both groups throughout the trial and at end-of-trial, the dose was 92 U (0.95 U/kg) for the Diet group and 94 U (0.97 U/kg) for the Control group.

Conclusions

This randomised, controlled, 26-week trial compared the impact of dietary intervention on weight change as well as the efficacy and safety of initiating treatment with insulin detemir in combination with metformin in subjects with type 2 diabetes mellitus inadequately controlled on OADs. The data support the following conclusions:

- After 26 weeks of treatment with insulin detemir, both groups had lost weight; on average subjects in the Diet group lost 1.05 kg and subjects in the Control group lost 0.56 kg. However, superiority of dietary intervention to no dietary intervention in terms of weight change from baseline to end of-trial could not be confirmed.
- In both groups, subjects in the highest BMI strata obtained a greater weight reduction at end-of-trial compared to subjects in the lowest BMI strata
- Glycaemic control as measured by HbA_{1c} and FPG improved throughout the trial in both groups; no differences were seen between the Diet and Control groups
- The proportion of subjects who achieved the HbA_{1c} targets of $\leq$7% and $\leq$6.5% was similar for the Diet and Control groups, and overall, no differences between the groups were seen in proportion of subjects who achieved the HbA1c targets without weight gain or without hypoglycaemia
- In both groups, caloric intake was reduced at end-of-trial; no difference was seen between the Diet and Control groups
- No safety issues were identified with insulin detemir; no difference in rate of hypoglycaemia was seen, and there was no apparent difference between the Diet and Control groups with respect to AEs or standard safety parameters in this trial

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).

The results presented reflect data available in the clinical database as of 5 December 2011 (database lock) and 2 April 2012 (relates to safety data).