CTR synopsis

Trial registration ID-number NCT01392573	**UTN – U1111-1121-4897** **IND number – 109121** **EudraCT number – 2011-002336-72**

TITLE OF TRIAL

DUAL™ II: A trial comparing the efficacy and safety of insulin degludec/liraglutide (IDegLira) and insulin degludec (IDeg) in subjects with type 2 diabetes.

A 26-weeks randomised, parallel, two-arm, double-blind, multi-centre, multinational, treat-to-target trial comparing fixed ratio combination of IDeg and liraglutide with IDeg in subjects with type 2 diabetes.

INVESTIGATOR(S)

A total of 75 principal investigators in 7 countries. The appointed signatory investigator was:

Dr. [redacted]

TRIAL SITE(S)

75 sites in 7 countries actively screened subjects: Bulgaria (6), Switzerland (2), Denmark (3), Hungary (3), India (6), Slovenia (3), and the United States (52).

PUBLICATIONS

None as of the date of this report.

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 28-Nov-2011 Completion date: 04-Oct-2012	Phase 3a

OBJECTIVES

As stated in the protocol and amendments, the objectives of the trial were:

Primary objective:

- To confirm the superiority of IDegLira vs. IDeg in controlling glycaemia in subjects with type 2 diabetes.

Secondary objectives:

- To compare the overall efficacy and safety parameters of IDegLira and IDeg after 26 weeks of treatment.

METHODOLOGY

The present trial was a 26-week, randomised, parallel two-arm, double-blind, multi-centre, multinational, treat-to-target trial in subjects with type 2 diabetes inadequately controlled with basal insulin and metformin with or without SU or glinides comparing the efficacy and safety of IDegLira once daily with IDeg once daily both added on to metformin. Inadequately controlled type 2 diabetes was defined as an HbA_{1c} level of 7.5-10.0% (both inclusive).

Eligible subjects were randomised 1:1 to 2 treatment arms consisting of once daily IDegLira or once daily IDeg both in combination with metformin. Pre-trial treatment with basal insulin and SU or glinides (if applicable) was to be discontinued at Visit 2. Throughout the trial, metformin treatment should be maintained at the stable, pre-randomisation dose and frequency, although dose adjustments for safety reasons were allowed.

The starting dose was 16 dose steps (16 units IDeg and 0.6 mg liraglutide) for IDegLira and 16 units for IDeg. The IDegLira starting dose of 16 dose steps is in accordance with the recommended start dose of 0.6 mg/day with Victoza®. This was followed by a treat-to-target approach with adjustment of doses to achieve the fasting plasma glucose target of 4.0−5.0 mmol/L equivalent to 72−90 mg/dL. Doses were titrated twice weekly according to the predefined titration algorithm, which was based on the mean of 3 preceding daily fasting self-measured pre-breakfast glucose levels values on 3 consecutive days. The maximum allowed dose was 50 dose steps (50 units IDeg/1.8 mg liraglutide) for IDegLira and 50 units for IDeg.Subjects were to measure fasting SMPG values during the trial. Starting at Visit 3, subjects were instructed to record the date, time and dose in the 3 days leading up to the titration day, in the diary.

Subject disposition

	IDegLira N (%)	IDeg N (%)	Total N (%)
Screened			831
Screening Failures			418
Withdrawn before Randomisation			0
Randomised	207 (100.0)	206 (100.0)	413 (100.0)
Exposed	207 (100.0)	206 (100.0)	413 (100.0)
Withdrawn at/after Randomisation	32 (15.5)	35 (17.0)	67 (16.2)
Adverse Event	1 (0.5)	3 (1.5)	4 (1.0)
Ineffective Therapy	1 (0.5)	2 (1.0)	3 (0.7)
Non-Compliance With Protocol	0 (0.0)	2 (1.0)	2 (0.5)
Withdrawal Criteria	13 (6.3)	15 (7.3)	28 (6.8)
Other	17 (8.2)	13 (6.3)	30 (7.3)
Completed	175 (84.5)	171 (83.0)	346 (83.8)
Full Analysis Set	199 (96.1)	199 (96.6)	398 (96.4)
Safety Analysis Set	199 (96.1)	199 (96.6)	398 (96.4)

NUMBER OF SUBJECTS PLANNED AND ANALYSED

Planned sample size was 191 in the IDegLira arm and 191 in the IDeg arm. Hence the total number of planned randomised subjects was set to 382. Full analysis set and safety analysis set each included 199 subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

- **Main inclusion criteria:** subjects with type 2 diabetes, male or female, age 18 years or above, HbA_{1c} 7.5–10.0 % (both inclusive). Subjects on stable daily doses for at least 90 days prior to screening of basal insulin (e.g. insulin glargine, insulin detemir, NPH insulin) (total daily dose within the range of 20–40 units, individual fluctuations of ±10% within the 90 days prior to screening) and metformin (≥ 1500 mg or maximum tolerated dose) with or without SU (≥ half of maximum approved dose according to local label) or glinides (≥ half of maximum approved dose according to local label), BMI ≥ 27 kg/m2, able and willing to perform self-monitoring of plasma glucose according to the protocol, to keep a diabetes diary and willing to use a pen-injector or FlexPen® device. Informed consent was obtained before any trial-related activities.
- **Main exclusion criteria:** Use of any drugs (except for basal insulin, metformin, SU or glinides), which in the Investigator's opinion could interfere with glucose level (e.g. systemic corticosteroids), treatment with GLP-1 receptor agonists e.g.exenatide, liraglutide), dipeptidyl peptidase 4 (DPP-4) inhibitors and/or thiazolidinediones within 90 days prior to trial, Subjects with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for type 2 diabetes), neurological, genitourinary or haematological system (except for conditions associated with type 2 diabetes), that in the opinion of the Investigator, may confound the results of the trial or pose additional risk in administering trial drug, impaired liver function, defined as ALAT ≥ 2.5 times UNR, impaired renal function defined as serum-creatinine ≥ 133 µmol/L (≥ 1.5 mg/dL) for males and ≥ 125 µmol/L (≥ 1.4 mg/dL) for females, screening calcitonin ≥ 50 ng/L
- **Main withdrawal criteria:** Initiation of any systemic treatment with products which in the investigator's opinion could interfere with glucose or lipid metabolism, pregnancy or intention of becoming pregnant, repeatable hyperglycaemia (11.1–15.0 mmol/L depending on trial progress), subjects diagnosed with acute pancreatitis were to be withdrawn from the trial

INVESTIGATIONAL MEDICINAL PRODUCT AND/OR INVESTIGATIONAL MEDICAL DEVICE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

IDegLira − 100 units/3.6 mg per mL (fixed dose ratio of IDeg and liraglutide, respectively), and supplied in a 3 mL prefilled FlexPen®. IDegLira was injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen once daily at the same time each day. Treatment with IDegLira was initiated at 16 dose steps (equivalent to 16 units IDeg and 0.6 mg liraglutide). Adjustment of IDegLira was performed twice weekly based on the mean of 3 preceding daily

fasting SMPG measurements on 3 consecutive days prior to each dose adjustment). Adjustments occurred in 2 dose steps (2 units IDeg and 0.072 mg liraglutide) until the fasting glycaemic target of 4.0–5.0 mmol/L (72–90 mg/dL) was reached. The maximum allowed dose was 50 dose steps (50 units IDeg/ 1.8 mg liraglutide). Batch No. AP51384..

DURATION OF TREATMENT

26 weeks

REFERENCE THERAPY AND/OR NON-INVESTIGATIONAL MEDICAL DEVICE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

IDeg – 100 units/mL, and supplied in a 3 mL prefilled FlexPen®. IDeg was injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen once daily at the same time each day. IDeg treatment was initiated with 16 units, and titrated twice weekly to the fasting glycaemic target of 4.0–5.0 mmol/L (72–90 mg/dL) based on the mean SMPG (fasting) from 3 preceding measurements as described for IDegLira above. The maximum allowed dose was 50 units. Batch No. AP51397.

CRITERIA FOR EVALUATION – EFFICACY

The following efficacy variables were assessed: HbA_{1c}, responders for HbA_{1c} (< 7% or ≤ 6.5%) without weight gain, without hypoglycaemic episodes or without hypoglycaemic episodes and weight gain, beta-cell function (fasting pro-insulin, fasting C-peptide, fasting insulin [and derived pro-insulin/insulin ratio], fasting glucagon, fasting plasma glucose [FPG]), withdrawal due to ineffective therapy, cardiovascular biomarkers (highly sensitive C-reactive protein [hsCRP], PAI-l, adiponectin, fibrinogen, brain natriurectic peptide [BNP]), fasting lipid profile (triglycerides, cholesterol, low density lipoprotein cholesterol [LDL], high density lipoprotein cholesterol [HDL], very high density lipoprotein cholesterol [VLDL], free fatty acids [FFA], apolipoprotein A-1 and B, self-measured plasma glucose (SMPG) including 9-point plasma glucose profile, body weight, waist circumference, systolic and diastolic blood pressure, insulin dose (IDegLira and IDeg).

CRITERIA FOR EVALUATION – SAFETY

The following safety variables were assessed: adverse events, hypoglycaemia, physical examinations, eye examinations, ECG, pulse, clinical laboratory tests (e.g., haematology, biochemistry, lipase, amylase, calcitonin), urinalysis, antibodies, albumin/creatinine ratio.

STATISTICAL METHODS

- Power calculation: For change in HbA_{1c}, the power for showing superiority of IDegLira vs. IDeg was 90.0%.
- Analysis sets:
  Due to overall compromised data integrity all subjects from site [redacted] was excluded from all the below three analysis sets. Sensitivity analyses were performed for the primary endpoint HbA_{1c} as well as for serious adverse events and hypoglycaemia, in order to compare results from analyses including and excluding data from site [redacted]
  - **Full Analysis Set (FAS):** included all randomised subjects. In exceptional cases, subjects were to be eliminated from the full analysis set. In such cases the elimination were justified and documented. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised".
  - **Safety Analysis Set (SAS):** included all subjects receiving at least one dose of the investigational product or comparators. Subjects in the safety set contributed to the evaluation "as treated".
  - **Completer Analysis Set (CAS):** included all randomised subjects who completed visit 33. Subjects in the completer analysis set contributed to the evaluation "as randomised".
- The change in HbA_{1c} from baseline after 26 weeks of treatment was analysed using a standard ANCOVA model. The model included treatment, previous antidiabetic treatment, and country as fixed factors and the corresponding baseline value as a covariate. The primary objective was fulfilled only if superiority of IDegLira vs. IDeg was confirmed.
- The primary analysis of change in HbA_{1c} from baseline after 26 weeks of treatment was repeated on the CAS for sensitivity purposes.
- The number of severe or minor hypoglycaemic episodes (confirmed 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, previous anti-diabetic treatment, and region as fixed factors.

- The daily insulin dose after 26 weeks of treatment was analysed using a standard ANCOVA model using FAS. The model included treatment, previous antidiabetic treatment and country as fixed factors and baseline HbA_{1c} value and baseline insulin dose as covariates.
- 2 dichotomous endpoints (responder/non-responder) were defined based on whether a subject met a specific HbA_{1c} target level after 26 of treatment: American Diabetes Association (ADA) HbA_{1c} target ($HbA_{1c} < 7.0\%$), International Diabetes Federation (IDF) HbA_{1c} target ($HbA_{1c} \leq 6.5\%$). Analysis of each of the 2 responder endpoints was based on a logistic regression model with treatment, region and previous anti-diabetic treatment as fixed factors and baseline HbA_{1c} value as a covariate. In addition, the following endpoints were defined: Responder for HbA_{1c} without weight gain after 26 weeks of treatment, responder for HbA_{1c} without hypoglycaemic episodes after 26 weeks of treatment, responder for HbA_{1c} without hypoglycaemic episodes and weight gain after 26 weeks of treatment.
- Change from baseline in FPG, body weight and waist circumference after 26 weeks of treatment were analysed using the standard ANCOVA model.
- Change from baseline in mean of the 9-point profile (SMPG) and postprandial increments endpoints after 26 weeks of treatment were analysed separately using the standard ANCOVA model. The endpoint obtained at baseline was used as covariate.
- Beta-cell function, systolic and diastolic blood pressure, cardiovascular biomarkers (except for PAI-l) and lipids were log-transformed and analysed using the standard ANCOVA model. For PAI-1, the log-transformed response after 26 weeks of treatment was analysed using an ANCOVA method with treatment, country, and previous antidiabetic treatment as fixed effects and this analysis was based on the observed data.
- Withdrawal due to ineffective therapy was analysed by a logistic regression model with treatment, country and previous antidiabetic treatment as fixed factors and baseline HbA_{1c} value as a covariate.
- Safety endpoint were summarised descriptively:

DEMOGRAPHY OF TRIAL POPULATION

The treatment groups were overall well matched with respect to baseline demographics and characteristics. Approximately 75% of the subjects were in the 40–65 years age group and 21.8% were >65 years old. Mean HbA_{1c} were 8.7% in the IDegLira group and 8.8% in the IDeg group. Duration of diabetes was ~10 years in the IDegLira group and ~11 years in the IDeg group.

Demographics and baseline characteristics

	IDegLira N (%)	IDeg N (%)	Total N (%)
Number of Subjects	199	199	398
Age Group			
N	199 (100.0)	199 (100.0)	398 (100.0)
18-40 yrs	5 (2.5)	11 (5.5)	16 (4.0)
40-65 yrs	156 (78.4)	139 (69.8)	295 (74.1)
65-75 yrs	34 (17.1)	43 (21.6)	77 (19.3)
> 75 yrs	4 (2.0)	6 (3.0)	10 (2.5)
Sex			
N	199 (100.0)	199 (100.0)	398 (100.0)
Female	87 (43.7)	93 (46.7)	180 (45.2)
Male	112 (56.3)	106 (53.3)	218 (54.8)
Ethnicity			
N	199 (100.0)	199 (100.0)	398 (100.0)
Hispanic or Latino	16 (8.0)	24 (12.1)	40 (10.1)
Not Hispanic or Latino	183 (92.0)	175 (87.9)	358 (89.9)

Demographics and baseline characteristics

	IDegLira N (%)	IDeg N (%)	Total N (%)
Race			
N	199 (100.0)	199 (100.0)	398 (100.0)
White	157 (78.9)	151 (75.9)	308 (77.4)
Black or African American	9 (4.5)	10 (5.0)	19 (4.8)
Asian Indian	31 (15.6)	34 (17.1)	65 (16.3)
Asian non-Indian	2 (1.0)	2 (1.0)	4 (1.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	1 (0.5)	1 (0.3)
Other	0 (0.0)	1 (0.5)	1 (0.3)

N = Number of Subjects, %= Percentages are based on N

Baseline and diabetes characteristics

	IDegLira N (%)	IDeg N (%)	Total N (%)
Age (years)			
N	199	199	398
Mean (SD)	56.8 (8.9)	57.5 (10.5)	57.2 (9.7)
Median	56.2	58.2	57.4
Min ; Max	31.4 ; 76.9	29.5 ; 85.8	29.5 ; 85.8
Height (m)			
N	199	199	398
Mean (SD)	1.68 (0.11)	1.66 (0.10)	1.67 (0.11)
Median	1.68	1.66	1.67
Min ; Max	1.41 ; 1.97	1.44 ; 1.95	1.41 ; 1.97
Body Weight (kg)			
N	199	199	398
Mean (SD)	95.4 (19.4)	93.5 (20.0)	94.5 (19.7)
Median	93.5	90.3	92.3
Min ; Max	57.5 ; 171.5	58.9 ; 191.9	57.5 ; 191.9
BMI (kg/m^2)			
N	199	199	398
Mean (SD)	33.6 (5.7)	33.8 (5.6)	33.7 (5.7)
Median	32.3	32.8	32.6
Min ; Max	26.5 ; 56.5	25.8 ; 54.7	25.8 ; 56.5
Duration of Diabetes (years)			
N	199	199	398
Mean (SD)	10.30 (6.01)	10.91 (7.04)	10.60 (6.54)
Median	8.7	9.5	9.1
Min ; Max	0.79 ; 30.42	0.76 ; 40.42	0.76 ; 40.42
HbA1c (%)			
N	199	199	398
Mean (SD)	8.7 (0.7)	8.8 (0.7)	8.8 (0.7)
Median	8.6	8.9	8.7
Min ; Max	7.2 ; 12.3	7.3 ; 10.9	7.2 ; 12.3

Baseline and diabetes characteristics

	IDegLira N (%)	IDeg N (%)	Total N (%)
FPG (mmol/L)			
N	198	199	397
Mean (SD)	9.7 (2.9)	9.6 (3.1)	9.6 (3.0)
Median	9.5	9.3	9.4
Min ; Max	3.0 ; 19.1	4.2 ; 29.9	3.0 ; 29.9

N = Number of Subjects, % = Percentages are based on N
18-40 yrs = age range from 18 to less than 40
40-65 yrs = age range from 40 to less than 65
65-75 yrs = age range from 65 to less than 75
> 75 yrs = age range from 75
yrs = years, BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose

EFFICACY RESULTS

After 26 weeks of treatment with IDegLira and IDeg all in combination with metformin, the following was concluded:

Overall glycaemic control

HbA_{1c}

- IDegLira effectively improved glycaemic control, and superiority to IDeg with regard to lowering of HbA_{1c} was confirmed at equivalent insulin doses (45 dose steps for IDegLira/45 units for IDeg). After 26 weeks of treatment the observed mean change from baseline in HbA_{1c} was reduced by 1.90%-point to a mean HbA_{1c} of 6.9% with IDegLira. For IDeg the mean observed change from baseline was reduced by 0.89%-point to a mean HbA_{1c} of 8.0%. The estimated mean treatment difference (IDegLira-IDeg) was -1.05% $[-1.25; -0.84]_{95\%CI}$, $p < 0.0001$. These results demonstrated a significant contribution of the liraglutide component to the overall glycaemic control.

Responders for HbA_{1c}

- 60.3% of subjects in the IDegLira treatment group achieved an $HbA_{1c} < 7\%$ after 26 weeks of treatment compared to 23.1% in the IDeg treatment group. Similarly, the proportion of subjects achieving an $HbA_{1c} \leq 6.5\%$ after 26 weeks of treatment was higher with IDegLira (45.2%) than with IDeg (13.1%). For both of these responder rates, the estimated treatment odds ratio (IDegLira vs. IDeg) was statistically significantly in favour of IDegLira.

Key contributors of glycaemic control

FPG

- FPG decreased during the trial by 3.46 mmol/L (62.4 mg/dL) with IDegLira and 2.58 mmol/L (46.4 mg/dL) with IDeg. A statistically significantly greater reduction in FPG was observed with IDegLira compared to IDeg; estimated mean difference was -0.73 mmol/L $[-1.19;-0.27]_{95\%CI}$, $p = 0.0019$.

9-point SMPG profile

- There was a statistically significantly greater reduction in mean of 9-point SMPG profile with IDegLira treatment compared to IDeg; estimated treatment difference -1.07 mmol/L $[-1.44; -0.70]_{95\%CI}$, $p < 0.0001$. Change from baseline in prandial increments from the 9-point SMPG profile across all meals after 26 weeks of treatment was statistically significantly smaller with IDegLira compared to IDeg; estimated treatment difference between IDegLira and IDeg was -0.37 mmol/L $[-0.69; -0.04]_{95\%CI}$, $p = 0.0260$.

Body weight

- Observed mean change in body weight after 26 weeks of treatment was -2.7 kg with IDegLira and 0.0 kg with IDeg. BMI and waist circumference changed according to change in body weight. A statistically significantly greater reduction in body weight was observed with IDegLira compared to IDeg: estimated treatment difference (IDegLira vs. IDeg) was -2.51 kg $[-3.21; -1.82]_{95\%CI}$, $p < 0.0001$.

SAFETY RESULTS

After 26 weeks of treatment, the following can be concluded regarding the safety of IDegLira and IDeg in this trial: Overall, treatment with IDegLira and IDeg was well tolerated and there were no new AE or tolerability issues observed with IDegLira. The safety conclusions for each of the investigated areas are summarised below:

Overall adverse event profile

- No deaths were reported.
- The AE rate per 100 PYE was similar with IDegLira (398.1 events) and IDeg (355.5 events). The majority of AEs were mild (521 of 686 events) and the majority of the events were judged to be unlikely related to trial products by the investigator (556 of 686 events).
- The most frequent AEs reported with IDegLira were gastrointestinal disorders (diarrhoea and nausea) and headache occurring in 6.0−6.5% of subjects, with a rate of 21.8−25.0 events per 100 PYE. Nasopharyngitis was the most frequently reported AE with IDeg, occurring in 6.0% of the subjects with a rate of 15.6 events per 100 PYE.
- 24 SAEs were reported by 18 subjects. No SAEs occurred in ≥1% of subjects, and the majority were unlikely related to trial product. 2 SAEs (in 2 subjects) were possibly or probably related to trial product: 1 in the IDegLira group (hypoglycaemia) and 1 in the IDeg group (convulsion).
- 1.0% (4/398) of the subjects withdrew or was withdrawn due to AEs: 1 subject from the IDegLira group ('major depression/acute renal failure') and 3 subjects from the IDeg group ('acute myocardial infarction', 'cholelithiasis' and 'ischaemic stroke'.

Adverse events within predefined safety areas of interest

- 5 cardiovascular events (in 3 subjects) were confirmed by adjudication and 3 of these events were MACEs (1 in the IDegLira group and 2 in the IDeg group). The rate of confirmed cardiovascular events was 1.1 events per 100 PYE with IDegLira and 4.4 with IDeg.
- 2 neoplasms (in 2 subjects) were confirmed by adjudication, both in the IDeg group.
- 26 events of 'lipase increased' or 'amylase increased' were reported in 22 subjects, with rates of 18.5 events per 100 PYE in the IDegLira group and 10.0 events per 100 PYE in the IDeg group. 4 subjects had not recovered by the end of trial.
- There were no events of pancreatitis, thyroid disease or medullary thyroid cancer reported for this trial.
- Based on the continuous calcitonin monitoring, 5 events of increased calcitonin (≥20 ng/L) were reported as AEs in 5 subjects: 2 in the IDegLira group and 3 in the IDeg group. None with clinical symptoms.
- Few events were reported within the pre-defined safety areas of special interest: altered renal function (10), allergic reactions (3) or injection site reactions (11). These events did not reveal significant new information compared with previous experience.
- There were 5 cases of medication error, all judged to be mild in severity. No AEs were reported in connection with the medication errors. All subjects recovered, and there was no apparent difference between treatment groups.
- 2 hyperglycaemic events were reported by 2 subject treated with IDegLira, whereas 7 events were reported by 7 subjects treated with IDeg.

Hypoglycaemia

- The percentage of subjects with confirmed hypoglycaemia was similar between the 2 treatment arms. The difference in rates (153.4 episodes per 100 PYE for IDegLira and 263.3 episodes for IDeg) was caused by few subjects in the IDeg group with a large number of episodes and was not statistically significant.
- The rate of nocturnal confirmed hypoglycaemic episodes was similar with IDegLira and IDeg, 21.8 vs. 32.2 episodes per 100 PYE, respectively. There was no statistically significantly difference between the 2 treatment groups.
- The observed rate of hypoglycaemic episodes according to the ADA classification was 1274.9 episodes per 100 PYE

with IDegLira, and 1426.6 episodes per 100 PYE with IDeg. The majority of the ADA classified events were documented symptomatic and asymptomatic events.
- 1 event of severe hypoglycaemia was reported in the IDegLira group. The event did not lead to change in dose.

Clinical laboratory evaluation
- No clinically relevant changes in haematology or biochemistry parameters were observed from baseline to end of treatment in any of the treatment groups.
- Minor increase in mean lipase and amylase was observed from baseline to end of trial in the IDegLira group, but all were within normal range.
- The most frequent clinical laboratory AE was 'lipase increased', reported by 6.0% of subjects on IDegLira, and 3.5% on IDeg.
- There were no clinically relevant treatment differences in mean calcitonin levels.

Vital signs, physical findings and other observations
- A mean increase in pulse was observed with IDegLira (2.5 beats/min), whereas pulse remained unchanged with IDeg. The increase in pulse with IDegLira was statistically significant compared to IDeg.
- No clinically relevant treatment differences in physical examination, fundoscopy or ECG findings were observed between treatment groups after 26 weeks of treatment.

Antibodies
- There was no relevant IDeg-specific antibodies developed during the 26 weeks of treatment with either IDegLira or IDeg, and only very few subjects in the two treatment groups developed antibodies cross-reacting with human insulin, with no difference between IDegLira and IDeg.
- Anti-liraglutide antibody development was limited. After 26 weeks of treatment < 1% of subjects on IDegLira had developed antibodies. No *in vitro* neutralising effect towards liraglutide was observed at the follow up visit.

CONCLUSIONS

The results of this 26-week trial comparing IDegLira and IDeg at a maximum allowed dose of 50 dose steps/50 units in subjects with type 2 diabetes previously treated with 20-40 units of basal insulin and metformin ± SU/glinides, can be summarised in the following conclusions:
- Treatment with IDegLira was superior to IDeg treatment at equivalent actual insulin doses in regard to change in HbA_{1c} supporting a contribution of the liraglutide component of the overall glycaemic control.
- Treatment with IDegLira had a statistically significant favourable effect on FPG, SMPG (mean 9-point SMPG profile and mean 9-point post prandial increments) and body weight when compared to IDeg supporting the contribution of the liraglutide component.
- Adverse event and tolerability profiles of IDeg were consistent with previous findings.
- No apparent AE and tolerability issues for IDegLira were observed, and no unexpected AEs in relation to what has been seen for IDeg and liraglutide were reported.

The trial was conducted in accordance with the Declaration of Helsinki[1] and ICH Good Clinical Practice[2]
The results presented in this report reflect the data available in the clinical database as of 28 Nov 2012, except for calcitonin reference ranges, which were updated as of 13 March-2013.