Clinical trial results:
DUAL™ III - GLP-1 switch: The efficacy of insulin degludec/liraglutide in controlling glycaemia in adults with type 2 diabetes inadequately controlled on GLP-1 receptor agonist and OAD therapy

Summary

EudraCT number	2012-000209-63
Trial protocol	SK HU
Global end of trial date	11 March 2014

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	28 July 2015

Trial information

Trial identification

Sponsor protocol code	NN9068-3851

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01676116
WHO universal trial number (UTN)	U1111-1127-1321

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2014
Global end of trial reached?	Yes
Global end of trial date	11 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of insulin degludec/liraglutide versus unchanged glucagon-like peptide-1 (GLP-1) receptor agonist therapy in controlling glycaemia in insulin naïve subjects with type 2 diabetes mellitus (T2DM) inadequately controlled on GLP-1 receptor agonist therapy in combination with metformin±pioglitazone±sulphonylurea.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (59th WMA Assembly, October 2008) and ICH Good Clinical Practice (May 1996) and 21 CFR 312.120.

Background therapy:

Subjects continued with the OADs Metformin, pioglitazone and sulphonylurea in stable pre-trial doses.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	29 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 41
Country: Number of subjects enrolled	United States: 262
Country: Number of subjects enrolled	Slovakia: 60
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Hungary: 35
Worldwide total number of subjects	438
EEA total number of subjects	135

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	326
From 65 to 84 years	112
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 81 sites in 5 countries as follows: Australia: 5 sites; France: 7 sites; Hungary: 4 sites; Slovakia 6 sites; United States: 59 sites.

Pre-assignment

Screening details:

The duration of the screening period was 2-weeks. All subjects continued GLP-1 receptor agonist and metformin±pioglitazone±SU treatments in their pre-trial doses during the screening period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin degludec/liraglutide + OADs

Arm description:

Subjects were treated with subcutaneous (under the skin) once daily (OD) insulin degludec/liraglutide. Insulin degludec/liraglutide was dosed on an individual basis. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) treatment without changing the frequency or dose throughout the trial, unless there was a safety concern.

Arm type	Experimental
Investigational medicinal product name	Insulin degludec/liraglutide PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec/liraglutide in a fixed insulin degludec/liraglutide ratio of 100 units/3.6 mg per mL was supplied in a 3 mL prefilled PDS290 pen-injector. Insulin degludec/liraglutide was injected s.c. in the thigh, upper arm (deltoid region) or abdomen once daily preferably at the same time every day. The insulin degludec/liraglutide dosing unit is defined as a dose step, where 1 insulin degludec/liraglutide dose step consists of 1 unit insulin degludec and 0.036 mg liraglutide. Treatment with insulin degludec/liraglutide was initiated at 16 dose steps containing 16 units insulin degludec and 0.6 mg liraglutide. Adjustment of the insulin degludec/liraglutide dose performed twice weekly based on the mean of 3 preceding daily fasting SMPG values on 3 consecutive days. The maximum allowed dose was 50 dose steps (50 units insulin degludec/1.8 mg liraglutide).

Arm title	Liraglutide or exenatide + OADs

Arm description:

Subjects continued on their pre-trial treatment with subcutaneous (under the skin) liraglutide (Victoza®) (GLP-1 receptor agonist) or exenatide (Byetta®) (GLP-1 receptor agonist) without changing the frequency or dose throughout the trial. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) without changing the frequency or dose throughout the trial, unless there was a safety concern.

Arm type	Active comparator

Investigational medicinal product name	Liraglitide or Exenatide
Investigational medicinal product code	
Other name	Victoza or Byetta
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The subjects continued their pre-trial GLP-1 receptor agonist treatment either with liraglutide or exenatide with the dose and treatment schedule unchanged throughout the trial period. Subjects also continued with the OADs - metformin, pioglitazone and SU - in stable pre-trial doses (unless there was a safety concern).

Number of subjects in period 1	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs
Started	292	146
Completed	276	117
Not completed	16	29
Adverse event, non-fatal	1	2
Other	4	10
Withdrawal criteria	2	14
Protocol deviation	9	3

Baseline characteristics

Reporting groups	
Reporting group title	Insulin degludec/liraglutide + OADs
Reporting group description:	
Subjects were treated with subcutaneous (under the skin) once daily (OD) insulin degludec/liraglutide. Insulin degludec/liraglutide was dosed on an individual basis. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) treatment without changing the frequency or dose throughout the trial, unless there was a safety concern.	
Reporting group title	Liraglutide or exenatide + OADs
Reporting group description:	
Subjects continued on their pre-trial treatment with subcutaneous (under the skin) liraglutide (Victoza®) (GLP-1 receptor agonist) or exenatide (Byetta®) (GLP-1 receptor agonist) without changing the frequency or dose throughout the trial. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) without changing the frequency or dose throughout the trial, unless there was a safety concern.	

Reporting group values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs	Total
Number of subjects	292	146	438
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.3	58.4	
standard deviation	± 9.9	± 8.8	-
Gender categorical Units: Subjects			
Female	139	75	214
Male	153	71	224
HbA1c Units: percentage of glycated haemoglobin			
arithmetic mean	7.8	7.7	
standard deviation	± 0.6	± 0.6	-
Body weight Units: kg			
arithmetic mean	95.6	95.5	
standard deviation	± 16.6	± 17.3	-
Fasting plasma glucose Units: mmol/L			
arithmetic mean	9	9.4	
standard deviation	± 2.1	± 2.3	-

End points

End points reporting groups

Reporting group title	Insulin degludec/liraglutide + OADs
Reporting group description:	
Subjects were treated with subcutaneous (under the skin) once daily (OD) insulin degludec/liraglutide. Insulin degludec/liraglutide was dosed on an individual basis. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) treatment without changing the frequency or dose throughout the trial, unless there was a safety concern.	
Reporting group title	Liraglutide or exenatide + OADs
Reporting group description:	
Subjects continued on their pre-trial treatment with subcutaneous (under the skin) liraglutide (Victoza®) (GLP-1 receptor agonist) or exenatide (Byetta®) (GLP-1 receptor agonist) without changing the frequency or dose throughout the trial. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) without changing the frequency or dose throughout the trial, unless there was a safety concern.	

Primary: Change in glycosylated haemoglobin (HbA1c) from baseline (randomisation, Visit 2).

End point title	Change in glycosylated haemoglobin (HbA1c) from baseline (randomisation, Visit 2).
End point description:	
The mean change from baseline in HbA1c, after 26 weeks of treatment.	
End point type	Primary
End point timeframe:	
After 26 weeks of treatment.	

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	146		
Units: percentage of glycosylated haemoglobin				
least squares mean (standard error)	-1.32 (± 0.05)	-0.37 (± 0.07)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment, pre-trial GLP-1 receptor agonist (Victoza® or Byetta®) and region as fixed factors and baseline HbA1c value as covariate.	
Comparison groups	Insulin degludec/liraglutide + OADs v Liraglutide or exenatide + OADs

Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Treatment Contrast
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.78

Secondary: Responders (Yes/No) achieving pre-defined target for HbA1c - HbA1c < 7.0% (53 mmol/mol).

End point title	Responders (Yes/No) achieving pre-defined target for HbA1c - HbA1c < 7.0% (53 mmol/mol).
End point description:	
Proportion of subjects achieving HbA1c below 7.0% after 24 weeks of treatment.	
End point type	Secondary
End point timeframe:	
After 26 weeks of treatment.	

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	146		
Units: Percentage				
number (not applicable)	75.3	35.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Responders (Yes/No) achieving pre-defined target for HbA1c - HbA1c ≤ 6.5% (48 mmol/mol).

End point title	Responders (Yes/No) achieving pre-defined target for HbA1c - HbA1c ≤ 6.5% (48 mmol/mol).
End point description:	
Proportion of responders achieving pre-defined target for HbA1c - HbA1c ≤ 6.5% (48 mmol/mol).	
End point type	Secondary
End point timeframe:	
After 26 weeks of treatment	

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	146		
Units: Percentage				
number (not applicable)	63	22.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight.

End point title	Change from baseline in body weight.

End point description:

Mean change in body weight after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	146		
Units: Kilograms				
arithmetic mean (standard deviation)	2 (± 3.9)	-0.8 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting plasma glucose (FPG).

End point title	Change from baseline in fasting plasma glucose (FPG).

End point description:

Mean change in fasting plasma glucose from baseline, after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	145		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.98 (± 2.28)	-0.6 (± 2.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent (confirmed) hypoglycaemic episodes.

End point title	Number of treatment-emergent (confirmed) hypoglycaemic episodes.

End point description:

Rate (event rate per 100 patient years of exposure) of treatment-emergent confirmed hypoglycaemic episodes. The pool of severe and minor hypoglycaemic episodes was referred to as confirmed hypoglycaemic episodes.
Severe hypoglycaemia was categorised as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Minor hypoglycaemic episodes were defined as an episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose <2.8 mmol/L (50 mg/dL) or PG <3.1 mmol/L (56 mg/dL), and which was handled by the subject himself/herself, or any asymptomatic blood glucose value <2.8 mmol/L (50 mg/dL) or PG value <3.1 mmol/L (56 mg/dL).

End point type	Secondary

End point timeframe:

During 26 weeks of treatment.

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	145		
Units: Event Rate				
number (not applicable)	281.7	12.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse events (AEs)

End point title	Number of treatment-emergent adverse events (AEs)

End point description:

Rate (event rate per 100 exposure years) of treatment-emergent adverse events (an event that had onset date (or an increase in severity) on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment) which occurred during the 26 weeks of treatment .

End point type	Secondary

End point timeframe:

During 26 weeks of treatment.

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	145		
Units: Event rate				
number (not applicable)	410.1	364.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient reported outcomes (PROs):-Treatment related impact measure – diabetes (TRIM-D).

End point title	Change from baseline in patient reported outcomes (PROs):-Treatment related impact measure – diabetes (TRIM-D).

End point description:

The mean change from baseline on the 'Treatment related impact measure for diabetes' (TRIM-D), after 26 weeks of treatment. A higher score on the 1–5 point TRIM-D scale indicates a better health state (less negative impact). The mean change in scores for all the sub domains (treatment burden, daily life, diabetes management, compliance and psychological health) and total scores were analysed. Sub-domain scores were calculated by summing across items in the same domain and total score was calculated by adding scores from all the domains.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	146		
Units: Scores				
arithmetic mean (standard deviation)				
TRIM-D Treatment Burden Score	10.8 (± 18.8)	5.7 (± 19.3)		
TRIM-D Daily Life Score	6.3 (± 18.4)	0.8 (± 18.2)		
TRIM-D Diabetes Management Score	10.9 (± 21.3)	4.1 (± 19.8)		
TRIM-D Compliance Score	8.9 (± 17.3)	4.3 (± 15.9)		

TRIM-D Psychological Health Score	7.3 (± 14.7)	1.4 (± 16.5)		
TRIM-D Total Score	8.7 (± 12)	3.1 (± 12.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient reported outcomes (PROs):-Diabetes treatment satisfaction questionnaire (DTSQ).

End point title	Change from baseline in patient reported outcomes (PROs):-Diabetes treatment satisfaction questionnaire (DTSQ).

End point description:

Mean change in diabetes treatment satisfaction questionnaire (DTSQs) scores from baseline. Higher total score on a 0–6 point scale indicates a general higher treatment satisfaction (items 1, 4, 5, 6, 7 and 8), whereas higher score on perceived frequency of hyperglycaemia (item 2) and perceived frequency of hypoglycaemia (item 3) indicate that blood glucose levels are out of the target range.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin degludec/liraglutide + OADs	Liraglutide or exenatide + OADs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	146		
Units: Score				
arithmetic mean (standard deviation)				
Treatment satisfaction scale total	3.1 (± 5.6)	1.1 (± 5)		
Hyperglycaemia	-1.8 (± 2)	-0.6 (± 2)		
Hypoglycaemia	0.2 (± 1.7)	-0.1 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events from the first trial-related activity after the subject had signed the informed consent until the end of the post-treatment follow-up period are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Liraglutide or exenatide + OADs

Reporting group description:

Subjects continued on their pre-trial treatment with subcutaneous (under the skin) liraglutide (Victoza®) (GLP-1 receptor agonist) or exenatide (Byetta®) (GLP-1 receptor agonist) without changing the frequency or dose throughout the trial. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) without changing the frequency or dose throughout the trial, unless there was a safety concern.

Reporting group title	Insulin degludec/liraglutide +OADs

Reporting group description:

Subjects were treated with subcutaneous (under the skin) once daily (OD) insulin degludec/liraglutide. Insulin degludec/liraglutide was dosed on an individual basis. Subjects also continued their pre-trial OADs (metformin±pioglitazone±SU) treatment without changing the frequency or dose throughout the trial, unless there was a safety concern.

Serious adverse events	Liraglutide or exenatide + OADs	Insulin degludec/liraglutide +OADs	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 145 (2.07%)	9 / 291 (3.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 145 (0.69%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Thrombectomy			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 145 (0.69%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Liraglutide or exenatide + OADs	Insulin degludec/liraglutide +OADs	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 145 (26.90%)	88 / 291 (30.24%)	

Investigations Lipase increased subjects affected / exposed occurrences (all)	 7 / 145 (4.83%) 8	 29 / 291 (9.97%) 31	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 9 / 145 (6.21%) 14	 27 / 291 (9.28%) 31	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 8 / 145 (5.52%) 9	 13 / 291 (4.47%) 18	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 8 / 145 (5.52%) 9 19 / 145 (13.10%) 20	 18 / 291 (6.19%) 18 26 / 291 (8.93%) 31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2013	The global amendment included: a) Changes in the pre-trial medication from GLP-1 and metformin therapy to allow GLP-1 in combination with OADs (metformin±pioglitazone±SU) due to recruitment facilitation and reflection of current diabetic patient population on GLP-1 receptor agonists. b) Changes to the endpoints and statistical sections as described in Section 9.8.2 of this CTR. c) Update of withdrawal criterion no. 1. Updates of the list of participating countries (Hungary added), recruitment timelines, blood volume to be drawn, protocol title, version and date of all appendices. d) Update of the following MESI's based on the learning's from previous insulin degludec/liraglutide trials: – Acute coronary syndrome (myocardial infarction [MI] or hospitalisation for unstable angina), incl. AMI caused by stent thrombosis: The wording ", incl. AMI caused by stent thrombosis" was deleted, as this information was already provided under Definitions in Appendix D. – Hospitalisation for cardiac arrhythmia: The word "hospitalisation" was removed, as reporting of hospitalisation for cardiac arrhythmia was not always applicable. Cardiac arrhythmia was still to be reported as a MESI. – Elevated lipase and/or amylase: Confirmatory testing removed. The single elevation >3xUNR of lipase/amylase was to be reported as a MESI. – Elevated calcitonin: Protocol text clarified and aligned to match Appendix D of the protocol. e) Removal of the initial aim to recruit approximately 50% of each type of GLP-1 receptor agonist. f) Update of the ICF regarding blood to be drawn and increased heart rate according to the recent investigator's brochure for liraglutide.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: