CTR synopsis

Trial registration ID-number NCT01336023	**UTN –** U1111-1119-1174 **IND number -** 109/121 **EudraCT number -** 2010-021560-15

TITLE OF TRIAL

DUAL I - DUal Action of Liraglutide and insulin degludec in type 2 diabetes: A trial comparing the efficacy and safety of insulin degludec/liraglutide, insulin degludec and liraglutide in subjects with type 2 diabetes.

A 26-week randomised, parallel three-arm, open-label, multi-centre, multinational treat-to-target trial comparing fixed ratio combination of insulin degludec and liraglutide versus insulin degludec or liraglutide alone, in subjects with type 2 diabetes treated with 1-2 oral anti-diabetic drugs (OADs) with a 26-week extension

This synopsis covers the full 52-week treatment period of the trial

INVESTIGATORS

A total of 286 principal investigators in 19 countries. The appointed signatory investigator was:

Professor [redacted]

TRIAL SITES

A total of 271 sites in 19 countries randomised subjects: Australia (7 sites), Canada (14 sites), Finland (5 sites), Germany (12 sites), Hungary (6 sites), India (23 sites), Ireland (2 sites), Italy (6 sites), Malaysia (5 sites), Mexico (2 sites), Russian Federation (11 sites), Singapore (3 sites), Slovakia (5 sites), South Africa (13 sites), Spain (8 sites), Taiwan (3 sites), Thailand (4 sites), United Kingdom (16 sites) and United States (126 sites).

PUBLICATIONS

None as of the date of this report

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 23-May-2011 Completion date: 22-Nov-2012	Phase 3a

OBJECTIVES

As stated in the protocol and amendments, some objectives were related to the 26-week main part of the trial whereas others were related to of the full 52 weeks of the trial (end of extended trial, marked in *italics* below):

Primary objective

- To confirm the efficacy of IDegLira in controlling glycaemia in subjects with type 2 diabetes.

Secondary objectives

- To confirm superiority of IDegLira vs. IDeg after 26 weeks of treatment on either weight control, hypoglycaemic episodes, glycaemic control in relation to a meal, or glycaemic control as indirectly measured by daily dose of IDeg
- *To confirm the efficacy of IDegLira in controlling glycaemia in subjects with type 2 diabetes after 52 weeks of treatment*
- *To compare general efficacy and safety of IDegLira, IDeg and liraglutide after* 26 and *52 weeks of treatment*

Originally, the secondary objectives only addressed efficacy and safety following 26 weeks of treatment. However, a 26-week extension was later added to the trial (amendment 2) and the data regarding the secondary objectives after 52 weeks of treatment will be presented in this synopsis covering the 52-week extended trial.

Pharmacokinetic objective

- To compare the PK of IDegLira and its individual components at clinically relevant doses during 26 weeks of treatment. Furthermore, the effects of pre-specified covariates on 26 plasma concentrations of pre-specified covariates were to be evaluated.
  Results are presented in a separate report.

METHODOLOGY

- The present trial was a 26-week randomised, controlled, parallel three-arm, open-label, multi-centre, multinational, treat-to-target trial in subjects with type 2 diabetes inadequately controlled with 1-2 OADs (metformin or metformin + pioglitazone) with a 26-week extension comparing the efficacy and safety of IDegLira once daily with the single components IDeg once daily and liraglutide once daily. Inadequately controlled type 2 diabetes was defined as an HbA1c level of 7.0-10.0% (both inclusive).
- Eligible subjects were randomised in a 2:1:1 manner to receive one of three parallel treatments consisting of once daily IDegLira, IDeg or liraglutide. Metformin or metformin + pioglitazone were continued at pre-trial doses and dosing frequency throughout the trial. The randomisation was stratified by previous treatment with metformin and metformin + pioglitazone as well as with regards to baseline HbA1c (≤ 8.3% and > 8.3%, respectively). All treatments were open-label.
- Subjects in the liraglutide arm followed a fixed dose escalation scheme with a dose increase of 0.6 mg weekly until the target dose of 1.8 mg was reached. Initial dose for IDegLira and IDeg was 10 dose steps and 10 units, respectively, and titrated twice weekly, according to the predefined titration algorithm based on fasting plasma glucose levels.
- At selected sites, a sub-study comprising continuous glucose monitoring (CGM) and a meal test was performed.
- 26 weeks after randomisation, all subjects were invited to enter additional 26 weeks treatment. The subjects were to continue the same treatment at unchanged dose (liraglutide arm) or dosing regimen (IDeg and IDegLira arms).

NUMBER OF SUBJECTS PLANNED AND ANALYSED

Planned sample size was 830 in the IDegLira arm and 415 in each of the IDeg and liraglutide arms, respectively. Hence the total number of randomised subjects was set to 1660. Sample size for the sub-study was 256 randomised subjects.

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Screened				3004
Screening Failures				1341
Withdrawn before Randomisation				0
Randomised	834 (100.0)	414 (100.0)	415 (100.0)	1663 (100.0)
Exposed	826 (99.0)	413 (99.8)	413 (99.5)	1652 (99.3)
Completed Main Trial	734 (88.0)	366 (88.4)	342 (82.4)	1442 (86.7)
Withdrawn at/after Randomisation and Before extension	100 (12.0)	48 (11.6)	73 (17.6)	221 (13.3)
Adverse Event	11 (1.3)	8 (1.9)	24 (5.8)	43 (2.6)
Ineffective Therapy	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Non-Compliance	2 (0.2)	1 (0.2)	0 (0.0)	3 (0.2)
Withdrawal Criteria	70 (8.4)	34 (8.2)	40 (9.6)	144 (8.7)
Other	16 (1.9)	5 (1.2)	9 (2.2)	30 (1.8)
Completed Main Trial Not Screened for Extension	69 (8.3)	33 (8.0)	29 (7.0)	131 (7.9)
Completed Main Trial Screening Failure in Extension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Subject disposition - continued

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Included in Extension	665 (79.7)	333 (80.4)	313 (75.4)	1311 (78.8)
Withdrawn during extension	44 (5.3)	28 (6.8)	28 (6.7)	100 (6.0)
Adverse Event	5 (0.6)	1 (0.2)	2 (0.5)	8 (0.5)
Ineffective Therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance	2 (0.2)	0 (0.0)	1 (0.2)	3 (0.2)
Withdrawal Criteria	19 (2.3)	14 (3.4)	16 (3.9)	49 (2.9)
Other	18 (2.2)	13 (3.1)	9 (2.2)	40 (2.4)
Completed Extension	621 (74.5)	305 (73.7)	285 (68.7)	1211 (72.8)
Full Analysis Set	833 (99.9)	413 (99.8)	414 (99.8)	1660 (99.8)
PP Analysis Set	755 (90.5)	374 (90.3)	362 (87.2)	1491 (89.7)
Safety Analysis Set	825 (98.9)	412 (99.5)	412 (99.3)	1649 (99.2)
Extension Trial Set	665 (79.7)	332 (80.2)	313 (75.4)	1310 (78.8)

N: Number of subjects
%: Proportion of randomised subjects, PP: Per Protocol

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

- **Main inclusion criteria**: subjects with type 2 diabetes, male or female, age 18 years or above (*for Singapore: Age 21 years or above, Taiwan [site [redacted]]: 20 years or above*), HbA1c 7.0–10.0 % (both inclusive) with the aim of a median HbA1c of 8.3%. Accordingly, when approximately 50% of the randomised subjects had an HbA1c above 8.3%, the remaining subjects randomised had to have an HbA1c of below or equal to 8.3%, or when approximately 50% of the randomised subjects had an HbA1c of below or equal to 8.3%, the remaining subjects randomised had to have an HbA1c above 8.3%, subjects on stable daily dose of 1–2 OADs (metformin [≥ 1500 mg or maximum tolerated dose] or metformin [≥ 1500 mg or maximum tolerated dose] + pioglitazone [≥ 30 mg]) for at least 90 days prior to screening, BMI ≤ 40 kg/m^2, 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.
- **Main exclusion criteria:** treatment with insulin (except for short-term treatment due to intercurrent illness at the discretion of the investigator), treatment with GLP-1 receptor agonists, sulphonylurea or dipeptidyl peptidase-4 (DPP-4) inhibitors within 90 days prior to trial, subject with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genitourinary or haematological system, 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, hyperglycaemia (confirmed), subjects diagnosed with acute pancreatitis were to be withdrawn from the trial.

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

IDegLira − fixed ratio of 100 units IDeg/3.6 mg liraglutide per mL, 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 10 dose steps (equivalent to 10 units IDeg and 0.36 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) to the fasting glycaemic target of 4.0–5.0 mmol/L (72–90 mg/dl). Maximum dose was 50 dose steps (50 units IDeg and 1.8 mg liraglutide). –Batch Nos. AP50043, YP52274, AP50044 and AP50017.

DURATION OF TREATMENT

26 weeks in main trial + 26 weeks in extension part of trial.

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 10 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. There was no maximum dose. Batch Nos. YP52252 and AP51402.

Liraglutide – 6 mg/mL, and supplied in a 3 mL prefilled pen-injector. Liraglutide was injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen once daily at the same time each day. Liraglutide treatment was started at 0.6 mg/day and subsequently increased by 0.6 mg in weekly dose escalation steps to a maximum dose of 1.8 mg/day. Liraglutide dose was to remain unchanged after dose escalation to 1.8 mg/day. Batch Nos. XP52720 and AP50533.

CRITERIA FOR EVALUATION – EFFICACY

The following efficacy variables were assessed: HbA1c, beta-cell function (fasting pro-insulin, fasting C-peptide, fasting insulin [and derived insulin/pro-insulin ratio, HOMA-B, HOMA-IR], fasting glucagon), fasting plasma glucose [FPG], cardiovascular biomarkers (highly sensitive C-reactive protein [hsCRP], adiponectin, fibrinogen, brain natriurectic peptide [BNP], plasminogen activator inhibitor 1 [PAI-1]), 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 and hip circumference, systolic and diastolic blood pressure, insulin dose (IDegLira and IDeg), continuous glucose monitoring (CGM) (sub-study only)

CRITERIA FOR EVALUATION – SAFETY

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

STATISTICAL METHODS

- **Power calculation:** The trial was powered to demonstrate non-inferiority of IDegLira vs IDeg and superiority of IDegLira vs liraglutide, respectively, with regards to change in HbA1c, after 26 weeks of treatment, which belongs to the main trial. For change in HbA1c after 26 weeks of treatment, the power for showing non-inferiority of IDegLira vs IDeg was 94.9% and for showing superiority of IDegLira vs liraglutide it was 98.6%, i.e., the combined power for meeting the primary objective was 94.9%*98.6% = 93.6%.
- **Analysis sets:**

Due to overall compromised data integrity all subjects from Site [redacted] were excluded from PP analysis set and all subjects from Site [redacted] were excluded from all analysis sets. Sensitivity analyses were performed for HbA1c as well as for serious adverse events and hypoglycaemia. This did not affect the overall conclusions.

- **Full Analysis Set (FAS):** included all randomised subjects. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as randomised".
- **Per Protocol (PP)** Analysis Set: included all subjects in the Full Analysis Set who fulfilled the following criteria: did not violate any inclusion criteria, did not fulfil any exclusion criteria, had a HbA1c measurement at screening and/or randomisation, had at least 12 actual treatment weeks of exposure, had at least one HbA1c measurement after 12 actual weeks of exposure.
- **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".
- **Extension Trial Set (ETS):** included all subjects who had entered the extension phase and attended visit 30 or any visits afterwards.
- **Completer Analysis Set (CAS):** included all randomised subjects who completed Visit 55, the whole active treatment phase of the trial. Subjects in the completer analysis set contributed to the evaluation "as randomised".

The change in HbA1c from baseline after 52 weeks of treatment was analysed using a standard ANCOVA model based on the FAS, and for sensitivity purposes repeated on the PP analysis set, the ETS and the CAS.

- All the efficacy analyses after 52 weeks of treatment are exploratory in nature. No multiplicity adjustment is needed.
- Change from baseline in body weight after 52 weeks of treatment was analysed using the standard ANCOVA model using the FAS.
- 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, baseline HbA1c stratum, sub-study participation and country as fixed factors. The statistical analysis was based on the FAS.
- The incremental AUC_{0-4h} ($iAUC_{0-4h}$) was derived from the glucose concentration profile from meal tests at baseline and after 52 weeks of treatment. The endpoint was defined as the area under the glucose curve that was over the basal value collected 10 minutes prior to meal intake. The incremental area under the glucose curve was calculated using the trapezoidal method divided by the actual measurement time, using the available valid glucose observations and the associated actual elapsed time point. Change from baseline after 52 weeks of treatment in $iAUC_{0-4h}$ was analysed by the standard ANCOVA model using the FAS.
- The daily insulin dose after 52 weeks of treatment was analysed using the standard ANCOVA model based on the FAS.
- 8 dichotomous endpoints (responder/non-responder) were defined based on whether a subject met a specific HbA1c target level after 52 weeks of treatment: American Diabetes Association (ADA) HbA1c target (HbA1c < 7.0%), International Diabetes Federation (IDF) HbA1c target (HbA1c ≤6.5%). Analysis of each of the 8 responder endpoints was based on a logistic regression model with treatment, region, baseline HbA1c stratum, sub-study participation and previous OAD treatment as fixed factors and baseline HbA1c value as a covariate. Bodyweight at baseline was included in the model as covariate for the endpoints related to weight gain. The results are presented with the 95% confidence intervals for the odds ratios (IDegLira over IDeg or liraglutide, respectively). The responder endpoints were: Responder for HbA1c without weight gain after 52 weeks of treatment, Responder for HbA1c without hypoglycaemic episodes after 52 weeks of treatment, Responder for HbA1c without hypoglycaemic episodes and weight gain after 52 weeks of treatment.

- Change from baseline in FPG and waist circumference and waist-to-hip-ratio after 52 weeks of treatment were analysed using the standard ANCOVA model.
- A series of endpoints from the 9-point self-measured plasma glucose profile obtained after 52 weeks was analysed: mean of the 9-point profile, mean post-prandial increment. A mixed effect model using an unstructured residual covariance matrix for measurements within subject was fitted to the 9-point profile data. The model included treatment, time-point, previous anti-diabetic treatment, baseline HbA1c stratum, sub-study participation, country and treatment by time-point interaction as fixed factors and baseline 9-point profile value as covariate.
- Beta-cell function, systolic and diastolic blood pressure, cardiovascular biomarkers and lipids were analysed using the standard ANCOVA model.
- **Meal test**: Change from baseline in $iAUC_{0-4h}$ after 52 weeks of treatment for C-peptide, insulin, pro-insulin and glucagon was analysed using the standard ANCOVA model excluding the sub-study participation factor.
- **CGM**: The endpoints were analysed using the standard ANCOVA model excluding the sub-study participation factor. Fluctuation and CV% were log-transformed before analysed and so was the corresponding baseline covariates.
- Safety and tolerability were addressed for the 52-week treatment period by data summaries based on the following safety assessments:

- Adverse events
- Number of treatment-emergent hypoglycaemic episodes
- Number of treatment-emergent nocturnal hypoglycaemic episodes
- Change in pulse from baseline
- Clinical evaluation (physical examination, eye examination and ECG)
- Clinical laboratory assessments (biochemistry, haematology, urinalysis, calcitonin, amylase and lipase, albumin/creatinine ratio)
- Anti-insulin degludec and anti-liraglutide antibodies

DEMOGRAPHY OF TRIAL POPULATION

- **Demographics and baseline characteristics**

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Number of Subjects	833	413	414	1660
Age Group				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
18-40 yrs	64 (7.7)	24 (5.8)	34 (8.2)	122 (7.3)
40-65 yrs	651 (78.2)	328 (79.4)	323 (78.0)	1302 (78.4)
65-75 yrs	107 (12.8)	52 (12.6)	48 (11.6)	207 (12.5)
> 75 yrs	11 (1.3)	9 (2.2)	9 (2.2)	29 (1.7)
Sex				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Female	398 (47.8)	213 (51.6)	206 (49.8)	817 (49.2)
Male	435 (52.2)	200 (48.4)	208 (50.2)	843 (50.8)
Ethnicity				
N	833 (100.0)	413 (100.0)	414 (100.0)	1660 (100.0)
Hispanic or Latino	127 (15.2)	67 (16.2)	56 (13.5)	250 (15.1)
Not Hispanic or Latino	706 (84.8)	345 (83.5)	357 (86.2)	1408 (84.8)
Not Applicable	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)

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

- **Baseline and diabetes characteristics**

	IDegLira N (%)	IDeg N (%)	Lira N (%)	Total N (%)
Age (years)				
N	833	413	414	1660
Mean (SD)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	55.0 (9.9)
Median	55.7	55.0	55.3	55.4
Min ; Max	27.8 ; 83.8	24.0 ; 79.1	24.4 ; 81.6	24.0 ; 83.8
Height (m)				
N	833	413	414	1660
Mean (SD)	1.67 (0.10)	1.67 (0.11)	1.67 (0.10)	1.67 (0.10)
Median	1.67	1.66	1.67	1.67
Min ; Max	1.35 ; 1.94	1.43 ; 1.98	1.40 ; 2.06	1.35 ; 2.06
Body Weight (kg)				
N	833	413	414	1660
Mean (SD)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	87.3 (18.8)
Median	85.6	86.6	87.1	86.2
Min ; Max	41.0 ; 147.1	43.5 ; 156.9	45.5 ; 143.8	41.0 ; 156.9
BMI (kg/m^2)				
N	833	413	414	1660
Mean (SD)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)	31.2 (5.1)
Median	31.3	31.0	31.3	31.2
Min ; Max	17.3 ; 45.2	16.8 ; 41.8	19.9 ; 40.5	16.8 ; 45.2
Duration of Diabetes (years)				
N	833	413	413	1659
Mean (SD)	6.63 (5.13)	6.99 (5.31)	7.15 (6.09)	6.85 (5.43)
Median	5.2	5.5	5.6	5.4
Min ; Max	0.03 ; 35.07	0.01 ; 32.34	0.01 ; 53.86	0.01 ; 53.86
HbA1c (%)				
N	833	413	414	1660
Mean (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)
Median	8.2	8.2	8.2	8.2
Min ; Max	6.0 ; 11.0	6.6 ; 11.3	6.4 ; 12.6	6.0 ; 12.6
FPG (mmol/L)				
N	809	409	409	1627
Mean (SD)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	9.2 (2.5)
Median	8.8	8.7	8.4	8.7
Min ; Max	2.7 ; 18.5	4.7 ; 19.4	3.1 ; 23.4	2.7 ; 23.4

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG= Fasting Plasma Glucose

EFFICACY RESULTS

The beneficial effects of IDegLira compared to IDeg or liraglutide seen after 26 weeks of treatment were sustained after 52 weeks of treatment with IDegLira, IDeg and liraglutide all in combination with OAD(s). The following was concluded after 52 weeks of treatment:

Overall glycaemic control

- **HbA1c**

IDegLira effectively improved glycaemic control. The estimated mean treatment differences IDegLira vs IDeg were -0.46%-point $[-0.57;-0.34]_{95\%CI}$, $p < 0.0001$ and for IDegLira vs liraglutide -0.65%-point $[-0.76;-0.53]_{95\%CI}$ $p < 0.0001$. Observed mean change in HbA1c was -1.84%-point with IDegLira, -1.40%-point with IDeg, and -1.21%-point with liraglutide. After 52 weeks of treatment, the observed mean HbA1c was 6.4% with IDegLira, 6.9% with IDeg, and 7.1% with liraglutide treatment.

- **Responders for HbA1c**

78.2% of subjects in the IDegLira treatment group achieved an HbA1c < 7% after 52 weeks of treatment compared to 62.5% in the IDeg and 56.5% in the liraglutide treatment group. Estimated treatment odds ratio (IDegLira vs.

IDeg) was 2.35 [1.77; 3.13]$_{95\%CI}$, p < 0.0001, and (IDegLira vs. liraglutide) 3.42 [2.58; 4.54]$_{95\%CI}$, p < 0.0001. Similarly, the highest proportion of subjects achieving an HbA1c ≤ 6.5% after 52 weeks of treatment was in the IDegLira treatment group (66.9%), followed by the IDeg (49.2%) and liraglutide treatment group (38.2%) and the estimated treatment odds ratio (IDegLira vs. IDeg) was 2.26 [1.74;2.93]$_{95\%CI}$, p < 0.0001 and (IDegLira vs. liraglutide) 3.94 [3.02; 5.14]$_{95\%CI}$, p < 0.0001. These results demonstrate a statistically significant better chance of achieving HbA1c target of < 7% or ≤ 6.5%with IDegLira compared to IDeg and liraglutide treatment.

- **Fasting SMPG profile for dose adjustment**

The mean fasting SMPG was close to the target for both titratable treatment groups after 52 weeks of treatment (IDegLira: 5.6 mmol/L [101 mg/dL] and IDeg: 5.4 mmol/L [97 mg/dL]). The similar SMPG indicates titration to a similar extent in the two arms.

- **Insulin dosing**

Daily insulin dose after 52 weeks of treatment with IDegLira statistically significantly lower compared to IDeg: estimated treatment difference (IDegLira vs. IDeg) -23.38 units [-26.44;-20.31]$_{95\%CI}$, p < 0.0001. After 52 weeks of treatment daily insulin dose was 39 units with IDegLira and 62 units with IDeg. The insulin dose ratio (IDegLira vs. IDeg) was 0.63 at Week 52, demonstrating a 37% lower insulin dose with IDegLira compared to IDeg.

Key contributors of glycaemic control

- **FPG**

FPG decreased during the trial by 3.45 mmol/L (62.1 mg/dL) with IDegLira, 3.40 mmol/L (61.2 mg/dL) with IDeg, and 1.67 mmol/L (30.2 mg/dL) with liraglutide treatment. The reduction in FPG was similar between IDegLira and IDeg after 52 weeks of treatment: estimated mean treatment difference (IDegLira vs. IDeg) was -0.20 mmol/L [-0.45; 0.05]$_{95\%CI}$, p = 0.1107. A statistically significantly greater reduction in FPG was observed with IDegLira compared to liraglutide (estimated mean difference was -1.67 mmol/L [-1.92;-1.42]$_{95\%CI}$, p <0.0001).

- **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 was -0.30 mmol/L [-0.50;-0.11]$_{95\%CI}$, p = 0.0025) and liraglutide (estimated treatment difference was -0.99 mmol/L [-1.19 ;-0.80]$_{95\%CI}$, p <0.0001).
Mean prandial increments across all meals were statistically significantly smaller with IDegLira compared to IDeg (estimated treatment difference between IDegLira and IDeg was -0.39 mmol/L [-0.57;-0.21]$_{95\%CI}$, p < 0.0001) and similar to liraglutide treatment (estimated treatment difference 0.10 mmol/L [-0.08; 0.27]$_{95\%CI}$, p = 0.2924).

- **Meal test –prandial increment (sub-population)**

Prandial increments ($iAUC_{0-4h}$) for glucose were statistically significantly lower with IDegLira compared to IDeg after 52 weeks of treatment: estimated treatment difference (IDegLira vs. IDeg) was -0.64 mmol/L [-1.11;-0.17]$_{95\%CI}$, p = 0.0073 There was no statistically significant difference between IDegLira and liraglutide after 52 weeks of treatment (estimated treatment difference 0.05 mmol/L [-0.43; 0.53]$_{95\%CI}$, p = 0.8417).

Effect on body weight

Observed mean change in body weight after 52 weeks of treatment was of -0.4 kg with IDegLira +2.3 kg with IDeg and -3.0 kg with IDegLira. Body weight after 52 weeks of treatment was statistically significantly lower with IDegLira than with IDeg: estimated mean treatment difference (IDegLira vs. IDeg) was -2.80 kg [-3.34;-2.27]$_{95\%CI}$, p < 0.0001.

SAFETY RESULTS

- After 52 weeks of treatment, the following can be concluded regarding the safety of IDegLira, IDeg and liraglutide in this trial: Overall, treatment with IDegLira, IDeg and liraglutide was well tolerated. The AE and tolerability profiles of IDeg and liraglutide were consistent with previous findings and there were no new AE or tolerability issues observed for IDegLira, the safety profile was consistent to what has been seen for the IDeg and liraglutide.
- The safety conclusions for each of the investigated areas are summarised below:
- ***Overall adverse event profile (other than hypoglycaemia)***
- 2 treatment-emergent deaths (both in the IDegLira group) were reported (one died from natural causes and one died from urinary tract infection and septic shock); the EAC classified both as a cardiovascular deaths. In addition, 1 non-treatment-emergent death (IDegLira; gun shot wound) was reported.

- The rate of AEs was similar in the IDegLira and IDeg groups, but lower than in the liraglutide group (407.9 vs. 383.3 vs. 507.3 events per 100 PYE). In all three treatment groups, the majority of AEs were mild in severity and judged to be unlikely related to trial products by the investigator.
- The most frequently reported AEs were headache, nausea, diarrhoea, vomiting, nasopharyngitis and upper respiratory tract infection. The combined rate of nausea, diarrhoea and vomiting was higher with IDegLira than with IDeg, but lower than with liraglutide (41 vs. 18 vs. 80 events per 100 PYE). There were no treatment differences in the rates for nasopharyngitis and upper respiratory tract infection.
- No SAEs occurred in ≥1% of subjects, and the majority were unlikely to be related to trial product. 10 SAEs (in 9 subjects) were possibly or probably related to trial product: 4 in the IDegLira group (severe hypoglycaemia, hypoglycaemic unconsciousness, malignant melanoma and appendicitis perforated), 1 in the IDeg group (cholecystitis) and 5 events in the liraglutide group (acute myocardial infarction, angina pectoris, gastritis, vomiting and gastroenteritis).
- 49 subjects (3.0%) had AEs leading to withdrawal, with the highest proportion in the liraglutide group (6.3%, mostly due to nausea or vomiting). Except for 6 subjects, all subjects recovered or were recovering
- ***Adverse events within predefined safety areas of interest***
- 38 treatment-emergent cardiovascular events (in 24 subjects, including 2 deaths) were sent for adjudication, 19 events (in 13 subjects) were confirmed of which 6 events were MACEs (4 in the IDegLira group and 1 in each of the IDeg and liraglutide groups). The rate of confirmed cardiovascular events was 1.1, 2.3 and 1.2 events per 100 PYE in the IDegLira, IDeg and liraglutide groups, respectively. 37 events of cardiac arrhythmia (in 32 subjects) were reported, with an event rate of 2.1, 2.6 and 3.9 events per 100 PYE, in the IDegLira, IDeg and liraglutide groups, respectively.
- 18 treatment-emergent events of pancreatitis or suspicion of pancreatitis were sent for adjudication of which 2 events (liraglutide) were confirmed as acute pancreatitis by the EAC. In addition, 1 non-treatment-emergent event (IDeg) was confirmed as acute pancreatitis.
- 152 events of 'lipase increased' or 'amylase increased' were reported in 111 subjects, the combined rates were 10.6, 8.0 and 14.7 events per 100 PYE in the IDegLira, IDeg and liraglutide groups, respectively. Most cases were asymptomatic.
- 45 treatment-emergent events potentially related to neoplasms (in 41 subjects) were sent for adjudication, of which 21 neoplasms (in 18 subjects) were confirmed, the rate of confirmed neoplasms was 1.8 vs. 1.4 vs. 0.9 events per 100 PYE in the IDegLira, IDeg and liraglutide groups, respectively. The most common confirmed neoplasms in the IDegLira group were 'basal cell carcinoma' events (4 events in 3 subjects; rate: 0.6 events per 100 PYE) which all were considered unlikely to be related to trial product and had all resolved by the end of trial. In addition, 1 non-treatment-emergent event of breast cancer (IDegLira) was confirmed by the EAC.
- Thyroid disorders requiring thyroidectomy and potential thyroid neoplasms were adjudicated. One thyroidectomy was performed; the event (goitre) was confirmed as a thyroid event by the EAC but not classified as a thyroid neoplasm. No medullary thyroid cancer events were reported.
- Based on the continuous calcitonin monitoring, 22 events of blood calcitonin increased (≥20 ng/L) were reported as AEs in 18 subjects (9 subjects with IDegLira [1.1%], 8 subjects with IDeg [1.9%] and 1 subject with liraglutide [0.2%]), none with clinical symptoms.
- The rate of adverse events related to altered renal function, hyperglycaemia and allergic reactions was slightly lower with IDegLira than with IDeg and liraglutide; only few events were reported.
- The rate of injection site reactions was similar with IDegLira and liraglutide (9.2 and 7.8 events per 100 PYE) and lower with IDeg (4.3 events per 100 PYE). The most frequent was 'injection site haematoma'.
- There were few AEs related to medication errors, none were judged to be severe, all subjects recovered, and accidental overdoses were only associated with AEs or hypoglycaemia in 2 subjects.
- ***Hypoglycaemia***
- The overall rate of confirmed hypoglycaemic episodes was lower with IDegLira than with IDeg, and higher than with liraglutide, 176.7 vs. 279.1 vs. 19.1 episodes per 100 PYE, respectively. The estimated rate ratios were 0.63 $[0.50; 0.79]_{95\%CI}$, $p < 0.0001$, for IDegLira vs. IDeg and 8.52 $[6.09; 11.93]_{95\%CI}$, $p < 0.0001$, for IDegLira vs. liraglutide.
- The majority of the ADA classified episodes were asymptomatic or documented symptomatic episodes.
- The overall rate of nocturnal confirmed hypoglycaemic episodes was similar with IDegLira and IDeg, and lower

with liraglutide; 22.3 vs. 36.6 vs. 1.8 episodes per 100 PYE, respectively.

- 7 severe hypoglycaemic episodes were reported during the 52-week treatment period; 3 in the IDegLira group and 2 in each of the IDeg and liraglutide groups.
- ***Pulse***
- A mean increase in pulse was observed in the IDegLira group (1.8 beats/min) and liraglutide (1.4 beats/min), whereas pulse remained unchanged with IDeg. The increase in pulse with IDegLira was statistically significant compared to IDeg, but similar compared to liraglutide.
- ***Clinical laboratory evaluation***
- Except from amylase and lipase, no clinically relevant changes in haematology or biochemistry parameters were observed from baseline to end of treatment in any of the treatment groups.
- A mean increase from baseline to end of treatment in lipase was observed in the IDegLira and liraglutide groups (8.3 and 12.5 U/L, respectively), whereas a decrease was seen in the IDeg group (-7.1 U/L). A similar, but less pronounced, mean increase was observed for amylase with IDegLira and liraglutide. The clinical relevance of these findings is unknown.
- There were no clinically relevant treatment differences in mean calcitonin levels.
- There were no statistically significant differences in the urinary albumin-to-creatinine ratios between IDegLira and IDeg and between IDegLira and liraglutide.
- The most frequent clinical laboratory AE were 'lipase increase' and/or 'amylase increased', reported by 6.4%, 5.1% and 9.0% of subjects in the IDegLira, IDeg and liraglutide groups, respectively.
- ***Physical examination, eye examination and ECG***
- No clinically relevant treatment differences in physical examination, fundoscopy or ECG findings were observed between treatment groups after 52 weeks of treatment.
- ***Antibodies***
  A few subjects developed low levels of IDeg-specific antibodies during the 52 weeks of treatment with either IDegLira or IDeg; this is not considered clinically relevant. 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 very limited. After 52 weeks of treatment, 2.6% and 3.8% of subjects treated with IDegLira and liraglutide, respectively, had developed antibodies, and of these, no subjects had antibodies cross-reacting with native GLP-1. *In vitro* neutralising effect towards liraglutide was detected in 5 of 27 subjects after wash-out at Week 53.

CONCLUSIONS

- Efficacy in controlling glycaemia was sustained after 52 weeks of treatment; treatment with IDegLira was statistically significantly better at reducing HbA1c from baseline to Week 52 than IDeg and liraglutide treatment.
- The lower HbA1c for subjects treated with IDegLira was reached with less insulin dose and was associated with a better post-prandial glycaemic control and with a significantly lower risk of hypoglycaemia compared to subjects in the IDeg group after 52 weeks of treatment. Furthermore, IDegLira treatment was not associated with weight gain.
- The lower HbA1c for subjects treated with IDegLira was explained by a greater reduction in FPG compared to the liraglutide treatment group.
- AEs and tolerability profiles of IDeg and liraglutide were consistent with previous findings. For IDegLira, the safety profile was consistent with what has been seen for the IDeg and liraglutide.
- Overall, the beneficial effects of IDegLira after 26 weeks of treatment were sustained over 52 weeks of treatment.

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

The results presented reflect the data available in the clinical database as of 15 Jan 2013. The database was re-opened in order to update important safety and efficacy information: 4 Feb 2013 (correction of PK values), 4 Mar 2013 (correction of calcitonin reference ranges), 11 Mar 2013 (correction of results for neutralising antibodies initially reported as negative).