Clinical trial results:
A randomised, double-blind, double-dummy, placebo-controlled, parallel-group multi-centre clinical proof-of-principle trial in adult subjects with newly diagnosed type 1 diabetes mellitus investigating the effect of NNC0114-0006 and liraglutide on preservation of beta-cell function.

Summary

EudraCT number	2014-001215-39
Trial protocol	AT PT DK FI ES IE PL BE
Global end of trial date	27 February 2019

Results information

Result version number	v1 (current)
This version publication date	28 February 2020
First version publication date	28 February 2020

Trial information

Trial identification

Sponsor protocol code	NN9828-4150

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02443155
WHO universal trial number (UTN)	U1111-1154-7172

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, 2880 (+1) 866-867-7178, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, 2880 (+1) 866-867-7178, 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	17 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2018
Global end of trial reached?	Yes
Global end of trial date	27 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of NNC0114-0006, liraglutide and the combination of NNC0114 0006 and liraglutide, compared to placebo, on preservation of beta-cell function after 54 weeks of treatment in adult subjects with newly diagnosed type 1 diabetes mellitus (T1DM).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents and FDA 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	10 November 2015
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	Austria: 17
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	United States: 13

Worldwide total number of subjects	308
EEA total number of subjects	155

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)	308
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

94 sites in 17 countries screened subjects. Number of sites randomised subjects were Austria:4, Belgium:1, Canada:10, Denmark:2, Finland:2 of 3 sites, Ireland:3, Israel:4, Italy:4, Norway:1 of 2 sites, Poland:4, Portugal:3 of 4 sites, Russian Fed:13 of 15 sites, Spain:6 of 7 sites, Sweden:1 of 2 sites, Ukraine:6, UK:12, US:6 of 11 screened sites.

Pre-assignment

Screening details:

Not applicable.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The trial was double-blinded and the investigator and subjects remained blinded throughout the trial. The sponsor was blinded for the treatment period, but unblinded for the observation period.

Arms

Are arms mutually exclusive?	Yes
Arm title	NNC0114-0006 + Liraglutide

Arm description:

Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Arm type	Experimental
Investigational medicinal product name	NNC0114-0006 C 100 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received NNC0114-0006 dose of 12 mg/kg every 6 weeks, intravenously, at trial site.

Investigational medicinal product name	Liraglutide, 6.0 mg/mL,
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects initiated 0.6 mg liraglutide, on the day of randomisation and the dose was escalated in increments of 0.6 mg liraglutide every 2 weeks until the target dose of 1.8 mg liraglutide was reached. Liraglutide was self-administered once daily, subcutaneously, either in the abdomen, thigh or upper arm daily with a pen-injector around the same time of the day.

Arm title	NNC0114-0006

Arm description:

Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took liraglutide placebo once daily, subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed

by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Arm type	Experimental
Investigational medicinal product name	NNC0114-0006 C 100 mg/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received NNC0114-0006 dose of 12 mg/kg every 6 weeks, intravenously, at trial site.

Investigational medicinal product name	Liraglutide placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects took liraglutide placebo once daily subcutaneously, with the volume of placebo equivalent to the volume Liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Liraglutide placebo was self-administered either in the abdomen, thigh or upper arm daily with a pen-injector around the same time of the day.

Arm title	Liraglutide

Arm description:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects initiated 0.6 mg liraglutide, on the day of randomisation and the dose was escalated in increments of 0.6 mg liraglutide every 2 weeks until the target dose of 1.8 mg liraglutide was reached. Liraglutide was self-administered once daily, subcutaneously, either in the abdomen, thigh or upper arm daily with a pen-injector around the same time of the day.

Investigational medicinal product name	NNC0114-0006 placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously, at trial site.

Arm title	Placebo

Arm description:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. In addition to that, subjects took liraglutide placebo once daily subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Arm type	Placebo

Investigational medicinal product name	NNC0114-0006 placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously, at trial site.

Investigational medicinal product name	Liraglutide placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects took liraglutide placebo once daily subcutaneously, with the volume of placebo equivalent to the volume Liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Liraglutide placebo was self-administered either in the abdomen, thigh or upper arm daily with a pen-injector around the same time of the day.

Number of subjects in period 1[1]	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide
Started	77	77	76
Completed	65	63	67
Not completed	12	14	9
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	4	7	3
Adverse event, non-fatal	3	4	1
Pregnancy	3	1	1
Unclassified	-	-	2
Lost to follow-up	1	2	-
Protocol deviation	1	-	1

Number of subjects in period 1[1]	Placebo
Started	77
Completed	61
Not completed	16
Adverse event, serious fatal	-
Consent withdrawn by subject	9
Adverse event, non-fatal	2
Pregnancy	2
Unclassified	1
Lost to follow-up	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One (1) subject was randomised to liraglutide but was withdrawn from the trial before exposure to trial products. Hence the number of subjects 'started' in Liraglutide arm is 76 and not 77.

Baseline characteristics

Reporting groups	
Reporting group title	NNC0114-0006 + Liraglutide
Reporting group description:	
Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.	
Reporting group title	NNC0114-0006
Reporting group description:	
Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took liraglutide placebo once daily, subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.	
Reporting group title	Liraglutide
Reporting group description:	
Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.	
Reporting group title	Placebo
Reporting group description:	
Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. In addition to that, subjects took liraglutide placebo once daily subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.	

Reporting group values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide
Number of subjects	77	77	76
Age Categorical Units: Subjects			
Adults (18-64 years)	77	77	76
Age Continuous Units: years			
arithmetic mean	28.0	28.6	28.0
standard deviation	± 7.5	± 7.9	± 7.1
Gender Categorical Units: Subjects			
Female	21	32	25
Male	56	45	51

Reporting group values	Placebo	Total	
Number of subjects	77	307	
Age Categorical Units: Subjects			
Adults (18-64 years)	77	307	

Age Continuous Units: years			
arithmetic mean	29.0		
standard deviation	± 7.0	-	
Gender Categorical Units: Subjects			
Female	28	106	
Male	49	201	

End points

End points reporting groups

Reporting group title	NNC0114-0006 + Liraglutide

Reporting group description:

Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Reporting group title	NNC0114-0006

Reporting group description:

Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took liraglutide placebo once daily, subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Reporting group title	Liraglutide

Reporting group description:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Reporting group title	Placebo

Reporting group description:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. In addition to that, subjects took liraglutide placebo once daily subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Primary: AUC0-4h, C-peptide, 54w/AUC0-4h, C-peptide, baseline: AUC0-4h for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve.

End point title	AUC0-4h, C-peptide, 54w/AUC0-4h, C-peptide, baseline: AUC0-4h for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve.

End point description:

Area under the curve, from 0 to 4 hours (AUC0-4h) for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 54 was measured as ratio to baseline value. C-peptide concentration was measured in unit 'nmol*h/L'.

End point type	Primary

End point timeframe:

At week 54 relative to baseline (defined as the MMTT performed at Visit 2)

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	65	68	63
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.934 (± 61.9)	0.783 (± 45.5)	0.709 (± 104.8)	0.660 (± 86.3)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

NNC0114-0006+Liraglutide/Placebo.

Ratio of week 54 to baseline are analysed using mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. Treatment, stratum and sex as factors and log baseline value and age as covariates, including the interaction between visit and all variables.

Comparison groups	Placebo v NNC0114-0006 + Liraglutide
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0017
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	1.89

Notes:

[1] - Due to the repeated analysis, the number of subjects included in the analysis were 148 and not only the 129 with an endpoint value at week 54.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

NNC0114-0006 /Placebo.

Ratio of week 54 to baseline are analysed using MMRM with an unstructured covariance matrix. Treatment, stratum and sex as factors and log baseline value and age as covariates, including the interaction between visit and all variables.

Comparison groups	NNC0114-0006 v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0927
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.57

Notes:

[2] - Due to the repeated analysis, the number of subjects included in the analysis were 148 and not only the 128 with an endpoint value at week 54.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Liraglutide/Placebo

Ratio of week 54 to baseline are analysed using MMRM with an unstructured covariance matrix. Treatment, stratum and sex as factors and log baseline value and age as covariates, including the interaction between visit and all variables.

Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.378
Method	Mixed models analysis
Parameter estimate	Treatment Ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.42

Notes:

[3] - Due to the repeated analysis, the number of subjects included in the analysis were 147 and not only the 131 with an endpoint value at week 54.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

NNC0114-0006 + liraglutide /NNC0114-0006

Ratio of week 54 to baseline are analysed using MMRM with an unstructured covariance matrix. Treatment, stratum and sex as factors and log baseline value and age as covariates, including the interaction between visit and all variables.

Comparison groups	NNC0114-0006 + Liraglutide v NNC0114-0006
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.1377
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.53

Notes:

[4] - Due to the repeated analysis, the number of subjects included in the analysis were 150 and not only the 131 with an endpoint value at week 54.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

NNC0114-0006 + liraglutide /Liraglutide.

Ratio of week 54 to baseline are analysed using MMRM with an unstructured covariance matrix. Treatment, stratum and sex as factors and log baseline value and age as covariates, including the interaction between visit and all variables.

Comparison groups	NNC0114-0006 + Liraglutide v Liraglutide
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0214
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.69

Notes:

[5] - Due to the repeated analysis, the number of subjects included in the analysis were 149 and not only the 134 with an endpoint value at week 54.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

NNC0114-0006 /Liraglutide.

Ratio of week 54 to baseline are analysed using MMRM with an unstructured covariance matrix. Treatment, stratum and sex as factors and log baseline value and age as covariates, including the interaction between visit and all variables.

Comparison groups	NNC0114-0006 v Liraglutide
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.4187
Method	Mixed models analysis
Parameter estimate	Treatmrnt ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.41

Notes:

[6] - Due to the repeated analysis, the number of subjects included in the analysis were 149 and not only the 133 with an endpoint value at week 54.

Secondary: Number of treatment emergent episodes of diabetic ketoacidosis (DKA)

End point title	Number of treatment emergent episodes of diabetic ketoacidosis (DKA)

End point description:

Number of treatment emergent episodes of diabetic ketoacidosis (DKA) from first dose of trial product to week 54

End point type	Secondary

End point timeframe:

From first dose of trial product to week 54

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77	77	76	77
Units: Number of episodes	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) and Novo Nordisk definitions.

End point title	Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) and Novo Nordisk definitions.

End point description:

Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) and Novo Nordisk definitions, from first dose of trial product to week 54.
ADA's definition of hypoglycaemia includes following categories: 1. Severe hypoglycaemia 2. Documented symptomatic hypoglycaemia 3. Asymptomatic hypoglycaemia 4. Probable symptomatic hypoglycaemia 5. Pseudo-hypoglycaemia.
Novo Nordisk definition of Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA 2013 classification or blood glucose (BG) confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia.

End point type	Secondary

End point timeframe:

From first dose of trial product to week 54

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77	77	76	77
Units: Number of episodes				
American Diabetes Association (ADA)	3354	3420	3224	3411
Novo Nordisk definitions	577	618	479	646

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-4h for MMTT stimulated C-peptide concentration time curve.

End point title	AUC0-4h for MMTT stimulated C-peptide concentration time curve.

End point description:

Area under the curve, from 0 to 4 hours (AUC0-4h) for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 80 was measured as ratio to baseline value. C-peptide concentration was measured in unit 'nmol*h/L'.

End point type	Secondary

End point timeframe:

At week 80 relative to baseline

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	62	58
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.566 (± 71.3)	0.598 (± 70.2)	0.373 (± 115.8)	0.571 (± 100.9)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-2h for MMTT stimulated C-peptide concentration time curve (at week 54) relative to baseline

End point title	AUC0-2h for MMTT stimulated C-peptide concentration time curve (at week 54) relative to baseline

End point description:

Area under the curve, from 0 to 2 hours (AUC0-2h) for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 54 was measured as ratio to baseline value. C-peptide concentration was measured in unit 'nmol*h/L'.

End point type	Secondary

End point timeframe:

At week 54 relative to baseline

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	65	68	63
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.961 (± 65.4)	0.824 (± 53.0)	0.646 (± 97.4)	0.655 (± 87.3)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-2h for MMTT stimulated C-peptide concentration time curve (at week 80) relative to baseline

End point title	AUC0-2h for MMTT stimulated C-peptide concentration time curve (at week 80) relative to baseline

End point description:

Area under the curve, from 0 to 2 hours (AUC0-2h) for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 80 was measured as ratio to baseline value. C-peptide concentration was measured in unit 'nmol*h/L'.

End point type	Secondary

End point timeframe:

At week 80 relative to baseline

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	62	58
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.590 (± 74.5)	0.619 (± 71.2)	0.370 (± 111.5)	0.540 (± 120.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum MMTT stimulated C-peptide concentration (Cmax, C-peptide) (at week 54) relative to baseline

End point title	Maximum MMTT stimulated C-peptide concentration (Cmax, C-peptide) (at week 54) relative to baseline

End point description:

Maximum mixed meal tolerance test (MMTT) stimulated C-peptide concentration (Cmax, C-peptide) at week 54 was measured as ratio to baseline value. Cmax was measured in unit 'nmol/L'.

End point type	Secondary

End point timeframe:

At week 54 relative to baseline

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	65	68	63
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.978 (± 70.3)	0.779 (± 47.6)	0.733 (± 110.4)	0.644 (± 89.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum MMTT stimulated C-peptide concentration (Cmax, C-peptide) (at week 80) relative to baseline

End point title	Maximum MMTT stimulated C-peptide concentration (Cmax, C-peptide) (at week 80) relative to baseline

End point description:

Maximum mixed meal tolerance test (MMTT) stimulated C-peptide concentration (Cmax, C-peptide) at week 80 was measured as ratio to baseline value. Cmax was measured in unit 'nmol/L'.

End point type	Secondary

End point timeframe:

At week 80 relative to baseline

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	64	62	58
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.580 (± 74.8)	0.592 (± 76.8)	0.389 (± 109.0)	0.568 (± 97.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting C-peptide (from baseline to week 54)

End point title	Change in fasting C-peptide (from baseline to week 54)

End point description:

Change in fasting C-peptide at week 54 was measured as ratio to baseline value. C-peptide concentration was measured in unit 'nmol/L'.

End point type	Secondary

End point timeframe:

From baseline to week 54

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	64	66	64
Units: Ratio				
geometric mean (geometric coefficient of variation)	1.01 (± 76.8)	0.70 (± 71.1)	0.65 (± 102.4)	0.66 (± 116.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting C-peptide (from baseline to week 80)

End point title	Change in fasting C-peptide (from baseline to week 80)

End point description:

Change in fasting C-peptide at week 80 was measured as ratio to baseline value. C-peptide concentration was measured in unit 'nmol/L'.

End point type	Secondary

End point timeframe:

From baseline to week 80

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	63	64	60
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.58 (± 112.9)	0.53 (± 106.2)	0.42 (± 132.5)	0.54 (± 154.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c (from baseline to week 54)

End point title	Change in HbA1c (from baseline to week 54)

End point description:

Change in glycosylated haemoglobin (HbA1c) from baseline to week 54

End point type	Secondary

End point timeframe:

From baseline to week 54

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	65	67	65
Units: percentage point				
arithmetic mean (standard deviation)	-0.7 (± 1.9)	-0.5 (± 1.4)	-0.3 (± 1.5)	-0.3 (± 1.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c (from baseline to week 80)

End point title	Change in HbA1c (from baseline to week 80)
End point description:	
Change in glycosylated haemoglobin (HbA1c) from baseline to week 80	
End point type	Secondary
End point timeframe:	
From baseline to week 80	

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	64	68	62
Units: percentage point				
arithmetic mean (standard deviation)	-0.1 (± 1.6)	-0.2 (± 1.5)	0.5 (± 2.1)	-0.4 (± 1.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (from baseline to week 54)

End point title	Change in fasting plasma glucose (from baseline to week 54)
End point description:	
Change in fasting plasma glucose from baseline to week 54.	
End point type	Secondary
End point timeframe:	
From baseline to week 54	

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	64	66	64
Units: mmol/L				
arithmetic mean (standard deviation)	0.5 (± 3.2)	0.2 (± 2.4)	-0.3 (± 3.1)	0.5 (± 2.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (from baseline to week 80)

End point title	Change in fasting plasma glucose (from baseline to week 80)
End point description:	
Change in fasting plasma glucose from baseline to week 80	
End point type	Secondary
End point timeframe:	
From baseline to week 80	

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	61	65	60
Units: mmol/L				
arithmetic mean (standard deviation)	1.1 (± 3.3)	0.3 (± 2.4)	0.2 (± 4.0)	1.0 (± 2.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Total daily insulin dose in units per kg (three day average) at week 54

End point title	Total daily insulin dose in units per kg (three day average) at week 54
End point description:	
Total daily insulin dose in units per kg (three day average) at week 54	
End point type	Secondary
End point timeframe:	
At week 54	

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	57	62	56
Units: U/kg				
arithmetic mean (standard deviation)	0.30 (± 0.19)	0.36 (± 0.22)	0.33 (± 0.23)	0.39 (± 0.23)

Statistical analyses

No statistical analyses for this end point

Secondary: Total daily insulin dose in units per kg (three day average) at week 80

End point title	Total daily insulin dose in units per kg (three day average) at week 80

End point description:

Total daily insulin dose in units per kg (three day average) at week 80

End point type	Secondary

End point timeframe:

At week 80

End point values	NNC0114-0006 + Liraglutide	NNC0114-0006	Liraglutide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	57	56	51
Units: U/kg				
arithmetic mean (standard deviation)	0.46 (± 0.25)	0.40 (± 0.25)	0.45 (± 0.24)	0.44 (± 0.23)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period from randomisation to end of trial (week 0 to week 80).

Adverse event reporting additional description:

All reported adverse events are treatment-emergent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	NNC0114-0006 + liraglutide

Reporting group description:

Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Reporting group title	NNC0114-0006

Reporting group description:

Subjects received 12 mg/kg dose of NNC0114-0006 every 6 weeks, intravenously for 54 weeks. Subjects took liraglutide placebo once daily, subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Reporting group title	Liraglutide

Reporting group description:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. Subjects took 0.6 mg of liraglutide, subcutaneously, for first two weeks, 1.2 mg for next 2 weeks and 1.8 mg for rest of the treatment period. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Reporting group title	Placebo

Reporting group description:

Subjects received NNC0114-0006 placebo (volume equivalent to NNC0114-0006 dose of 12 mg/kg) every 6 weeks, intravenously for 54 weeks. In addition to that, subjects took liraglutide placebo once daily subcutaneously, with the volume of placebo equivalent to the volume liraglutide 0.6 mg, 1.2 mg and 1.8 mg. Subjects received treatment for 54 weeks followed by an off-treatment observation period of 26 weeks. Subjects continued their pre-trial insulin treatment throughout the trial.

Serious adverse events	NNC0114-0006 + liraglutide	NNC0114-0006	Liraglutide
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 77 (9.09%)	5 / 77 (6.49%)	9 / 76 (11.84%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign soft tissue neoplasm			

subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Routine health maintenance			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Cytomegalovirus test positive			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary contusion			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic shock			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Spinal muscular atrophy			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			

subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic coma			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoid tissue hyperplasia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Genital herpes			
subjects affected / exposed	0 / 77 (0.00%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital herpes simplex			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillitis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tooth abscess			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	2 / 77 (2.60%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketosis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 77 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign soft tissue neoplasm			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Routine health maintenance			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal septum deviation			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

Cytomegalovirus test positive				
subjects affected / exposed	0 / 77 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Clavicle fracture				
subjects affected / exposed	0 / 77 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	0 / 77 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pulmonary contusion				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic shock				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 77 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Spinal muscular atrophy				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrioventricular block second degree				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 77 (1.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	0 / 77 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				

subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic coma			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoid tissue hyperplasia			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Genital herpes			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Genital herpes simplex			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral herpes			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonsillitis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ketosis			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	NNC0114-0006 + liraglutide	NNC0114-0006	Liraglutide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 77 (74.03%)	55 / 77 (71.43%)	62 / 76 (81.58%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	2 / 76 (2.63%)
occurrences (all)	4	2	2

Blood immunoglobulin E increased			
subjects affected / exposed	1 / 77 (1.30%)	3 / 77 (3.90%)	7 / 76 (9.21%)
occurrences (all)	1	3	7
Lipase increased			
subjects affected / exposed	5 / 77 (6.49%)	1 / 77 (1.30%)	1 / 76 (1.32%)
occurrences (all)	6	1	1
Weight decreased			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	1 / 76 (1.32%)
occurrences (all)	4	2	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences (all)	5	2	0
Skin laceration			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 76 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 77 (14.29%)	10 / 77 (12.99%)	10 / 76 (13.16%)
occurrences (all)	21	12	11
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 77 (5.19%)	4 / 77 (5.19%)	6 / 76 (7.89%)
occurrences (all)	4	4	6
Pyrexia			
subjects affected / exposed	3 / 77 (3.90%)	7 / 77 (9.09%)	7 / 76 (9.21%)
occurrences (all)	4	9	12
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 77 (2.60%)	4 / 77 (5.19%)	4 / 76 (5.26%)
occurrences (all)	2	5	4
Abdominal distension			
subjects affected / exposed	3 / 77 (3.90%)	0 / 77 (0.00%)	4 / 76 (5.26%)
occurrences (all)	3	0	4
Abdominal pain			

subjects affected / exposed	9 / 77 (11.69%)	0 / 77 (0.00%)	4 / 76 (5.26%)
occurrences (all)	11	0	4
Abdominal pain upper			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	7 / 76 (9.21%)
occurrences (all)	1	0	8
Diarrhoea			
subjects affected / exposed	15 / 77 (19.48%)	9 / 77 (11.69%)	13 / 76 (17.11%)
occurrences (all)	21	15	22
Dyspepsia			
subjects affected / exposed	5 / 77 (6.49%)	3 / 77 (3.90%)	3 / 76 (3.95%)
occurrences (all)	8	6	5
Nausea			
subjects affected / exposed	19 / 77 (24.68%)	6 / 77 (7.79%)	42 / 76 (55.26%)
occurrences (all)	33	10	62
Vomiting			
subjects affected / exposed	14 / 77 (18.18%)	0 / 77 (0.00%)	17 / 76 (22.37%)
occurrences (all)	24	0	34
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 77 (7.79%)	4 / 77 (5.19%)	5 / 76 (6.58%)
occurrences (all)	7	4	7
Oropharyngeal pain			
subjects affected / exposed	10 / 77 (12.99%)	13 / 77 (16.88%)	5 / 76 (6.58%)
occurrences (all)	11	18	8
Respiratory disorder			
subjects affected / exposed	4 / 77 (5.19%)	2 / 77 (2.60%)	0 / 76 (0.00%)
occurrences (all)	4	2	0
Rhinorrhoea			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	2 / 76 (2.63%)
occurrences (all)	1	0	4
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 77 (1.30%)	0 / 77 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	1 / 76 (1.32%)
occurrences (all)	4	1	1
Back pain			
subjects affected / exposed	1 / 77 (1.30%)	4 / 77 (5.19%)	5 / 76 (6.58%)
occurrences (all)	1	6	6
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 77 (3.90%)	6 / 77 (7.79%)	5 / 76 (6.58%)
occurrences (all)	4	7	6
Influenza			
subjects affected / exposed	6 / 77 (7.79%)	12 / 77 (15.58%)	2 / 76 (2.63%)
occurrences (all)	7	14	3
Nasopharyngitis			
subjects affected / exposed	20 / 77 (25.97%)	27 / 77 (35.06%)	25 / 76 (32.89%)
occurrences (all)	35	63	50
Pharyngitis			
subjects affected / exposed	3 / 77 (3.90%)	4 / 77 (5.19%)	0 / 76 (0.00%)
occurrences (all)	3	5	0
Respiratory tract infection viral			
subjects affected / exposed	5 / 77 (6.49%)	1 / 77 (1.30%)	3 / 76 (3.95%)
occurrences (all)	7	1	6
Rhinitis			
subjects affected / exposed	5 / 77 (6.49%)	3 / 77 (3.90%)	3 / 76 (3.95%)
occurrences (all)	5	3	5
Sinusitis			
subjects affected / exposed	1 / 77 (1.30%)	2 / 77 (2.60%)	1 / 76 (1.32%)
occurrences (all)	1	5	1
Upper respiratory tract infection			
subjects affected / exposed	8 / 77 (10.39%)	5 / 77 (6.49%)	4 / 76 (5.26%)
occurrences (all)	13	9	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 77 (18.18%)	2 / 77 (2.60%)	11 / 76 (14.47%)
occurrences (all)	15	2	13
Hypoglycaemia			

subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	0 / 76 (0.00%)
occurrences (all)	15	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 77 (70.13%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	3		
Blood immunoglobulin E increased			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	5		
Lipase increased			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	3		
Skin laceration			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 77 (14.29%)		
occurrences (all)	17		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	4		
Pyrexia			

subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	4		
Abdominal distension			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	7 / 77 (9.09%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	11		
Dyspepsia			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	11		
Respiratory disorder			

subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	6		
Rhinorrhoea			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	3		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	25 / 77 (32.47%)		
occurrences (all)	45		
Pharyngitis			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences (all)	4		
Respiratory tract infection viral			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	6		
Sinusitis			

subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	7 / 77 (9.09%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	0 / 77 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2015	Changes to protocol due to requirements from Voluntary Harmonisation Procedure (VHP).
18 April 2016	Reduction in number of subjects included in the full PK analysis. Updates to inclusion criteria and exclusion criteria.
11 November 2016	Flowchart updated Change in biomarker panel: Discontinued biomarkers: islet-specific auto reactive CD8+ and isotypes of GAD and IAA Newly added biomarker: Immune phenotyping of PBM
23 May 2017	Reinstatement of Visit 4 as a phone contact with only safety monitoring. Allowing use of Continuous Glucose Monitoring (CGM) and Flash Glucose Monitoring devices.
26 March 2018	Partial DBL added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported