CTR synopsis

Trial registration ID-number NCT01388361	**UTN –** U1111-1120-2782 **IND number –** 076496 **EudraCT number –** 2011-001493-25

TITLE OF TRIAL
A trial comparing the efficacy and safety of adding liraglutide versus addition of insulin aspart with the largest meal to insulin degludec, both in combination with metformin, in subjects with type 2 diabetes qualifying for treatment intensification.

INVESTIGATOR(S)
One principal investigator was appointed for each trial site. The following investigator was designated signatory investigator for the trial:

Dr. [redacted]

TRIAL SITE(S)
The trial was conducted at 119 sites in 12 countries: Austria (4), Belgium (4), Canada (15), Czech Republic (4), Denmark (6), Finland (6), France (4), Germany (12), Norway (6), Serbia (5), Spain (7), and the United States (46). These sites enrolled subjects in the randomised or non-randomised arms of the trial.

PUBLICATIONS
There have been no publications to date based on the results of this trial.

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 19 September 2011 Completion date: 9 July 2012	Phase 3b

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

Primary objective:
To compare the efficacy of adding liraglutide versus adding IAsp to the largest meal on top of IDeg (OD) + metformin in controlling glycaemia.

Secondary objectives:
To compare the safety of adding liraglutide versus adding IAsp to the largest meal on top of IDeg OD + metformin.

Objective of the non-randomised arm:
To evaluate the durability of IDeg to maintain glycaemic control over an additional 26 weeks in subjects who achieved the target $HbA_{1c} < 7\%$ after 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643.

METHODOLOGY
This trial was a 26-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing the efficacy and safety of adding liraglutide (Lira) versus addition of insulin aspart (IAsp) with the largest meal to insulin degludec (IDeg) once daily (OD) + metformin, in subjects with type 2 diabetes who had completed approximately 104 weeks of treatment with IDeg + metformin in NN1250-3579 and the extension trial, NN1250-3643, with an end of treatment $HbA_{1c} \geq 7.0\%$ thus qualifying for treatment intensification.

A third treatment arm consisted of non-randomised subjects who completed NN1250-3643 and achieved the glycaemic target of HbA_{1c} <7.0% at end of treatment. These subjects continued treatment with IDeg OD + metformin in order to further evaluate the long-term sustainability of glycaemic control. No comparisons were made between the non-randomised and the randomised treatment arms.

Subjects completing NN1250-3643 treated with IDeg OD + metformin with an HbA_{1c} ≥7.0% at end of treatment qualified to enter this trial and were screened for eligibility to be randomised (specifically ensuring that subjects met criteria for the initiation of liraglutide). At the screening visit (V1, which was the same day as the follow-up visit for NN1250-3643), subjects discontinued treatment with Neutral Protamine Hagedorn (NPH) (intermediate acting insulin, administered for basal insulin coverage during the one-week follow-up period for NN1250-3643 in order to reduce interference with antibody measurements) and resumed treatment with IDeg OD + metformin at the doses taken at the end of treatment in NN1250-3643. At Visit 2, eligible subjects were randomised 1:1 to add liraglutide once daily or IAsp with the largest meal as intensification of current treatment with IDeg OD + metformin. Subjects completing NN1250-3643 treated with IDeg OD + metformin with an end of treatment HbA_{1c} < 7% did not undergo randomisation, but continued treatment with IDeg + metformin (with doses unchanged) to further evaluate the long-term sustainability of glycaemic control with IDeg.

In the subsequent 26 weeks of treatment, the subject's insulin dose was titrated once weekly based on self-measured plasma glucose (SMPG) to ensure the enforced titration towards a predefined glycaemic target < 5 mmol/L (90 mg/dL). The starting dose of IDeg at Visit 1 (screening) was to be the same dose taken at end of treatment in NN1250-3643. At randomisation, subjects in the IDeg + IAsp group were to start IAsp at 4U once daily with the largest meal and continue the IDeg dose they received prior to randomisation. In the IDeg + Lira group, subjects were to reduce their IDeg dose by 20% at randomisation and maintain this dose until Visit 8. Subjects in the IDeg + Lira arm started liraglutide at 0.6 mg/day and increased to 1.2 mg/day after one week. At Visit 7, liraglutide was to be increased to 1.8 mg/day if warranted based on the mean of three prebreakfast SMPG values ≥ 5 mmol/L (90 mg/dL) measured just prior to Visit 7. If the mean of 3 prebreakfast SMPG values was < 5.0 mmol/L (measured just prior to Visit 7) the dose of liraglutide was to remain at 1.2 mg. From Visit 8 onwards, if the mean of 3 prebreakfast SMPG values was ≥ 5.0 mmol/L, either the dose of liraglutide could be increased to 1.8 mg or the IDeg dose could be increased (in accordance with the titration guideline) at the investigator's discretion. However it was recommended to consider increasing the liraglutide dose to 1.8 mg prior to further adjustment of the IDeg dose.

Verbal and written information was provided to the subjects and the informed consent form was signed by the subject and the investigator prior to trial participation.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

Sample size in the randomised part of this trial was determined by the number of subjects continuing from Trial NN1250-3643 (extension trial to NN1250-3579). Only subjects who completed approximately 104 weeks of treatment with IDeg OD + metformin with an end of treatment HbA_{1c} ≥7.0% were eligible to be randomised in this trial.
Of the 659 subjects who completed NN1250-3643, it was estimated that approximately 210 subjects would be eligible to be randomised in NN1250-3948. The actual number of subjects included in the trial is shown below:

	IDeg N (%)	IDeg + Liraglutide N (%)	IDeg + IAsp OD N (%)	Total N (%)
Screened				419
Randomisation Failures				6
Withdrawn before Randomisation				0
Randomised or Enrolled*	236 (100.0)	88 (100.0)	89 (100.0)	413 (100.0)

	IDeg N (%)	IDeg + Liraglutide N (%)	IDeg + IAsp OD N (%)	Total N (%)
Exposed	234 (99.2)	87 (98.9)	86 (96.6)	407 (98.5)
Withdrawn at/after Randomisation or Enrolment*	12 (5.1)	12 (13.6)	14 (15.7)	38 (9.2)
Adverse Event	0 (0.0)	5 (5.7)	1 (1.1)	6 (1.5)
Non-Compliance With Protocol	0 (0.0)	0 (0.0)	2 (2.2)	2 (0.5)
Withdrawal Criteria	12 (5.1)	7 (8.0)	10 (11.2)	29 (7.0)
Other	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)
Completed	224 (94.9)	76 (86.4)	75 (84.3)	375 (90.8)
Full Analysis Set	0 (0.0)	88 (100.0)	89 (100.0)	177 (42.9)
PP Analysis Set	0 (0.0)	73 (83.0)	74 (83.1)	147 (35.6)
Safety Analysis Set	0 (0.0)	87 (98.9)	86 (96.6)	173 (41.9)
Non-randomised Analysis Set	236 (100.0)	0 (0.0)	0 (0.0)	N/A

N: Number of subjects
%: Proportion of randomised subjects or enrolled subjects
*: Randomised/Randomisation for IDeg + Liraglutide and IDeg + IAsp OD, Enrolled/Enrolment for IDeg
N/A: Not applicable

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Insulin-naïve male or female subjects aged ≥ 18 years, with type 2 diabetes mellitus (diagnosed clinically) ≥ 6 months, HbA_{1c} 7.0-10.0 % (both inclusive) by central laboratory analysis, body mass index (BMI) ≤ 40.0 kg/m^2 and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogue (sulphonylurea [SU] or glinide), dipeptidyl peptidase-IV (DPP-IV) inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to Visit 1 were included in NN1250-3579. In NN1250-3579, subjects were randomised to IDeg OD + metformin ± DPP-IV inhibitor or insulin glargine (IGlar) OD + metformin ± DPP-IV inhibitor. Subjects who completed the first 52 weeks of treatment in main trial NN1250-3579 were eligible to participate in the 52-week extension trial (NN1250-3643), in which the NN1250-3579 treatment was continued. To participate in the present trial, NN1250-3948, subjects must have completed the end-of-treatment visit of NN1250-3643 taking IDeg OD + metformin only.

For subjects to be eligible for randomisation in the present trial, NN1250-3948, and potentially initiate treatment with liraglutide, subjects must have completed trial NN1250-3643 with HbA_{1c} ≥7% at end of treatment, calcitonin <50 ng/L at Visit 1 of Trial 3948, no personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2), no history of pancreatitis, and no clinically significant disease that in the investigator's opinion could confound trial results or pose additional risk in administering trial drug.

Subjects were not eligible for participation in NN1250-3948 if they had participated in NN1250-3643 and received treatment with IGlar + metformin ± DPP-IV inhibitor or IDeg + metformin + DPP-IV inhibitor. Subjects could not have been pregnant or breast-feeding or have the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements. Subjects were not to have had previous treatment with GLP-1 receptor agonists, or have known or suspected hypersensitivity to any of the trial products or related products, impaired renal or liver function, stroke, heart disease within the last 24 weeks prior to Visit 1, recurrent severe hypoglycaemia, any clinically significant disease or disorder except for conditions associated with type 2 diabetes which, in the investigator's opinion, could have interfered with the results of the trial, previous participation in this trial, or noncompliance with any of the eligibility criteria.

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

IDeg 100 U/mL, 3 mL prefilled pen PDS290.
IDeg was to be injected subcutaneously OD with the main evening meal in the thigh, upper arm (deltoid region) or abdomen.
Batch No.: AP50303, AP50535, AP50670, BP50085

IAsp (NovoLog®)100 U/mL, 3 mL prefilled FlexPen®.
IAsp was to be injected subcutaneously OD, preferably in the abdomen.
Batch No.: AP50125, AP51131, YP51436, YP51527

Liraglutide (Victoza®) 6 mg/mL, 3 mL prefilled pen-injector.
Liraglutide was to be injected subcutaneously OD just before the largest meal in the abdomen, thigh or upper arm (deltoid region).
Batch No.: AP50533

DURATION OF TREATMENT

The total duration of treatment was 26 weeks for each subject in the randomised groups and 27 weeks for each subject in the non-randomised group. The total duration of the trial for each subject was approximately 28 weeks including screening and follow-up visits.

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

Metformin was considered a non-investigational medicinal product and was not supplied by Novo Nordisk A/S. Metformin was purchased by subjects or otherwise delivered to the subjects according to local health plans.

CRITERIA FOR EVALUATION – EFFICACY

- HbA_{1c}
- FPG
- SMPG
  - Prebreakfast measurements used for titration
  - 9-point profile
  - Mean of the 9-point profiles
  - Fluctuation in the 9-point profile
  - Prandial plasma glucose (PG) increment from 9-point profile
- IDeg dose
- Body weight
- Waist and hip circumference, including waist-to-hip ratio (for subjects with $HbA_{1c} \geq 7.0\%$ at end of treatment in NN1250-3643)
- Fasting lipid profile (total cholesterol, low density lipoprotein [LDL] cholesterol, very low density lipoprotein [VLDL] cholesterol, high density lipoprotein [HDL] cholesterol, triglycerides and free fatty acids [FFA]) for subjects with $HbA_{1c} \geq 7.0\%$ at end of treatment in NN1250-3643
- Blood pressure (for subjects with $HbA_{1c} \geq 7.0\%$ at end of treatment in NN1250-3643)

CRITERIA FOR EVALUATION – SAFETY

- Adverse events (AEs)
- Hypoglycaemia
  - Number of treatment emergent confirmed and severe hypoglycaemic episodes according to the ADA definition and the Novo Nordisk definition (the pool of severe and minor [plasma glucose <3.1 mmol/L] hypoglycaemic episodes is referred to as confirmed hypoglycaemia)

- Number of treatment emergent nocturnal (00:01-05:59 am [both included]) confirmed and severe hypoglycaemic episodes
- Clinical evaluations
  - Physical examination
  - Vital signs (including blood pressure and pulse)
  - Fundoscopy or fundus photography
  - 12-lead electrocardiogram (ECG)
- Central laboratory assessments:
  - Haematology (haemoglobin, haematocrit, erythrocytes, thrombocytes and leucocytes)
  - Biochemistry (creatinine, alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], alkaline phosphatase [AP], sodium, potassium, albumin and total bilirubin for all subjects; calcium and calcium (albumin corrected) for subjects with $HbA_{1c} \geq 7\%$ at the end of NN1250-3643)
  - Fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides)
  - Calcitonin (for subjects with $HbA_{1c} \geq 7\%$ at the end of NN1250-3643)
  - Amylase and lipase (for subjects with $HbA_{1c} \geq 7\%$ at the end of NN1250-3643)

STATISTICAL METHODS

The following analysis sets were defined:

- Full Analysis Set (FAS): included all randomised subjects. In exceptional cases subjects from the FAS could be eliminated. In such cases the elimination was justified and documented. 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 subjects in the FAS who fulfilled the following criteria:
  - Have not violated any inclusion or randomisation criteria
  - Have not fulfilled any exclusion criteria
  - Have an HbA_{1c} value at screening or randomisation
  - Have at least one HbA_{1c} value after 12 weeks of exposure
  - Have at least 12 weeks of exposure
  - Was included in the PP analysis set of NN1250-3579
- Non-randomised Analysis Set (NAS): included all subjects who completed NN1250-3643 having achieved $HbA_{1c} < 7.0\%$ at end of treatment who consented participation in the present trial.
- Safety Analysis Set (SAS): included all subjects that received at least one dose of the investigational product or its comparator. Subjects in the safety set contributed to the evaluation "as treated".

Efficacy endpoints were summarised using the FAS and NAS. Safety endpoints were summarised using the SAS and NAS. All formal statistical analyses were based on the FAS. The analysis of primary endpoint change in HbA_{1c} was repeated on the PP analysis set.

Primary Efficacy Analysis

- Change from baseline in HbA_{1c} after 26 weeks of treatment was analysed using an analysis of variance (ANOVA) method with treatment, sex and region as fixed factors and age and baseline HbA_{1c} as covariates. Region was a factor with two levels (EU and North America).

Secondary Efficacy Analyses

- HbA_{1c} responder ($HbA_{1c} <7\%$ at end of trial) was a dichotomous endpoint. The HbA_{1c} responder endpoint was analysed based on a logistic regression model using same factors and covariates as for the HbA_{1c} analysis.
- Responder without hypoglycaemic episodes ($HbA_{1c} <7.0\%$ at end of trial and no confirmed hypoglycaemic episodes) was a dichotomous endpoint that was defined based on whether a subject had met the American Diabetes Association (ADA) HbA_{1c} target at end of trial without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment. Responder analysis was based on a logistic

regression model using the same factors and covariates as for the primary analysis.

- Responder without hypoglycaemic episodes and weight gain (HbA_{1c} <7.0% at end of trial and no confirmed hypoglycaemic episodes) was a dichotomous endpoint that was defined based on whether a subject had met the American Diabetes Association (ADA) HbA_{1c} target at end of trial without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment and without weight gain. Responder analysis was based on a logistic regression model using the same factors and covariates as for the primary analysis.
- Change from baseline in FPG after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis.
- 9-point profile (SMPG): The analysis of the 9-point SMPG profile was based on a mixed model (as specified in the trial protocol) but with a repeated measurement model having the same mean structure without the random subject effect and with an unstructured residual covariance matrix. The model included treatment, time, interaction between treatment and time, sex and region as fixed factors, age and the 9-point SMPG profile at baseline as covariates. From this model, mean profile by treatment and relevant treatment differences were estimated and explored.
- Mean and logarithmically transformed fluctuations (mmol/L) in the 9-point profile (SMPG) and prandial PG increment endpoints after 26 weeks of treatment were analysed separately using an ANOVA method similar to that used for the HbA_{1c} analysis.
- SMPG values used for dose adjustment: The mean of before breakfast PG values after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis. From the mean before-breakfast PG value, a dichotomous endpoint (responder/non-responder) will be derived to show if a subject achieved the titration target at each visit. A time-to-event endpoint was derived as the time from randomisation until the date a subject met the titration target for the first time. The time-to-event endpoint was analysed in a Cox proportional hazards model including treatment, sex and region as fixed factors and age as covariate. The logarithmically transformed SMPG values available before breakfast were analysed as repeated measures in a linear mixed model with treatment, sex and region as fixed factors, age as covariate and subject as random factor. The model assumed independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment was calculated from the corresponding residual variance.
- Prescribed and actual IDeg dose per day were recorded. The IDeg dose was summarised descriptively according to regimen as dose in units and units/kg.
- Change from baseline in lipid endpoints after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis.
- Change from baseline in body weight after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis.
- Change from baseline in waist circumference, hip circumference and waist to hip ratio after 26 weeks of treatment were analysed separately using an ANOVA method similar to that used for the HbA_{1c} analysis.
- Change from baseline in systolic and diastolic blood pressure after 26 weeks of treatment were analysed separately using an ANOVA method similar to that used for the HbA_{1c} analysis. From both the diastolic blood pressure (DBP) and the systolic blood pressure (SBP) a dichotomous endpoint (responder/non-responder) was derived based on whether a subject achieved a DBP below 80 mmHg and a SBP below 130 mmHg at end of trial, respectively. The analyses of the responder endpoints were based on a logistic regression model using treatment, sex and region as fixed factors, and age and the relevant baseline blood pressure as covariates.

Safety Analyses

- A treatment emergent adverse event (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.0).
  Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes are also presented as the rate of the events per 100 patient years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent using the same definition as for TEAE above.

Confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (56 mg/dL). A hypoglycaemic episode with time of onset between 00:01 and 05:59 a.m. (both included) was considered nocturnal. 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, sex and region as fixed factors, and age as covariate. Confirmed and nocturnal confirmed hypoglycaemic episodes were analysed separately. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on PG measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia.

- Remaining laboratory parameters, physical examination, ECG, fundoscopy / fundus photography and vital signs were evaluated based on descriptive statistics.

DEMOGRAPHY OF TRIAL POPULATION

Demographic and baseline characteristics were collected at screening (Visit 1) of NN1250-3948 for all subjects included in the trial. The demographics, baseline and diabetes characteristics (FAS) were generally similar between the treatment groups; however, the IDeg + Lira group included 28.4% female subjects while the IDeg + IAsp group included 40.4% female subjects. Most subjects that reported their race were White (91.5%) and of non-Hispanic/Latino ethnicity (80.2%). The second-largest race group consisted of Black or African American subjects (5.1%), with 6.8% in the IDeg + Lira group and 3.4% in the IDeg + IAsp group. The population consisted of male and female subjects with type 2 diabetes mellitus with a mean age of 61.0 years (ranging from 35.5 to 81.3 years), a mean HbA_{1c} of 7.7% and a mean BMI of 32.2 kg/m^2 (these three characteristics were similar for both treatment groups). IDeg + Lira-treated subjects had a higher mean body weight (95.4 kg) than IDeg + IAsp subjects (91.3 kg); however, this could be due to the larger proportion of females in the IDeg + IAsp group. IDeg + Lira-treated subjects also had a slightly longer duration of diabetes (12.9 years) than IDeg + IAsp subjects (11.8 years). The demographics and baseline characteristics of all randomised subjects (FAS) are summarised in the table below.

	IDeg + Liraglutide	IDeg + IAsp OD	Total
Number of Subjects	88	89	177
Age (years)			
N	88	89	177
Mean (SD)	61.1 (9.5)	60.9 (8.8)	61.0 (9.2)
Median	61.4	61.7	61.4
Min ; Max	35.5 ; 81.3	36.6 ; 80.0	35.5 ; 81.3
Body Weight (kg)			
N	87	89	176
Mean (SD)	95.4 (19.2)	91.3 (16.8)	93.3 (18.1)
Median	92.7	88.6	90.2
Min ; Max	56.5 ; 145.6	52.4 ; 152.0	52.4 ; 152.0
BMI (kg/m^2)			
N	87	89	176
Mean (SD)	32.5 (5.4)	32.0 (4.8)	32.2 (5.1)
Median	31.7	31.2	31.4
Min ; Max	23.4 ; 48.8	19.5 ; 45.2	19.5 ; 48.8
Duration of Diabetes (years)			
N	88	89	177
Mean (SD)	12.9 (6.4)	11.8 (6.5)	12.4 (6.4)
Median	12.3	10.6	12.1
Min ; Max	3.3 ; 36.3	2.3 ; 31.4	2.3 ; 36.3

	IDeg + Liraglutide	IDeg + IAsp OD	Total
HbA1c (%)			
N	88	89	177
Mean (SD)	7.7 (0.6)	7.7 (0.8)	7.7 (0.7)
Median	7.5	7.5	7.5
Min ; Max	6.8 ; 9.4	6.6 ; 9.9	6.6 ; 9.9
FPG (mmol/L)			
N	86	84	170
Mean (SD)	6.4 (2.4)	6.1 (1.7)	6.3 (2.1)
Median	6.2	5.8	6.0
Min ; Max	2.9 ; 14.7	3.3 ; 10.8	2.9 ; 14.7

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

The demographic and baseline characteristics of the subjects in the NAS were in accordance with the analysis based on FAS except that subjects in the non-randomised analysis set had a lower HbA_{1c} at baseline (6.4%) and a slightly shorter duration of diabetes (10.8 years).

EFFICACY RESULTS

After 26 weeks of treatment with IDeg + Lira or IDeg + IAsp, in combination with metformin, the following can be concluded:

Primary endpoint

- **HbA_{1c}**: The estimated mean reduction in HbA_{1c} during the trial was −0.73 %-points with IDeg + Lira and −0.40 %-points with IDeg + IAsp, with a statistically significant estimated mean difference in favour of IDeg + Lira of −0.32 %−points $[-0.53; -0.12]_{95\%CI}$. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.0 (0.8) % with IDeg + Lira and 7.3 (0.8) % with IDeg + IAsp.

Secondary endpoints

- **Responders for HbA_{1c}:** The observed proportion of subjects achieving HbA_{1c} <7% was 58.0% with IDeg + Lira and 44.9% with IDeg + IAsp. There was no statistically significant difference between treatment groups in terms of achieving HbA_{1c} <7%; the estimated odds ratio (IDeg + Lira/IDeg + IAsp) was 1.87 $[0.96; 3.64]_{95\% CI}$.
- **Responders for HbA_{1c} without hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemia during the last 12 weeks of treatment was 54.3% with IDeg + Lira and 19.3% with IDeg + IAsp. The odds of achieving HbA_{1c} target <7% without confirmed hypoglycaemia was statistically significantly greater with IDeg + Lira than with IDeg + IAsp; estimated odds ratio (IDeg + Lira/IDeg + IAsp) 5.57 $[2.67; 11.63]_{95\% CI}$. There were no severe hypoglycaemic episodes in either of the randomised treatment arms. The observed proportion of subjects achieving HbA_{1c} <7% without severe hypoglycaemia during the last 12 weeks of treatment was 61.7% with IDeg + Lira and 48.2% with IDeg + IAsp. There was no statistically significant difference between treatment groups in terms of achieving HbA_{1c} <7% without severe hypoglycaemia; the estimated odds ratio (IDeg + Lira/IDeg + IAsp) was 1.91 $[0.96; 3.83]_{95\% CI}$.
- **Responders for HbA_{1c} without hypoglycaemia and without weight gain:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemia during the last 12 weeks of treatment and without weight gain was 49.4% with IDeg + Lira and 7.2% with IDeg + IAsp. The odds of achieving HbA_{1c} target <7% without confirmed hypoglycaemia and without weight gain was statistically significantly greater with IDeg + Lira than with IDeg + IAsp, with an estimated odds ratio (IDeg + Lira/IDeg + IAsp): 13.79 $[5.24; 36.28]_{95\% CI}$.
- **FPG:** Overall, there were minimal changes in FPG from baseline to end of treatment. The estimated mean reduction from baseline in FPG during this trial was 0.12 mmol/L with IDeg + Lira and 0.18 mmol/L with IDeg + IAsp; the estimated mean difference (IDeg + Lira−IDeg + IAsp) was 0.06 mmol/L $[-0.65; 0.77]_{95\%CI}$. There was no

statistically significant difference between treatment groups.

- **9-point SMPG profiles:** 9-point SMPG values improved for all time points in both treatment arms with no statistically significant difference between groups at the end of the trial at any time point. After 26 weeks of treatment, the observed mean of the 9-point SMPG profile was 7.0 mmol/L both for subjects treated with IDeg + Lira and with IDeg + IAsp, with no statistically significant difference between groups. The observed mean prandial increments were slightly higher in the IDeg + Lira group than in the IDeg + IAsp group at lunch, evening meal and across all meals; no statistically significant differences between treatment groups were seen at any time points. The estimated mean fluctuation was not statistically significantly different with IDeg + Lira (1.08 mmol/L) vs. IDeg + IAsp (1.00 mmol/L); the estimated treatment ratio (IDeg + Lira/IDeg + IAsp) was 1.08 $[0.92; 1.26]_{95CI\%}$.
- **SMPG for titration**: Mean prebreakfast SMPG was reduced with IDeg + Lira and IDeg + IAsp. There was no statistically significant difference between treatment groups in terms of the estimated mean prebreakfast SMPG value. There was a statistically significant difference between treatment groups in favour of IDeg + Lira with regard to within-subject variation (CV%) in prebreakfast SMPG (estimated treatment ratio [IDeg + Lira/IDeg + IAsp] 0.73 $[0.62; 0.84]_{95\%CI}$.
- **Body weight**: There was a statistically significant difference in weight change between treatment groups in favour of IDeg + Lira after 26 weeks of treatment; the estimated mean weight change was −3.03 and 0.72 kg with IDeg + Lira and IDeg + IAsp, respectively, with an estimated treatment difference (IDeg + Lira−IDeg + IAsp) of −3.75 kg $[-4.70; -2.79]_{95\%CI}$.
- **Waist and hip circumference**: The reduction from baseline in waist circumference was statistically significantly greater with IDeg + Lira compared to IDeg + IAsp with an estimated treatment difference (IDeg + Lira−IDeg + IAsp) of −1.84 cm $[-3.18$ cm; -0.49 cm$]_{95\%CI}$. There was no statistically significant difference between treatment groups in hip circumference or waist to hip ratio, with estimated treatment differences (IDeg + Lira−IDeg + IAsp) of −0.69 cm $[-2.04; 0.66]_{95\%CI}$ and −0.01 cm $[-0.03 ; 0.00]_{95\%CI}$, respectively.
- **Fasting lipid profile**: No statistically significant differences were seen between IDeg + Lira and IDeg + IAsp with regard to changes in total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, triglycerides and free fatty acids.
- **Blood pressure**: The estimated mean change in diastolic blood pressure (DBP) during the trial was 0.46 mmHg with IDeg + Lira and 0.00 mmHg with IDeg + IAsp. The estimated mean change in systolic blood pressure (SBP) during the trial was −2.39 mmHg with IDeg + Lira and −0.75 mmHg with IDeg + IAsp. There was no statistically significant difference between treatment groups with regard to blood pressure, with estimated treatment differences (IDeg + Lira−IDeg + IAsp) of 0.46 mmHg $[-1.61; 2.53]_{95\%CI}$ (DBP) and −1.64 mmHg $[-5.15; 1.87]_{95\%CI}$ (SBP).

For the non-randomised arm the following can be concluded after 26 weeks of treatment with IDeg in combination with metformin:

- **HbA_{1c}:** The observed mean change in HbA_{1c} from baseline to end-of-trial was 0.10 %-points with IDeg. After 26 weeks of treatment the observed mean (SD) HbA_{1c} was 6.5 (0.5) % with IDeg.
- **Responders for HbA_{1c}:** At end of trial, the proportion of IDeg-treated subjects who maintained the HbA_{1c} target of <7.0% was 80.5%.
- **Responders for HbA_{1c} without hypoglycaemia:** An observed proportion of 60.4% and 80.4% of subjects treated with IDeg achieved the HbA_{1c} target <7.0% without confirmed and severe hypoglycaemic episodes, respectively, during the last 12 weeks of treatment.
- **FPG:** The observed mean (SD) FPG value at baseline was 6.7 (1.8) mmol/L in the IDeg group, which decreased to 5.4 (1.4) mmol/L at the end of treatment.
- **9-point SMPG profiles:** 9-point SMPG profiles were similar at baseline and end of treatment. After 26 weeks of treatment, the observed mean of the 9-point SMPG was 6.8 mmol/L for subjects treated with IDeg. Both the mean prandial increments and mean fluctuation values remained stable.
- **SMPG for titration**: Mean prebreakfast SMPG remained stable with IDeg during the trial and was 5.1 mmol/L at end of trial.
- **Body weight**: Body weight remained stable; the observed mean (SD) body weight at baseline and at the end of the trial was 91.3 kg (17.3) and 91.3 kg (17.5) in the IDeg group.

SAFETY RESULTS

After 26 weeks of treatment with IDeg + Lira or IDeg + IAsp, both in combination with metformin, the following can be concluded with regard to the safety analysis set:

Primary Endpoints

- **Adverse events:** The percentages of subjects reporting AEs were 70.1% and 54.7% in the IDeg + Lira and IDeg + IAsp groups, respectively. The observed rate of AEs was 517 events per 100 PYE in the IDeg + Lira group and 274 events per 100 PYE in the IDeg + IAsp group. The most frequently reported AEs in the IDeg + Lira treatment group were nausea, diarrhoea and nasopharyngitis. The most frequently reported AE in the IDeg + IAsp group was nasopharyngitis. Apart from more gastrointestinal side effects reported with IDeg + Lira than with IDeg + IAsp, there was no apparent clinically relevant difference between treatment arms with respect to AEs. The majority of AEs were mild or moderate. The majority of subjects in both groups recovered from the AEs at the end of trial.
- **Deaths, serious adverse events (SAEs) and other significant adverse events:** No deaths were reported in this trial. A total of 4 (4.6%) and 5 (5.8%) subjects reported 9 total SAEs in the IDeg + Lira (4 events) and IDeg + IAsp groups (5 events), respectively. The rate of SAEs per 100 PYE was 10 in the IDeg + Lira group and 12 in the IDeg + IAsp group. One (1) serious neoplasm event (bladder cancer; considered unlikely related to trial product by the investigator) occurred in the IDeg + Lira arm. Three (3) thyroid-related events (goitre, hypothyroidism and blood calcitonin increased) were reported in the IDeg + Lira group. One (1) pancreatitis event (considered unlikely related to trial product by the investigator) was reported in the IDeg + IAsp group. One (1) major adverse cardiovascular event (stroke) was reported in the IDeg + IAsp group. One (1) medication error (underdosing of liraglutide) was reported in the IDeg + Lira group and no medication errors were reported in the IDeg + IAsp group. Six (6) randomised subjects (5 in the IDeg + Lira group and 1 in the IDeg + IAsp group) were withdrawn due to adverse events.
- **Hypoglycaemic episodes:** The percentage of subjects who experienced confirmed hypoglycaemic episodes was lower in the IDeg + Lira group (27.6%) compared with the IDeg + IAsp group (67.4%), with an observed rate of confirmed hypoglycaemic episodes of 100 and 815 per 100 PYE for the IDeg + Lira and IDeg + IAsp groups, respectively. The estimated rate of confirmed hypoglycaemia was significantly lower by 87% with IDeg + Lira than with IDeg + IAsp; the estimated rate ratio (IDeg + Lira/IDeg + IAsp) for confirmed hypoglycaemic episodes was 0.13 $[0.08; 0.21]_{95\%\ CI}$. The observed rate of nocturnal confirmed hypoglycaemic episodes was 17 and 111 per 100 PYE for IDeg + Lira and IDeg + IAsp groups, respectively. The estimated rate of nocturnal confirmed hypoglycaemia was significantly lower by 86% with IDeg + Lira than with IDeg + IAsp; estimated rate ratio (IDeg + Lira/IDeg + IAsp) was 0.14 $[0.05; 0.40]_{95\%CI}$. No subjects in the IDeg + Lira or IDeg + IAsp groups experienced severe hypoglycaemia during the trial.
- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: No clinically relevant differences from baseline to end-of-treatment between the IDeg + Lira and IDeg + IAsp treatment groups were observed for vital signs, ECG, fundoscopy/ fundus photography and physical examination. Median amylase and lipase values were below the upper limit of normal. Median calcitonin values were below the upper limit of normal; one case of calcitonin ≥20 ng/L was reported as a thyroid-related AE in the IDeg + Lira arm. There were no clinically relevant differences in haematology, biochemistry or lipid laboratory values between the IDeg + Lira and IDeg + IAsp groups.
- **Dosing**: In the IDeg + Lira arm, the mean IDeg dose at baseline was 0.70 U/kg. At Week 1, the mean IDeg dose was 0.57 U/kg, reflecting the per protocol 20% reduction of the IDeg dose when initiating liraglutide at randomisation (Week 0). Consistent with protocol recommendations, the mean IDeg dose did not increase in this arm until after Week 6. After 26 weeks of treatment, the mean IDeg dose in the IDeg + Lira group was 0.65 U/kg, lower than the pre-randomisation mean IDeg dose. In the IDeg + IAsp arm, the mean IDeg dose at baseline was 0.66 U/kg and remained steady throughout the trial. After 26 weeks of treatment, the mean IDeg dose in the IDeg + IAsp arm was 0.64 U/kg. After 26 weeks, the mean daily IAsp dose was 0.21 U/kg in the IDeg + IAsp arm. At Week 25, IAsp was injected before breakfast by 5.4% of subjects, before lunch by 47.3% of subjects and before main evening meal by 47.3% of subjects; this distribution of IAsp dose administration remained relatively constant throughout the trial. By Week 26, 28 (32.2%) of IDeg + Lira subjects took 1.2 mg/day and 57 (65.5%) took 1.8 mg/day of liraglutide.

For the non-randomised arm the following can be concluded with regard to safety after 26 weeks of treatment with IDeg in combination with metformin:

- **Adverse events:** The percentage of subjects reporting AEs was 54.7% in the IDeg group and the observed rate of AEs was 331 events per 100 PYE. The majority of AEs were mild or moderate and most subjects recovered by the end of the trial. The rate of severe AEs and the rate of AEs considered possibly or probably related to trial product by the investigator was 9 and 10 events per 100 PYE, respectively. The most frequently reported AE was nasopharyngitis.
- **Deaths, serious adverse events (SAEs) and other significant adverse events:** No deaths were reported in this trial. A total of 11 (4.7%) IDeg-treated subjects reported 15 SAEs. The rate of SAEs per 100 PYE was 13. One major adverse cardiovascular event (acute coronary syndrome/myocardial infarction/NSTEMI) was reported in the IDeg group. No medication errors were reported in the IDeg group. No subjects in the IDeg group were withdrawn due to AEs.
- **Hypoglycaemic episodes:** The percentage of subjects who experienced confirmed hypoglycaemic episodes was 43.2% in the IDeg group, with an observed rate of confirmed hypoglycaemic episodes of 264 per 100 PYE. The observed rate of nocturnal confirmed hypoglycaemic episodes was 20 per 100 PYE for IDeg-treated subjects. One (1) subject in the IDeg group experienced a single severe confirmed hypoglycaemic episode during the trial.
- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: No clinically relevant differences from baseline to end-of-treatment were observed for haematology, biochemistry or lipid laboratory values, vital signs, ECG, fundoscopy/ fundus photography or physical examination in the IDeg group.
- **Dosing**: The IDeg dose remained relatively stable throughout the trial in the IDeg group. After 26 weeks of treatment, the mean IDeg dose was 0.59 U/kg.

CONCLUSIONS

The results of this randomised, controlled, 26-week trial demonstrate the efficacy and safety of adding liraglutide (Lira) vs. insulin aspart (IAsp), both once daily (OD), to IDeg OD + metformin in subjects with type 2 diabetes who completed approximately 104 weeks of IDeg + metformin treatment in NN1250-3579/3643, with end-of-treatment $HbA_{1c} \geq 7.0\%$.

The data support the following conclusions of adding Lira once daily vs. IAsp with the largest meal to IDeg OD + metformin:

- Addition of Lira to IDeg + metformin results in a greater reduction in HbA_{1c} compared to addition of IAsp with the largest meal. Thus, addition of Lira to IDeg + metformin in subjects with T2DM offers an effective intensification regimen.
- FPG remains constant with both treatment arms
- A greater proportion of subjects achieve $HbA_{1c} < 7\%$ without confirmed hypoglycaemia and without weight gain with IDeg + Lira compared to IDeg + IAsp
- Subjects treated with IDeg + Lira experience a lower rate of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia compared to IDeg + IAsp
- Subjects treated with IDeg + Lira lose weight compared to subjects treated with IDeg +IAsp
- In this trial, apart from more gastrointestinal side effects with IDeg + Lira than with IDeg + IAsp, there is no apparent difference between treatment arms with respect to AEs and standard safety parameters

In the third, non-randomised treatment arm, consisting of subjects treated with IDeg OD + metformin who achieved the target $HbA_{1c} < 7\%$ after approximately 104 weeks of IDeg + metformin treatment in NN1250-3579/3643, the durability of IDeg OD + metformin is established as the HbA_{1c} during the subsequent 26 weeks is maintained.

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 06-Aug-2012

This page intentionally left blank.