2 Synopsis

Trial registration ID number – NCT01165684	**UTN –** U1111-1116-0908 **IND number –** 51,789 (Levemir®), 48,231 (NovoLog®) **EudraCT number –** 2010-018974-19

TITLE OF TRIAL

A randomised, controlled, open-label, multicentre, multinational, treat-to-target trial investigating the efficacy and safety of intensification with addition of bolus insulin aspart in subjects with type 2 diabetes inadequately controlled on basal insulin with or without oral anti-diabetic drugs: Step-wise addition versus complete basal–bolus therapy

INVESTIGATORS

There was 1 principal investigator for each trial site ([redacted] Dr. [redacted] was the co-ordinating investigator for Site [redacted] [redacted]])
Dr. [redacted] and [redacted] Dr. [redacted] were appointed signatory investigators for the trial

TRIAL SITES

The trial was conducted at 69 sites in 7 countries: Argentina (7), Brazil (5), Canada (12), France (7), Macedonia (1), Slovenia (4), and the US (31). Of 12 sites in Canada, one site (Site [redacted]) closed early on [redacted]. In addition, 2 sites were approved by the Institutional Review Board/Independent Ethics Committee but did not enrol any subjects (Sites [redacted] and [redacted] in the US).

PUBLICATIONS

At finalisation of the clinical trial report, there were no publications based on this study

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 27 October 2010 Completion date: 25 April 2012	Phase 4

OBJECTIVES

As stated in the protocol, the objectives of the trial were as follows:

Primary objective

- To confirm efficacy of step-wise addition of bolus insulin in terms of glycaemic control assessed by change in HbA_{1c}

Secondary objectives

- To assess and compare efficacy in terms of the following:
  - Fasting plasma glucose (FPG) values
  - 7-self-measured plasma glucose (SMPG) profile
- Evaluate insulin dose
- To assess and compare diabetes treatment satisfaction
- To assess and compare safety and tolerability in terms of the following:
  - hypoglycaemic episodes
  - adverse events (AEs)
  - clinical and laboratory assessments
  - change in body weight and BMI

METHODOLOGY

This trial was a randomised, open-labelled, 2-armed, parallel-group, multicentre, multinational, efficacy, safety and treat-to-target trial. The trial comprised a 2-week, screening period followed by an 8-week, run-in period and a 32-week treatment period. Subjects with type 2 diabetes inadequately controlled on basal insulin with HbA_{1c} 7.0–9.0% were transferred to insulin detemir and self-adjusted their insulin detemir dose during the run-in period. After the run-in period, subjects with HbA_{1c} 7.0–9.0% and FPG ≤9.0 mmol/L (≤162 mg/dL) were randomised (1:1) to step-wise arm and basal–bolus arm. The subjects were stratified at randomisation according to the HbA_{1c} intervals: HbA_{1c} 7.0–8.0% and HbA_{1c} 8.1–9.0%. Surveillance of insulin titration was performed centrally by a Titration Committee.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

- The planned number to complete the trial was 320 subjects.
- In total, 1008 subjects were screened, 401 subjects were randomised and 397 exposed to trial products.

- 321 subjects completed the trial.
- Subjects were stratified according to HbA_{1c} values (225 and 176 subjects in HbA_{1c} 7.0–8.0% and HbA_{1c} 8.1–9.0% strata, respectively).

	Step-wise N (%)	Basal-bolus N (%)	Total N (%)
Screened			1008
Screening Failures			418
Run in Failures			189
Randomised	201 (100.0)	200 (100.0)	401 (100.0)
Exposed	198 (98.5)	199 (99.5)	397 (99.0)
Withdrawals	28 (13.9)	52 (26.0)	80 (20.0)
Adverse Event	1 (0.5)	1 (0.5)	2 (0.5)
Ineffective Therapy	2 (1.0)	1 (0.5)	3 (0.7)
Non-Compliance	7 (3.5)	15 (7.5)	22 (5.5)
Withdrawal Criteria	2 (1.0)	13 (6.5)	15 (3.7)
Other	16 (8.0)	22 (11.0)	38 (9.5)
Completed Trial	173 (86.1)	148 (74.0)	321 (80.0)
Safety Analysis Set	198 (98.5)	199 (99.5)	397 (99.0)
Full Analysis Set	201 (100.0)	200 (100.0)	401 (100.0)
PP Analysis Set	172 (85.6)	149 (74.5)	321 (80.0)

N = Number of Subjects, % = Percentage of subjects

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

- **Key inclusion criteria:** Male or female aged ≥18 years, subjects with type 2 diabetes (diagnosed clinically) for ≥12 months, basal insulin treatment (NPH once or twice daily, insulin glargine once daily or insulin detemir once daily) ≥6 months, HbA_{1c} 7.0–9.0% (both inclusive) and BMI <40.0 kg/m^2
- **Randomisation criteria:** Subjects should fulfil both criteria: HbA_{1c} 7.0–9.0% and FPG ≤9.0 mmol/L (≤162 mg/dL); both measured at Visit 9 (Week −1)
- **Withdrawal criteria:** Pregnancy or intention of becoming pregnant, hypoglycaemia during the treatment period posing a safety problem as judged by the investigator, major protocol deviation having influence on efficacy or safety data as judged by the investigator, initiation or significant change of any systemic treatment, including OADs, which in the investigator's opinion could interfere with glucose metabolism (inhaled corticosteroids were allowed, pausing metformin treatment for a planned radiographic procedure including the use of iodine containing contrast material was allowed), donation of blood or participation in other intervention trials throughout the trial

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Insulin detemir was injected subcutaneously preferably in the thigh, and insulin aspart was injected in the abdomen. The trial products used in both treatment arms were as follows:

Insulin detemir 100 U/mL was provided as follows:

- in 3 mL FlexPen® (to be used in countries outside Canada) – Batch numbers: YP51419 and YP52299
- in 3 mL Penfill® (to be used with NovoPen®4 in Canada only) – Batch numbers: AQ50152 and YQ50224

Insulin aspart 100 U/mL provided as follows:

- in 3 mL FlexPen® (to be used in countries outside Canada) – Batch numbers: YP50474 and YP51142
- in 3 mL Penfill® (to be used with NovoPen®4 in Canada only) – Batch numbers: AQ50053 and YQ50135

DURATION OF TREATMENT

The trial duration was approximately 42 weeks which comprised a 2-week screening period followed by an 8-week run-in period and a 32-week treatment period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Not applicable

CRITERIA FOR EVALUATION – EFFICACY

The following efficacy variables were assessed: HbA_{1c}, FPG, 7-SMPG, proportion of subjects with post-prandial readings ≤10.0 mmol/L (180 mg/dL), mean PG increment over 3 meals (breakfast, lunch and dinner), insulin dose (total, basal and bolus), distribution of bolus injections, patient reported outcome questionnaires (Diabetes Medication Satisfaction Questionnaire [DiabMedSat], Treatment Satisfaction Questionnaire [TRIM-D], Diabetes Productivity Measure Questionnaire [DPM])

CRITERIA FOR EVALUATION – SAFETY

The following safety variables were assessed: AEs, body weight and BMI, hypoglycaemic episodes, physical examination, vital signs, funduscopy/fundusphotography, 12-lead ECG, clinical laboratory safety variables

STATISTICAL METHODS

- **Power calculation - t**he minimum sample size required to meet the primary objective with at least 90% power was 320 subjects (160 subjects in each arm) with an assumed standard deviation of 1.1%. As this was a non-inferiority trial, sample size was determined such that the anticipated power was at least 90% in the evaluation of the PP analysis set. In this trial an estimate of 21% was used, and sample size was ceiled in the FAS to have integer sample size for each group that adhered exactly to the group allocation weights (1:1). Hence, the total number of subjects to be randomised was to be 406 subjects (203 subjects in each arm) to have at least 90% power in the evaluation of the PP analysis set. The anticipated number in the FAS was 203 in each arm, whereas in the PP analysis set the anticipated number was 160 subjects in each arm.
- **Definition of analysis sets** - the following analysis sets were defined in accordance with the ICH-E9:
  - Full analysis set (FAS): Included all randomised subjects. In exceptional cases subjects from the FAS could be excluded. In such cases the exclusion was justified and documented. The statistical evaluation of the FAS followed 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 affected the primary endpoint. Moreover, subjects must have been exposed to a step-wise regimen or basal–bolus regimen for more than 28 weeks 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 aspart. Subjects in the safety analysis set contributed to the evaluation "as treated".
- **Analysis of primary endpoint** - change from baseline in HbA_{1c} after 32 weeks of treatments was analysed using a normal linear regression model (an Analysis of Covariance [ANCOVA] method) with treatment, strata and region as factors and baseline HbA_{1c} as covariate. The model was fitted to all the data simultaneously and from this model the relevant treatment differences were estimated. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) is below or equal to 0.4% or equivalently if the p-value for the one-sided test of H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$, was less than or equal to 2.5%, where D is the mean treatment difference (step-wise regimen minus basal–bolus regimen). If non-inferiority was confirmed, the superiority of the step-wise regimen over the basal–bolus regimen was to be investigated. Superiority was considered confirmed if the upper bound of the two-sided 95% CI, which was calculated using the FAS, was below 0%. The PP analysis was considered supportive.
  - ***Sensitivity analysis - s***ensitivity analyses were performed using the FAS only. All observed HbA_{1c} measurements (change from baseline) available post randomisation at scheduled measurement times were analysed in a linear mixed model using an unstructured residual covariance matrix (if possible). The results were compared to the results of the last observation carried forward (LOCF) method for dealing with missing data.
- **Analysis of other secondary endpoints -** DiabMedSat, TRIM-D and DPM: Scores were analysed separately using a normal linear regression model (an ANCOVA method) including treatment, strata and region as factors, and the corresponding baseline score as covariate.
- **Analysis of secondary endpoints**
  - Change from baseline in HbA_{1c} after 10 and 21 weeks of treatment was analysed using a statistical model similar to the model for the primary endpoint. Change from baseline in HbA_{1c} after 10 and 21 weeks of treatment – per strata – was summarised descriptively by treatment.

- HbA_{1c} responder was a dichotomous endpoint (responder/non-responder) that was defined based on whether a subject met the ADA HbA_{1c} target at a given time point (HbA_{1c} <7% at 10, 21 and 32 weeks/end of trial). Responder analysis after 10, 21 and 32 weeks of treatments/end of trial was based on a logistic regression model using treatment, strata and region as factors, and baseline HbA_{1c} as covariate. Responders – per strata - after 10, 21 and 32 weeks of treatment were summarised descriptively by treatment
- FPG after 32 weeks of treatment, was analysed using a normal linear regression model (an ANCOVA method), with treatment, strata and region as factors, and baseline FPG as covariate. FPG after 10 and 21 weeks of treatment was summarised descriptively by treatment.
- A linear mixed effects model was fitted to the 7-point SMPG profile data after 32 weeks of treatment/end of trial. The 7-point SMPG profile after 10, 21 and 32 weeks of treatment was summarised descriptively by treatment.
- Post-prandial responder was a dichotomous endpoint (responder/non-responder). If a subject had 3 post-prandial readings ≤10.0 mmol/L (180 mg/dL) (1 reading from each main meal) at a given time point, the person was a responder at that time point. Responders after 10, 21 and 32 weeks of treatment/end of trial were summarised descriptively by treatment.
- Prandial PG increment for each meal was derived from the 7-point SMPG profile as the difference between PG values available 90 minutes after meal and before meal. Prandial PG increment for each meal was analysed using a normal linear regression model (an ANCOVA method) with treatment, strata and region as factors, and the relevant baseline value as covariate.
- The mean prandial PG increment over all meals was derived as the mean of all available meal increments. The endpoint after 32 weeks was analysed using a normal linear regression model (an ANCOVA method) with treatment, strata and region as factors, and the mean PG increment at baseline as covariate. The mean PG increment over 3 meals at 10 and 21 weeks of treatment was summarised descriptively by treatment.
- Prescribed and actual insulin dose per day were recorded together with time of administration. The prescribed and actual insulin dose (total, basal and bolus) were summarised descriptively according to treatment as dose in units and units/kg.
- The distribution of bolus injections was summarised descriptively.

- **Analysis of safety endpoints**
  - Treatment emergent AEs (TEAEs) were summarised descriptively. The summaries of TEAEs were made displaying the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per 100 subject years of exposure. These summaries were done by seriousness, severity, relation to insulin treatment, withdrawal due to AEs and outcome.
  - Body weight and BMI after 32 weeks of treatment were analysed using a normal linear regression model (an ANCOVA method) with treatment, strata and region as factors, and the relevant baseline value as covariate.
  - The summaries of treatment emergent hypoglycaemic episodes were made by displaying the number of subjects with at least one event, the percentage of subjects with at least one event, the number of events and the event rate per subject years of exposure. Separate summaries were made by severity considering all episodes, daytime and nocturnal episodes using the ADA definition and the additional minor category. The number of hypoglycaemic episodes was analysed using a negative binomial regression model. The model included treatment, strata and region as factors. Separate analyses were performed for severe or minor episodes considering all episodes, daytime and nocturnal episodes separately. A sensitivity analysis using the Wilcoxon test was done.
  - When analysing the periods separately, the ITT principle was violated for the 2 last periods (Week 11 to Week 22 and Week 22 to Week 32), because some subjects may have dropped out. These analyses were therefore considered exploratory. The analysis of each time period was similar to the analysis of the endpoint hypoglycaemic episodes at 32 weeks/end of trial.
  - Funduscopy and fundusphotography, physical examination, vital signs, ECG 12-lead findings and their change from baseline were summarised descriptively.
  - Change in laboratory values from baseline was summarised descriptively. Change from baseline in lipid endpoints was analysed separately using a normal linear regression model (an ANCOVA method) with treatment, strata and region as factors, and baseline value as covariate. Some of the endpoints may have needed to be log-transformed before they were analysed.

DEMOGRAPHY OF TRIAL POPULATION

- **Demographics and baseline characteristics**

	Step-wise	Basal-bolus	Total
Number of Subjects	201	200	401
Age (years)			
N	200	200	400
Mean (SD)	60.0 (9.1)	59.6 (9.5)	59.8 (9.3)
Median	59.7	59.4	59.7
Min ; Max	32.1 ; 84.8	35.0 ; 83.2	32.1 ; 84.8
Sex, N (%)			
N	201 (100.0)	200 (100.0)	401 (100.0)
Female	97 (48.3)	101 (50.5)	198 (49.4)
Male	104 (51.7)	99 (49.5)	203 (50.6)
Ethnic Origin, N (%)			
N	200 (100.0)	200 (100.0)	400 (100.0)
White	177 (88.5)	180 (90.0)	357 (89.3)
Black or African American	11 (5.5)	12 (6.0)	23 (5.8)
Asian	2 (1.0)	2 (1.0)	4 (1.0)
American Indian or Alaska Native	1 (0.5)	0 (0.0)	1 (0.3)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (4.5)	6 (3.0)	15 (3.8)
Ethnicity, N (%)			
N	192 (100.0)	193 (100.0)	385 (100.0)
Hispanic or Latino	75 (39.1)	70 (36.3)	145 (37.7)
Not Hispanic or Latino	117 (60.9)	123 (63.7)	240 (62.3)
Height (m)			
N	201	200	401
Mean (SD)	1.67 (0.11)	1.67 (0.10)	1.67 (0.10)
Median	1.67	1.67	1.67
Min ; Max	1.41 ; 2.01	1.43 ; 1.93	1.41 ; 2.01
Body Weight (kg)			
N	201	200	401
Mean (SD)	88.9 (18.7)	86.1 (15.2)	87.5 (17.1)
Median	86.9	85.0	85.5
Min ; Max	53.5 ; 158.8	46.7 ; 127.5	46.7 ; 158.8
BMI (kg/m^2)			
N	201	200	401
Mean (SD)	31.5 (4.8)	30.7 (4.6)	31.1 (4.7)
Median	31.2	30.8	31.0
Min ; Max	20.3 ; 41.5	20.5 ; 44.5	20.3 ; 44.5
Duration of Diabetes (year)			
N	201	200	401
Mean (SD)	12.8 (7.7)	12.5 (8.4)	12.6 (8.0)
Median	11.4	10.8	11.3
Min ; Max	1.4 ; 40.6	1.1 ; 58.6	1.1 ; 58.6

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

At randomisation, the mean HbA_{1c} in both treatment arms was 7.9. The mean FPG was 6.9 mmol/L, ranging from 3.1 to 14.1 mmol/L. There were no clinically relevant differences between the trial populations in the 2 treatment arms.

EFFICACY RESULTS

- **Primary endpoint - Change from baseline in HbA_{1c} at Week 32 (end of trial)**: The step-wise regimen was confirmed non-inferior to the basal-bolus regimen with respect to change from baseline in HbA_{1c} after 32 weeks. Sensitivity analyses supported the conclusion from the primary analysis. At Week 32 (end of trial), mean HbA_{1c} had decreased from baseline in both treatment arms, and there was no statistical significant difference between the treatments (mean change: −0.98% [step-wise arm] and −1.12% [basal-bolus arm]); treatment difference: 0.14% (absolute value) (−0.02; 0.30) $_{95\% CI}$ (p=0.088).
- **Secondary endpoints**
  - **Change from baseline in HbA_{1c} at 10 and 21 weeks:** The change from baseline in HbA_{1c} after 10 weeks (mean

change: −0.45% [step-wise arm] and −1.00% [basal-bolus arm]; treatment difference: 0.55 [0.42; 0.69] $_{95\% CI}$ [p<0.001]) and 21 weeks (mean change: −0.78 and −1.15; treatment difference: 0.37 [0.21; 0.53] $_{95\% CI}$ [p<0.001]) was significantly smaller for the step-wise regimen compared to the basal-bolus regimen.

- **Proportion of subjects reaching HbA_{1c} <7.0%:** The step-wise regimen had a significantly lower number of responders at Week 10 (estimated odds ratio (OR): 6.85 [4.12;11.39] $_{95\% CI}$, p<0.001) and Week 21 (estimated OR: 2.38 [1.56; 3.64] $_{95\% CI}$, p<0.001) compared to the basal-bolus regimen. At Week 32 there was no difference between the treatment arms (estimated OR: 1.36 [0.90; 2.07]] $_{95\% CI}$, p=0.146).
- **FPG:** There was no difference between the treatment arms in the observed mean FPG at Weeks 10, 21 and 32. At end of trial, the estimated mean FPG was 7.12 mmol/L in the step-wise arm and 7.01 mmol/L in the basal-bolus arm. There was no statistically significant difference between the treatment arms (0.12 [−0.37; 0.60] $_{95\%}$ CI; p=0.635).
- **7-point SMPG profile:** At 90 minutes after start of breakfast, before lunch and before bedtime the SMPG-values (mmol/L) were significantly higher (0.65 [0.05, 1.26] $_{95\% CI}$, 0.57 [0.10, 1.04] $_{95\% CI}$ and 0.73 [0.27, 1.20] $_{95\% CI}$) in the step-wise regimen compared to the basal-bolus regimen at Week 32. For the remaining time points no difference was observed.
- **Proportion of subjects with post-prandial readings ≤10.0 mmol/L (180 mg/dL):** There was a greater proportion of responders in the basal-bolus arm than in the step-wise arm (60.1% vs. 31.2% [Week 10], 59.2% vs. 40.0% [Week 21] and 61.0% vs.45.7% [Week 32]).
- **Mean PG increment over 3 meals (breakfast, lunch and dinner):** The estimated mean prandial increment (mmol/L) was statistically significantly larger in the step-wise arm than in the basal-bolus arm (estimated treatment difference: 0.36 [0.01; 0.71]; p=0.046) at Week 32.
- **Prandial PG increments at breakfast, lunch and dinner:** At Week 32, the observed mean prandial PG increments for breakfast was greater for the step-wise arm (2.5 mmol/L) than the basal-bolus arm (1.8 mmol/L); this was statistically significant with an estimated treatment difference of 0.61 [0.07; 1.16] $_{95\% CI}$ (p= 0.028). At lunch and dinner there were no noticeable differences between the treatment groups.
- **Insulin dose, total, basal and bolus:** The actual mean daily basal insulin dose (U) was similar in the treatment groups at Week 0, but was slightly higher in the step-wise arm than in the basal-bolus arm at Weeks 10, 21 and 32. The actual mean daily bolus insulin dose (U) increased rapidly in the basal-bolus arm until Week 10 (as expected); whereas in the step-wise arm there was a gradual increase during the trial from Week 0 until Week 32 (end of trial). The mean total insulin dose (U) was higher in the basal-bolus arm than in the step-wise arm from Week 0 until Weeks 24 mainly due to a higher bolus insulin dose in the basal-bolus arm. From Week 24 till end of trial the mean total insulin dose (U) was similar in the treatment arms.
- **Distribution of bolus injections (number, meal and dose):** 59.2% of the subjects in the step-wise arm added their first bolus injection at lunch, 32.8% at dinner and 4.5 % at breakfast. At Week 32 (end of trial), most subjects on 1 bolus were injecting at lunch and in those subjects on 2 bolus injections most subjects were injecting at lunch and dinner. At end of trial, 40.3% of all subjects in the step-wise arm required 3 bolus injections. The distribution of bolus injections within the treatment arms while taking strata into consideration as well as the distribution of bolus injections per meal during trial by treatment week and strata seemed similar.
- **Association of duration of previous basal therapy with HbA_{1c}:** There was no clear connection between the duration of previous basal therapy and the HbA_{1c} change from baseline obtained in this trial in either of the treatment arms at Week 32.

- **Quality of life assessments**
  - **DiabMedSat**: The DiabMedSat measure was scored as an overall score (0-100 scale) as well as 3 subscale scores: burden, efficacy and symptoms. At end of trial, for burden, efficacy and overall score, subjects were more content in the step-wise arm than in the basal-bolus arm: burden (treatment difference: 4.67 [1.66; 7.67] $_{95\% CI}$; p= 0.002), efficacy (5.86 [1.86; 9.86]$_{95\% CI}$; p-value 0.004) and overall score (3.59 [0.98; 6.21]$_{95\% CI}$; p= 0.007).
  - **TRIM-D**: The TRIM-D measure was scored as an overall score as well as 5 subscale scores: Treatment burden, daily life, diabetes management, compliance and psychological health. There were no statistically significant treatment differences between the step-wise arm and the basal-bolus arm for any of the categories at end of trial.
  - **DPM**: The DPM was scored in two domains: life productivity and work productivity. No overall score was calculated. There were no statistically significant treatment differences between the step-wise arm and the basal-bolus arm for any of the DPM domains at end of trial (p=0.881 and p=0.568, respectively).

SAFETY RESULTS

- **AEs:** The percentage of subjects reporting TEAEs was similar in the treatment arms. The event rate for TEAEs was lower for subjects in the step-wise arm than for those in the basal-bolus arm (280.3 vs. 304.7 events/100 exposure years, respectively). The most frequently reported TEAEs in both treatment arms were nasopharyngitis and influenza.
- **SAEs:** In the step-wise arm, 18 subjects had 23 SAEs and in the basal-bolus arm 15 subjects had 18 SAEs. Except for 'hypoglycaemia' for which there were 2 cases (3 events) and 5 cases (6 events) in the step-wise arm and basal-bolus arm, respectively; and 3 cases (3 events) of 'hypoglycaemic unconsciousness' in the basal-bolus arm, none of the preferred terms reported as SAEs occurred in more than 1 subject. There were no SAEs leading to withdrawal.
- **Deaths:** There were 3 deaths during this trial: 1 in the basal-bolus arm (due to severe acute myocardial infarction and [redacted]), 1 during the run-in period (due to severe anaesthetic complication [redacted] surgery) and 1 during screening (due to [redacted] and [redacted] [tumour] in [redacted] lung [redacted]).
- **Central laboratory assessment:** No clinically relevant changes were observed from baseline to end of treatment in the 2 treatment groups in mean laboratory values, and there was no clinically relevant difference between the treatment groups.
- **Body weight and BMI at Week 32:** The mean body weight and the mean BMI increased in both treatment arms. There was no statistically significant difference between the treatment arms at end of trial for mean body weight and BMI.
- **Hypoglycaemic episodes:** Overall, subjects in the step-wise arm had fewer hypoglycaemic episodes (all) compared to subjects in the basal-bolus arm. The rate of hypoglycaemic episodes (all) was higher in the basal-bolus regimen throughout the trial.
- **Vital signs, ECG, funduscopy, physical examination and laboratory values:** No clinically relevant differences between the treatment arms were observed.

CONCLUSIONS

- The step-wise regimen was non-inferior to the basal-bolus regimen with respect to change from baseline in HbA_{1c} after 32 weeks
- The change from baseline in HbA_{1c} after 10 and 21 weeks was statistically significantly smaller in the step-wise arm than in the basal-bolus arm. The step-wise regimen had a significantly lower number of responders at Week 10 and 21 compared to the basal-bolus regimen and at Week 32 there was no difference between the treatment arms. There was no difference in FPG between the treatment groups.
- The estimated mean prandial increment was statistically significantly larger in the step-wise arm than in the basal-bolus arm at Week 32.
- Patient reported outcomes indicated that subjects in the step-wise arm were just as or more content that subjects on the basal-bolus regimen
- In the step-wise regimen there was a statistically significantly lower rate of hypoglycaemia than in the basal-bolus arm
- No clinically relevant differences were observed between the treatment groups with respect to AEs, safety laboratory parameters, ECG, physical examination, funduscopy or vital signs
- A higher proportion of subjects withdrew from the trial in the basal-bolus arm than in the step-wise arm
- Overall, both a complete basal-bolus treatment regimen and a step-wise addition of bolus insulin can be used to obtain a significant improvement in overall glycaemic control after 32 weeks of treatment. For the prandial increments and post-prandial responders, the difference was in favour of initiation of a complete basal-bolus regimen. However, a significantly lower rate of hypoglycaemia was seen in the step-wise regimen.

The trial was conducted in accordance with the Declaration of Helsinki (59th WMA General Assembly, 2008) *and ICH Good Clinical Practice* (E6(R1), Step 4, 1996).

The results presented reflect the data available in the clinical database as of 14-May-2012