2 Synopsis

Trial registration ID-number NCT01326026	**UTN –** U1111-1117-0616 **IND number –** 76,496. Seq no: 0138 **EudraCT number –** 2010-022337-29
Title of trial A trial comparing the efficacy and safety of insulin degludec once daily in insulin naïve subjects with type 2 diabetes mellitus when titrated using two different titration algorithms (BEGIN™:ONCE SIMPLE USE)	
Investigators There were 43 principal investigators (1 principal investigator was appointed per site) [redacted] was appointed signatory investigator, [redacted]	
Trial sites The trial was conducted at 43 sites in 4 countries: Finland (5 sites), Germany (6 sites), Spain (6 sites) and United States (26 sites)	
Publications None	
Trial period Initiation date: 30 March 2011 Completion date: 20 December 2011	**Development phase** Phase 3b

Objectives

Primary objective:

- To confirm the efficacy of the insulin degludec (IDeg) once daily(OD) simple titration algorithm + metformin in controlling glycaemia with respect to change from baseline HbA_{1c} after 26 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDeg OD using the simple algorithm + metformin and IDeg OD using the step wise algorithm + metformin, to a non-inferiority limit of 0.4%

Secondary objectives:

- To compare the efficacy and safety of the two different titration algorithms after 26 weeks of treatment in terms of:
  - Other parameters for glycaemic control
  - Safety
- To describe subject satisfaction with the investigational pen PDS290

Methodology

This was a 26-week, randomised, open labelled, stratified, multinational, multi-centre, two-armed parallel group, treat-to target efficacy and safety trial comparing two self-titration algorithms for IDeg OD in combination with metformin treatment in insulin naïve subjects with type 2 diabetes mellitus inadequately treated on oral antidiabetics (OADs) alone. After discontinuation of all OADs other than metformin, subjects were randomised 1:1 into one of two parallel IDeg OD treatment arms. Subjects were instructed to continue with the same dose of metformin as before start of the trial. The treatment arms differed by the titration algorithm applied: a simple titration algorithm vs. the step wise titration algorithm. All subjects were instructed and encouraged to self titrate in accordance with their respective algorithms. The investigator was overall responsible for the titration and supervised dose adjustments at the visits/telephone contacts and in between visits, if needed. Total trial duration for the individual subjects was approximately 28 weeks.

Number of subjects planned and analysed

The number of subjects planned to be randomised was at least 218 subjects, in order to have at least 85% power for the evaluation of the per protocol (PP) analysis set. The subject disposition is shown in Table 1.

Table 1 Subject disposition

	IDeg Simple N (%)	IDeg Step wise N (%)	Total N (%)
Screened			313
Screening Failures			91
Withdrawn before Randomisation			0
Randomised	111 (100.0)	111 (100.0)	222 (100.0)
Exposed	110 (99.1)	111 (100.0)	221 (99.5)
Withdrawn at/after Randomisation	12 (10.8)	13 (11.7)	25 (11.3)
Adverse Event	4 (3.6)	3 (2.7)	7 (3.2)
Withdrawal Criteria	5 (4.5)	7 (6.3)	12 (5.4)
Other	3 (2.7)	3 (2.7)	6 (2.7)
Completed	99 (89.2)	98 (88.3)	197 (88.7)
Full Analysis Set	111 (100.0)	111 (100.0)	222 (100.0)
PP Analysis Set	104 (93.7)	102 (91.9)	206 (92.8)
Safety Analysis Set	110 (99.1)	111 (100.0)	221 (99.5)

N. Number of subjects, %: Proportion of randomised subjects

Diagnosis and main criteria for inclusion

Male or female subjects ≥ 18 years of age with type 2 diabetes (diagnosed clinically) for ≥ 24 weeks prior to randomisation, who were insulin naïve and currently treated with metformin (≥1000 mg/day) ± any combination with 1 or 2 other OADs including insulin secretagogues (sulfonylurea or glinide), dipeptidyl peptidase IV (DPP-IV) inhibitors, α-glucosidase inhibitors, thiazolidinediones (TZDs) all with unchanged dosing for at least 12 weeks prior to randomisation, with HbA_{1c} 7.0-10.0% (inclusive) and body mass index (BMI) ≤ 45 kg/m^2. Subjects were excluded if they had been treated with GLP-1 receptor agonists within the last 12 weeks prior to randomisation, or were diagnosed with a life threatening disease. Subjects were to be withdrawn from the trial if they were judged to be non compliant with trial procedures.

Investigational medicinal product and/or investigational medical device, dose and mode of administration, batch number

The IDeg formulation used in this trial was: Insulin degludec 100 U/mL, containing 600 nmol/mL in 3 mL prefilled investigational pen (PDS290). Batch number YP5228. IDeg was to be injected subcutaneously OD. A variation of injection time from day to day was allowed, with a minimum of 8 hours and a maximum of 40 hours between injections. Subjects were to follow a simple titration algorithm: self-titration was performed once weekly based upon a single pre-breakfast self measured plasma glucose (SMPG) value measured on the day of insulin titration.

Duration of treatment

The planned duration of treatment was 26 weeks. The mean duration of exposure was 0.47 years.

Reference therapy dose and mode of administration, batch number

The same investigational product was used in both treatment arms. The IDeg formulation used in this trial was: Insulin degludec 100 U/mL, containing 600 nmol/mL in 3 mL prefilled investigational pen (PDS290). Batch number YP5228. IDeg was to be injected subcutaneously OD. A variation of injection time from day to day was allowed, with a minimum of 8 hours and a maximum of 40 hours between injections. Subjects were to follow a step wise

titration algorithm: self-titration was performed once weekly based on the lowest value of three pre-breakfast SMPG values measured on three consecutive days, the two days prior to and on the day of insulin titration.

Criteria for evaluation – efficacy

- HbA_{1c}
- Fasting plasma glucose (FPG)
- SMPG
  - Pre-breakfast SMPG used for titration
  - 8–point SMPG profiles
  - Prandial increment
  - fluctuation

Criteria for evaluation – other

- Patient Reported Outcome (PRO)

Criteria for evaluation – safety

- Adverse events
- Hypoglycaemia
- Body weight
- Insulin dose
- Fundoscopy/fundus photography
- Vital signs
- Physical examination
- ECG
- Laboratory safety variables

Statistical methods

The sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in subjects with type 2 diabetes treated with insulin, an estimate for the standard deviation (SD) of 0.9% for HbA_{1c} was used in the sample size calculation. The specifications applied for the sample size calculation are shown in Table 2. The minimum sample size required to meet the primary objective with at least 85% power was 184 subjects with an assumed SD of 0.9%.

Table 2 Specification Assumed for Sample Size Calculation

Statistical test	One sided significance level	Non-inferiority margin	SD	Mean difference	Randomisation scheme	Required power
Two-group t test	2.5%	0.4% (absolute)	0.9	0.0	1:1	85%

The analysis sets were defined as follows:

- Full Analysis Set (FAS): includes all randomised subjects. The statistical evaluation of the FAS will follow the intention-to-treat principle and subjects contribute to the evaluation "as randomised"
- Per Protocol (PP) Analysis Set: includes all subjects in the FAS who have not violated any inclusion/exclusion criteria, have a non-missing HbA_{1c} at screening or randomisation and have at least one non-missing HbA_{1c} after 12 weeks of exposure. Moreover, subjects must be exposed for more than 12 weeks. Subjects in the PP analysis set contribute "as treated"
- Safety Analysis Set: includes all subjects receiving at least one dose of IDeg. Subjects in the safety set contribute to the evaluation "as treated"

Statistical Analysis

Change from baseline in HbA_{1c} after 26 weeks of treatment was analysed using an Analysis of Variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors and age and baseline HbA_{1c}

as covariates. The antidiabetic therapy at screening was a factor with the following three levels: 1) metformin monotherapy 2) metformin + additional OAD excluding TZD 3). metformin + additional OAD including TZD. Region is a factor with 2 levels: 1) EU and 2) North America. A non-inferiority approach was used and non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4% or equivalent, if the p-value for the one-sided test of

H0: $D > 0.4\%$ against HA: $D \leq 0.4\%$,

is less than or equal to 2.5%, where D is the mean treatment difference (IDeg simple minus IDeg step wise). Sensitivity Analyses- Sensitivity analyses were performed using the FAS only. All observed HbA_{1c} measurements available post randomisation (at scheduled measurement times) were also analysed in a linear mixed model with the same fixed effects as for the primary analysis, together with an interaction between visit and treatment and using an unstructured residual covariance matrix (if possible). Change in HbA_{1c} from baseline was also analysed using a model with treatment as the only fixed factor and baseline HbA_{1c} as covariate to assess the sensitivity of the results to the inclusion/exclusion of fixed factors and covariates. The primary efficacy analysis was also repeated on the set of all completed subjects.

FPG- Change from baseline in FPG was analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline FPG as covariates.

Responder for HbA_{1c} endpoints-Two dichotomous endpoints (responder/non-responder) were defined based on whether a subject met the American Diabetes Association (ADA) target ($HbA_{1c} < 7.0\%$) and the International Diabetes Federation (IDF) target ($HbA_{1c} \leq 6.5\%$). Responder without hypoglycaemic episodes is a dichotomous endpoint (responder/non-responder) that was defined based on whether a subject had met the target of $HbA_{1c} < 7\%$ at end of trial without treatment emergent severe or minor hypoglycaemic episodes during the last 12 weeks of treatment, or within 7 days after the last randomised treatment. A similar responder endpoint was defined where the definition is instead based on whether a subject met the target $HbA_{1c} \leq 6.5\%$.

8-point SMPG Profile- An 8-point SMPG profile includes measurements before and 90 minutes after start of breakfast, lunch and main evening meal, measurements prior to bedtime, and one measurement before breakfast the following day. The mean of the 8-point SMPG profile was defined as the area under the profile divided by the measurement time and was calculated using the trapezoidal method. The fluctuation in the 8-point SMPG profile was defined as

$$\frac{1}{T}\int_0^T \left| PG(t) - \overline{PG} \right| dt$$

where T, PG(t) and $\overline{PG}$ denotes the length of the profile, the PG value at time *t* and the mean of the profile, respectively. Prandial PG increment for each meal were derived from the 8-point SMPG profile as the difference between PG values available 90 minutes after meal and before meal. Mean prandial PG increment over all meals was derived as the mean of all available meal increments. A mixed effect model was to be fitted to the 8-point SMPG profile data. The model included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, , sex and region as fixed factors, age and baseline value as covariate and subject as random effect. From this model, mean profile by treatment and relevant treatment differences were estimated and explored. Mean and fluctuation in the 8-point SMPG profile as well as prandial PG increment was analysed separately using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and the relevant baseline value as covariates. Fluctuation in the 8-point SMPG profile was logarithmically transformed before being analysed.

Adverse events- A treatment emergent adverse event (TEAE) was defined as an event that has 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 summarised using descriptive statistics.

Hypoglycaemic Episodes- 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 7 days after the last day of randomised treatment. A nocturnal hypoglycaemic episode was defined as a hypoglycaemic episode with time of onset between 00:01 and 05:59 a.m. (both included). Hypoglycaemic episodes were classified according to the ADA into the following five categories based on blood glucose measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Furthermore, confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and minor hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (56 mg/dL). The number of treatment emergent confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate.

Other safety endpoints- Physical examination, vital signs, laboratory assessments, fundoscopy and fundus photography, and ECG were summarised descriptively including the change from baseline. Change from baseline in lipid endpoints was analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline value as covariates.

The insulin dose was summarised descriptively according to regimen as dose in units.

Change from baseline in body weight after 26 weeks of treatment was analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline body weight as covariates.

Patient Reported Outcome- Device Specific Questionnaires I and II were used to describe subject satisfaction with the investigational pen. The score was summarised descriptively.

Demography of trial population

The trial population was generally well matched with only small differences between the treatment arms. The population consisted of subjects with type 2 diabetes mellitus, with a mean age of 58.9 years (range 32.5-79.4 years) and a mean duration of diabetes of 9.2 years (range 0.5–43.7 years), mean HbA_{1c} of 8.1 % and a mean BMI of 32.4 kg/m^2. Overall more male subjects were enrolled (64.4%) than females, this trend was apparent in both treatment arms. Approximately 28% of subjects in each treatment arm were elderly (>65 years of age). The mean body weight and BMI were slightly higher in the IDeg simple arm compared to the IDeg step wise arm, as shown in Table 3. The majority of subjects were White (88.3%).

Table 3 Demographics

	IDeg Simple N (%)	IDeg Step wise N(%)	Total N (%)
Number of Subjects	111	111	222
Sex			
N	111 (100.0)	111 (100.0)	222 (100.0)
Female	43 (38.7)	36 (32.4)	79 (35.6)
Male	68 (61.3)	75 (67.6)	143 (64.4)
Age (years)			
N	111	111	222
Mean (SD)	59.4 (9.5)	58.5 (11.1)	58.9 (10.3)
Median	60.6	58.7	59.4
Min ; Max	32.5 ; 77.4	34.9 ; 79.4	32.5 ; 79.4
Body Weight (kg)			
N	111	111	222
Mean (SD)	95.7 (18.9)	91.3 (18.2)	93.5 (18.7)
Median	92.2	87.8	90.9
Min ; Max	56.0 ; 158.1	52.0 ; 138.0	52.0 ;158.1

BMI (kg/m^2)			
N	111	111	222
Mean (SD)	33.4 (5.8)	31.5 (5.2)	32.4 (5.6)
Median	32.6	31.0	31.6
Min ; Max	22.0 ; 44.7	21.2 ; 44.4	21.2 ; 44.7
Duration of Diabetes (years)			
N	111	111	222
Mean (SD)	8.9 (5.5)	9.6 (7.2)	9.2 (6.4)
Median	7.9	8.8	8.5
Min ; Max	0.5 ; 29.8	0.7 ; 43.7	0.5 ; 43.7
HbA_{1c} (%)			
N	111	111	222
Mean (SD)	8.1 (0.9)	8.2 (0.9)	8.1 (0.9)
Median	7.8	8.0	8.0
Min ; Max	6.8 ; 10.4	6.9 ; 10.2	6.8 ; 10.4
FPG (mmol/L)			
N	108	107	215
Mean (SD)	9.3 (2.6)	9.4 (2.8)	9.4 (2.7)
Median	8.7	9.2	8.9
Min ; Max	4.9 ; 18.5	3.8 ; 19.1	3.8 ; 19.1

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation. Some subjects experienced changes in HbA_{1c} between screening and randomisation, all randomised subjects had an HbA_{1c} value at screening of 7.0-10.0%

Efficacy results

After 26 weeks of treatment with IDeg OD + metformin using a step wise or a simple titration algorithm, the following was concluded:

- **Primary endpoint**: IDeg adjusted using a simple titration algorithm effectively improved glycaemic control in terms of lowering HbA_{1c} (non-inferiority to IDeg step wise was confirmed); estimated mean treatment difference (IDeg simple−IDeg step wise): -0.16%- points $[-0.39;0.07]_{95\%\ CI}$ with an estimated reduction of -1.13%-points in the IDeg simple arm and -0.97%-points in the IDeg step wise arm. After 26 weeks observed HbA_{1c} was lowered from 8.1% (0.9) to 7.0% (1.0) with IDeg simple and 8.2% (0.9) to 7.2% (0.9) with IDeg step wise.

- **Fasting plasma glucose**: Mean observed FPG (SD) was lowered from 9.3 (2.6) to 6.1 (2.8) mmol/L in the IDeg simple arm and from 9.4 (2.8) to 6.8 (2.9) mmol/L in the IDeg step wise arm at end of trial, representing an estimated change from baseline of -3.24 mmol/L and -2.68 mmol/L. There was no statistically significant difference between the groups (estimated mean treatment difference IDeg simple–IDeg step wise of –0.57mmol/L $[-1.30 ; 0.17]_{95\%\ CI}$).

- **Subjects achieving HbA_{1c} targets**: After 26 weeks of treatment, a significantly greater proportion of subjects achieved the HbA_{1c} <7.0% target in the IDeg simple arm compared to the IDeg step wise arm (56.8% vs 41.4% respectively, estimated odds ratio 1.93 $[1.04 ; 3.55]_{95\%\ CI}$) whilst the proportions of subjects achieving $HbA_{1c} \leq 6.5\%$ (37.8% vs 24.3% respectively) were not significantly different. More subjects achieved $HbA_{1c} < 7.0\%$ without confirmed hypoglycaemia with IDeg simple (40.6%) than with IDeg step wise (34.6%) although this difference was not statistically significant. Likewise, 25.5% (IDeg simple) and 20.2% (IDeg step wise) of subjects achieved $HbA_{1c} \leq 6.5\%$ without confirmed hypoglycaemia (not significant).

- **8-Point SMPG:** Mean SMPG decreased in both groups during the course of the trial and the mean 8-point SMPG profiles in each treatment group were similar (estimated mean treatment difference

IDeg simple–IDeg step wise: –0.03 mmol/L [-0.54 ; 0.48] $_{95\% CI}$). There were no statistically significant differences between groups in the 8-Point SMPG endpoints.

- After 26 weeks of treatment, the fluctuation was similar (1.0 mmol/L) in both groups.
- Prandial increments at baseline and end of trial were similar in both groups.

- **SMPG for titration**: The observed mean pre-breakfast SMPG after 26 weeks of treatment was 5.6 mmol/L in the IDeg simple arm and 5.9 mmol/L in the IDeg step wise arm.

Other endpoints

- **Patient reported outcome**: The majority of subjects reported satisfaction with the investigational device PDS290, and at 26 weeks all subjects responded that they would recommend the pen.

Safety results

- **Adverse events:** The percentage of subjects reporting treatment emergent AEs was similar in the IDeg simple (60.0%) and IDeg step wise (62.2%) arms, and the event rate for AEs was similar in the 2 groups. The rate of AEs possibly or probably related to trial product was 53 (IDeg simple) and 40 (IDeg step wise) events per 100 patient years exposure (PYE). The most frequently reported AEs in both treatment groups were headache and nasopharyngitis. The percentage of subjects experiencing injection site reactions was 2.7% in the IDeg simple arm (3 events in 3 subjects) and 4.5% in the IDeg step wise arm (16 events in 5 subjects).

- **Deaths, serious adverse events and other significant adverse events:** One death occurred in this trial in the IDeg simple treatment group (metastases to liver from primary lung cancer). A total of 5 (4.5%) subjects reported 8 SAEs in the IDeg simple arm while 7 (6.3%) subjects reported 8 SAEs in the IDeg step wise arm. The rate of SAEs was the same in both groups (15 events per 100 PYE).

- **Hypoglycaemia:** The rate of confirmed hypoglycaemia was 160 vs. 117 events per 100 PYE in the IDeg simple arm vs. the IDeg step wise arm respectively, the difference was not statistically significant (estimated treatment ratio IDeg simple/IDeg step wise: 1.25 [0.72 ; 2.14]$_{95\% CI}$). The rate of nocturnal confirmed hypoglycaemia was low in both groups (21 vs. 10 events per 100 PYE respectively), with no statistically significant difference between groups. One case of severe hypoglycaemia was reported, in the IDeg simple arm. This event was nocturnal and occurred [redacted] days after last trial product administration.

- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values:** No clinically relevant differences from baseline to end of trial, or between the two treatment arms were observed.

- **Insulin dose:** The mean insulin total daily dose after 26 weeks was higher in the IDeg simple arm (62 U, 0.61 U/kg) compared with the IDeg step wise arm (48 U, 0.50 U/kg). The mean insulin total daily dose ratio IDeg simple/IDeg step wise at 26 weeks was 1.28.

- **Body weight:** Mean body weight increased from 95.7 kg to 97.3 kg in the IDeg simple arm and from 91.3 kg to 92.4 kg in the IDeg step wise arm. The estimated treatment difference (IDeg simple −IDeg step wise) was 0.46 kg [-0.35; 1.26]$_{95\%CI}$ showing no significant difference between the treatment arms.

Conclusions

The results of this randomised, controlled, 26-week trial demonstrate the efficacy and safety of IDeg OD when titrated using two different titration algorithms, in insulin-naïve subjects with type 2 diabetes mellitus inadequately treated on OADs alone. The data support the following conclusions:

- IDeg titrated using a simple titration algorithm effectively improves long-term glycaemic control as measured by HbA_{1c} and the data confirm non-inferiority to IDeg using a step wise titration algorithm.
- FPG decreases to a similar level with IDeg titrated using a simple titration algorithm or step wise algorithm.
- The proportion of subjects achieving the treatment target ($HbA_{1c} < 7\%$) without confirmed hypoglycaemia is similar in both treatment arms.
- The rate of confirmed hypoglycaemic episodes is not statistically significantly different between treatment arms. The rate of nocturnal confirmed hypoglycaemic episodes is low and not statistically significantly different between treatment arms.
- In this trial no safety issues are identified with IDeg; there are no apparent differences between IDeg simple titration and IDeg step wise titration with respect to AEs and standard safety parameters.

The trial was conducted in accordance with the Declaration of Helsinki (1)and ICH Good Clinical Practice (2)

The results presented reflect data available in the clinical database as of 23 January 2012