Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02443155
Sponsor trial ID:	NN9828-4150
Official title of study:	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
Document date:	17 September 2019

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID: NN9828-4150

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

Trial phase: 2

Protocol originator
Name: [redacted]
Department: ClinOps 1, Insulin, GH & Devices

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
AUC	area under the curve
BG	blood glucose
CHO	carbohydrate
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
C_{max}	maximum concentration
CMV	cytomegalovirus
CPOP	clinical proof of principle
CRF	case report form
CT	calcitonin
CTR	clinical trial report
DAS	Disease Activity Score
DFU	direction for use
DKA	diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DUN	dispensing unit number
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency

FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
HBcAb	hepatitis B core antibody
HB_sAg	hepatitis B surface antigen
HB_sAb	Hepatitis B surface antibody
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
IA2	islet antigen-2
IAA	insulin autoantibodies
ICMJE	International Committee of Medical Journal Editors
IgG	immunoglobulin G1
IB	Investigator's Brochure
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
i.v.	intravenous(ly)
IV/WRS	interactive voice/web response system
LADA	latent autoimmune diabetes of adults
LPFV	last patient first visit
LPLV	last patient last visit
LSMeans	least square mean

mAb	monoclonal antibody
MAO	monoamine oxidase
MEN2	Multiple Endocrine Neoplasia Type 2
MESI	medical event of special interest
MMRM	mixed model for repeated measurements
MMTT	mixed meal tolerance test
MRT	mean residence time
NK	natural killer
NOD	non-obese-diabetic
NPH	neutral protamine Hagedorn
NYHA	New York Heart Association
PBMCs	periphery blood mononuclear cells
PG	plasma glucose
PPG	postprandial glucose
RIP-LCMV-GP	Rat-Insulin-Promoter-Lymphocytic-Choriomeningitis-Glyco-Protein
PK	pharmacokinetic
PRO	patient reported outcome
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous(ly)
SD	standard deviation
SF-36v2	Short Form Health Survey version 2
SLE	systemic lupus erythematosus
SMBG	self-measured blood glucose
SMPG	self-measured plasma glucose
SS	steady state
SUSAR	suspected unexpected serious adverse reaction

TB	tuberculosis
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TMM	Trial Materials Manual
T_{reg}	regulatory T-cells
TSH	Thyroid-stimulating hormone
T-T-T	treat-to-target
ZnT8	zinc-transporter 8

1 Summary

Objective(s) and endpoint(s):

Primary objective

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)

Secondary objectives

- Objectives related to treatment period (from baseline to week 54):
    - To assess safety and tolerability of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess effect on glycaemic parameters (including insulin usage and insulin regimen) of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
- Objectives related to the post-treatment observation period (from week 54 to week 80):
    - To assess post-treatment safety and tolerability of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess post-treatment effect on preservation of beta-cell function of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess post-treatment effect on glycaemic parameters (including insulin usage and insulin regimen) of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM

Primary endpoint

The primary endpoint is $AUC_{0\text{-}4h}$ for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 54 relative to baseline (defined as the MMTT performed at Visit 2).

- $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$

Key secondary endpoints

- Number of treatment emergent episodes of diabetic ketoacidosis (DKA) from first dose of trial product to week 54
- 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
- $AUC_{0\text{-}4h}$ for MMTT stimulated C-peptide concentration time curve at week 80 relative to baseline
- $AUC_{0\text{-}2h}$ for MMTT stimulated C-peptide concentration time curve at week 54 and week 80 relative to baseline
- Maximum MMTT stimulated C-peptide concentration ($C_{max,\ C\text{-}peptide}$) at week 54 and week 80 relative to baseline
- Change in fasting C-peptide from baseline to week 54 and week 80
- Change in HbA_{1c} from baseline to week 54 and week 80
- Change in fasting plasma glucose from baseline to week 54 and week 80
- Total daily insulin dose in units per kg (three day average) at week 54 and week 80

Trial design:

The trial is a randomised, multi-centre, multinational, placebo-controlled, double-dummy, double-blind, efficacy, safety and pharmacokinetic clinical proof of principle (CPOP) trial in subjects with newly diagnosed T1DM. The trial includes four parallel treatment groups, one with NNC0114-0006 12 mg/kg intravenously every 6 week and liraglutide 1.8 mg subcutaneously daily, one with NNC0114-0006 12 mg/kg intravenously every 6 week, one with liraglutide 1.8 mg subcutaneously daily, and, one placebo arm randomised in a even ratio. The liraglutide dose may be reduced to 1.2 mg, if 1.8 mg is not tolerated. Subjects will continue their pre-trial insulin treatment.

The randomisation will be stratified according to the non-fasting C-peptide value at screening. The stratification factor has two levels according to C-peptide value: ≥0.2 nmol/l to ≤0.6 nmol/l and >0.6 nmol/l.

The exposure period for NNC0114-0006 and liraglutide in combination or alone is 54 weeks followed by a 26 weeks observation period. All groups will receive insulin treatment according to a treat-to-target regimen throughout the entire trial.

Trial population:

304 adult subjects with newly diagnosed T1DM are required according to the sample size calculation. A maximum number of 314 subjects will be randomised.

Key inclusion criteria:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. T1DM (as diagnosed clinically*) ≤ 12 weeks prior to randomisation
3. Male or female, aged 18-45 (both inclusive) at the time of signing the informed consent form
4. Non-fasting C-peptide ≥0.2 nmol/l
5. BMI ≥18.5 kg/m^2
6. Presence of one or more islet specific auto antibodies (glutamic acid decarboxylase (GAD), islet antigen-2 (IA2) or zinc-transporter 8 (ZnT8)) at screening
7. Insulin dependence unless in temporary spontaneous remission (honeymoon period).

*The clinical diagnosis of T1DM is defined as by the following two paragraphs:

1. One or more of the following:

- HbA1c ≥ 6.5% or
- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or
- a 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test with a glucose load of 75 grams anhydrous glucose in water or
- classical symptoms of hyperglycaemia and a random plasma glucose ≥ 11.1 mmol/l (200 mg/dl)[1]
  In the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing.

2. In order to:

- ensure that the aetiology is autoimmune, the clinical diagnosis needs to be confirmed by the presence of islet-specific auto-antibodies
- exclude type 2 diabetes mellitus (T2DM) and latent autoimmune diabetes of adults (LADA) the subjects should be without severe insulin resistance (i.e. total daily insulin dose larger than 1 U/kg per day at screening).

Key exclusion criteria:

1. Daily insulin usage > 1 U/kg per day at screening or use of continuous subcutaneous insulin infusion (CSII)
2. History of recurrent (e.g. several times a year) of severe (e.g. pneumonia) or chronic infections or conditions predisposing to chronic infections (e.g., bronchiectasis and chronic osteomyelitis)

3. History of severe systemic fungal infection within the past 12 months prior to screening unless treated and resolved with appropriate documented therapy
4. Vaccination within 4 weeks before randomisation, Visit 3 (V3)
5. Receipt of any other concomitant medications or herbal products that can influence the immune system within 90 days prior to screening (V1)
6. History of pancreatitis (acute or chronic)
7. Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN2) or Medullary Thyroid Carcinoma (MTC)
8. Any past or current diagnosis of malignant neoplasms
9. Known impairment of the immune system, except for T1DM

Assessments:

The primary efficacy assessment is MMTT stimulated C-peptide concentration at week 54.

The secondary efficacy assessments are HbA_{1c}, and other glycaemic parameters (fasting plasma glucose, 4- and 7-point profiles) after 54 weeks of treatment and at week 80.

The key safety parameters include physical examination, adverse events, hypoglycaemia and hyperglycaemia episodes, blood pressure, pulse, electrocardiogram, biochemistry (including amylase and lipase), calcitonin, urine dipsticks, haematology and antibodies against NNC0114-0006 and liraglutide.

Trial product(s):

The following trial products will be provided:

- NNC0114-0006 C 100 mg/ml, in a 3.0 ml cartridge for i.v. infusion
- NNC0114-0006 C 0 mg/ml, in a 3.0 ml cartridge for i.v. infusion
- Liraglutide 6.0 mg/ml, in a 3 ml pre-filled injector for s.c. injection
- Liraglutide placebo, in a 3 ml pre-filled injector for s.c. injection

NNC0114-0006 C 100 mg/ml or NNC0114-0006 C 0 mg/ml will be administered i.v. according to instructions.

2 Flow chart

Visit 1 to 37 procedures

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	D-10	0	1D	3D	W1	W2	W2 + 1D	3	4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1		± 1	± 1		± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
SUBJECT RELATED INFO/ASSESSMENTS																																	
Informed consent	x																																
Genotyping consent, optional	x																																
Long term retention consent, optional	x																																
In/exclusion criteria	x	x	x																														
Randomisation			x																														
Randomisation criteria			x																														
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dosing day exclusion criteria[1]			x										x				x				x				x				x				
Abuse of alcohol	x																																
Abuse of drugs	x																																
Medical history	x																																
Concomitant illness	x																																
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																																

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	D-10	0	1D	3D	W1	W2	W2 + 1D	3	4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1		± 1	± 1		± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
Diagnosis of diabetes	x																															
Diabetes treatment history	x																															
Pregnancy test[2]	x																															
Smoking habits	x																															
Family history of diabetes	x																															
Diabetes complications	x																															
Blood sample for genotyping (optional)			x																													
EFFICACY																																
Glucose metabolism	x		x										x				x				x				x				x			
Meal test[3]		x															x								x							
Self-measured plasma glucose:																																
7-point profile prior to visit			x	x	x	x		x			x		x		x		x				x				x				x			
4-point profile prior to visit[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
PRO questionnaires			x																						x							
Biomarkers:																																
Differential methylated *INS* DNA			x										x				x								x							
Antibodies (autoantibodies)	x		x										x				x								x							
Immunology		x	x										x				x								x							
Vitamin D (1,25 dehydroxy-			x										x				x								x							

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	D-10	0	1D	3D	W1	W2	W2 + 1D	3	4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1		± 1	± 1		± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
calciferol																																	
Dose of insulin administrations		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Carbohydrate intake		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
SAFETY																																	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Hyperglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Technical complaints		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Body measurements[5]	x	x	x			x	x			x			x		x		x		x		x		x		x		x		x			
ECG	x[6]		x		x								x				x								x							
Eye examination			x[7]																													
Physical examination	x		x		x	x							x				x								x							
Vital signs	x		x		x	x	x			x			x		x		x				x				x				x			
Antibodies:																																	
Anti-NNC0114-0006 antibodies			x														x								x							
Anti-liraglutide antibodies			x														x								x							
IgE			x			x							x				x								x							
Biochemistry	x		x			x							x				x								x							
Coagulation parameters	x		x			x							x				x								x							
Haematology	x		x			x							x				x								x							

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	D-10	0	1D	3D	W1	W2	W2 + 1D	3	4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1		± 1	± 1		± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
Cytokines			x										x				x								x							
Urine dipsticks	x		x			x							x				x								x							
Hepatitis B	x									x					x				x				x				x					
Hepatitis C	x																															
Tuberculosis screening test (QuantiFERON)	x																															
Epstein–Barr virus	x									x					x				x				x				x					
CMV[8]	x									x					x				x				x				x					
HIV	x																															
Hormones	x																x								x							
Lipids			x														x								x							
OTHER ASSESSMENTS																																
PK sampling NNC0114-0006			x[9]	x	x	x	x			x			x		x		x				x				x				x			x
PK sampling Liraglutide[10]			x	x	x	x	x			x			x		x		x				x				x				x			x
TRIAL MATERIAL																																
IV/IWRS	x		x										x				x				x				x				x			x
Administration and dispensing of trial product NNC0114-0006/placebo			x										x				x				x				x				x			x
Dispensing of liraglutide/placebo[11]			x										x				x				x				x				x			x

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	D-10	0	1D	3D	W1	W2	W2 + 1D	3	4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1		± 1	± 1		± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
Drug accountability for IMP[12]			x										x				x				x				x				x			
REMINDERS																																
Handout ID cards	x																															
Handout direction for use[13]			x																													
Handout and instruct in e-diary		x																														
Investigator review of e-diary			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Handout and instruct in BG meter use		x																														
Attend fasting visit		x	x										x				x				x				x				x			
Blood sample for long term retention (optional)			x																						x							

1. Only for NNC0114-0006
2. For woman of childbearing potential only. Blood sample at V1. For all subsequent visits a urine stick must only be measured for females of childbearing potential if a menstrual period is missed or as required by law. Austria: Urine-stick pregnancy test will be performed at all visits to the clinic
3. The MMTT may be re-scheduled twice within 10 days
4. 4-point profile will be used for T-T-T
5. At V1 height and weight will be measured and BMI will be calculated via the eCRF. At the following visits only weight must be measured
6. A baseline ECG performed for any reason unrelated to the trial within 30 days prior to V1 is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime
7. A baseline fundoscopy/ fundus photography performed for any reason unrelated to the trial within 90 days prior to V3 is acceptable
8. Cytomegalovirus

9. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
10. PK sample at any time during the visit
11. Liraglutide/liraglutide placebo will be administered once daily
12. Investigational medicinal product
13. Injection of liraglutide will be trained at V3 and at following visits as needed.

Visit 38 to 90 procedures

Trial period	Treatment																				Follow-up								
Visit type: C: Clinic, P: Phone contact	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]		
Timing of visit (weeks (w), or days (D) if specified)	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80			
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7		
SUBJECT RELATED INFO/ASSESSMENTS																														
Withdrawal criteria	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Dosing day exclusion criteria[2]				x				x				x																		
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[3]																			x											
Diabetes complications																			x								x			
EFFICACY																														
Glucose metabolism				x				x				x							x		x		x		x		x			
Meal test[4]				x															x				x				x			
Self measured plasma glucose:																														
7-point profile prior to visit				x				x				x							x		x		x		x		x			
4-point profile prior to visit[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
PRO questionnaires																			x								x			
Biomarkers:																														
Differential methylated *INS* DNA				x															x				x				x			
Antibodies (autoantibodies)				x															x				x				x			
Immunology				x															x				x				x			
Vitamin D (1,25 dehydroxy-calciferol)				x															x				x				x			
Dose of insulin administrations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Carbohydrate intake	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Trial period	Treatment																Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit **(weeks (w), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7
SAFETY																												
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hyperglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x									
Body measurements		x		x		x		x		x		x			x		x		x		x		x		x	x	x
ECG				x								x							x				x			x	x
Eye examination[6]																			x								x	
Physical examination				x								x							x				x			x	x
Vital signs				x				x				x							x		x		x		x	x	x
Antibodies:																												
Anti-NNC0114-0006 antibodies				x															x							x	x
Anti-liraglutide antibodies				x															x		x					x	x
IgE				x								x							x		x		x			x	x
Biochemistry				x								x							x				x			x	x
Coagulation parameters				x								x							x				x			x	x
Haematology				x								x							x				x			x	x
Cytokines				x								x							x				x			x	x
Urine dipsticks				x								x							x				x			x	x
Hepatitis B		x				x				x									x								
EBV		x				x				x									x								
CMV		x				x				x									x								

Trial period	Treatment																				Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit **(weeks (w), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7
Hormones				x								x							x				x				x	x
Lipids				x								x							x				x				x	x
OTHER ASSESSMENTS																												
PK sampling NNC0114-0006				x				x				x[7]	x	x	x		x		x		x		x		x		x	x
PK sampling Liraglutide				x				x				x	x	x	x		x		x									
TRIAL MATERIAL																												
IV/IWRS				x				x				x							x								x	
Administration and dispensing of trial product NNC0114-0006/placebo				x				x				x																
Dispensing of liraglutide/placebo				x				x				x																
Drug accountability for IMP				x				x				x							x									
REMINDERS																												
Investigator review of e-diary	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Attend fasting visit				x				x				x							x		x		x		x		x	x
Blood sampling for long term retention (optional)																			x								x	
End of dosing												x[8]							x[9]									
Collection of e-diary																											x	x
Collection of BG meter																											x	x
End of trial																											x	x
Sign off Casebook																											x	x

1. Safety follow-up visit. To be conducted for subjects who have been withdrawn less than 14 weeks after last dose of NNC0114-0006/placebo. The visit should be conducted 15 weeks ± 1 week after last dose of NNC0114-0006/placebo
2. Only for NNC0014-0006
3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. **Austria:** Urine-stick pregnancy test will be performed at all visits to the clinic
4. The MMTT may be re-scheduled twice within 10 days
5. 4-point profile will be used for T-T-T
6. A fundoscopy/ fundus photography may be performed up to 2 weeks before or after V63 and up to 2 weeks before V89
7. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
8. Last dosing of NNC0114-0006/placebo
9. Last dosing of liraglutide/liraglutide placebo is the day prior to V63

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [2] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki [3].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a disorder that arises following the selective autoimmune destruction of the insulin-producing beta-cells [4]. A cure for T1DM would aim at ensuring that the necessary endogenous functional beta-cell mass required for adequate insulin production is preserved or increased. As the beta-cell destruction is immune-mediated in most cases, many efforts to stop or modify this destruction have focused on immunomodulatory, antigen-specific or anti-inflammatory interventions. Genetically susceptible individuals can, following a putative environmental trigger, seroconvert and develop islet autoantibodies before the clinical diagnosis of T1DM. It is assumed, but never formally proven, that the beta-cell mass continuously decreases in an otherwise silent fashion before diagnosis. In single autoantibody-positive individuals there is no evidence of histopathological abnormalities (insulitis); only individuals with multiple autoantibodies have been shown to correspond with on-going insulitis and the multiple autoantibodies are a strong indicators of future progression toward clinical T1DM [4]. At clinical diagnosis, most patients still harbour functional beta-cell mass as evidenced by their C-peptide level [4]. It is hypothesised that a relatively modest recovery and/or preservation of beta-cell mass could re-establish a pre-diagnosis ‘silent’ state.

NNC0114-0006

Interleukin-21(IL-21) is a multifunctional cytokine that plays a role in activation and differentiation of the immune system cells such as T-cells, B-cells, natural killer (NK) cells and some cell types of the myeloid lineage (macrophages and dendritic cells) [5,6]. IL-21 is a secreted autocrine factor from T helper 17 (T_{H17}) cells [5-7] and follicular T_H cells [8], with function on both induction and persistence of these cells. Furthermore, IL-21 inhibits the generation of the regulatory T-cells (T_{reg}). IL-21 is also essential for optimal B-cell proliferation, differentiation and antibody production [9].

The anti-IL-21 monoclonal antibody (mAb), NNC0114-0006 is a recombinant human mAb of the immunoglobulin G1 (IgG_1) isotype with five amino acid substitutions to eliminate or reduce Fc-effector functions, including activation of the classic complement pathway. NNC0114-0008 is the murine equivalent of NNC0114-0006. NNC0114-0006 binds to IL-21 with high affinity (disassociation constant, Kd = 0.19 pM), and neutralises IL-21 in cell-based assays with a half-maximal inhibitory concentration (IC50) in the sub- or low nM range. NNC0114-0006 is not

expected to be engaged in antibody-dependent cellular cytotoxicity as it is not designed to target the cell membrane, but will bind soluble IL-21. It is hypothesised that inhibition of IL-21 in chronic inflammation is beneficial by restoring the balance between effector T-cells and T_{reg} cells and also by inhibiting pathologic antibody production [5,6].

By binding to and neutralising IL-21, NNC0114-0006 is intended to reduce the inflammation mediated by IL-21. The multiple pathways affected by IL-21 suggest that NNC0114-0006 may have the potential to alter a wide range of chronic inflammatory conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn's disease and T1DM. NNC0114-0006 has been administered in clinical trials to healthy subjects, subjects with RA, SLE or Crohn's disease and no safety concerns have been raised. Statistically significant and clinically relevant improvements in Disease Activity Score (DAS) 28 (CRP) have been observed in patients with RA in the Clinical Proof of Principle (CPoP) trial (NN8828-3842), in which two intravenous (i.v.) doses of NNC0114-0006 (12 mg/kg) were given 6 weeks apart.

In accordance with the ICH M3 guideline76, reproductive and developmental studies have not been performed at this stage of development because developmental toxicity studies for mAbs can be performed in parallel with the conduct of phase 3 clinical trials. Full histopathological examination of both male and female reproductive organs was included in the 8 week, the 13 week and the 39-week repeat-dose toxicity studies in cynomolgus monkeys. No treatment related effects were observed. Sexually mature animals were included the 39 week toxicity study.

Please refer to the current version of the NN9828 Investigator's Brochure (IB), edition 1, 2015, and any updates hereof for further information about non-clinical data.

Liraglutide

Liraglutide is an analogue of the naturally occurring human hormone Glucagon-Like Peptide-1 (GLP-1), and is suitable for once daily administration. GLP-1 is an incretin hormone secreted from the L-cells in the small intestine. An incretin hormone is a gut-derived peptide with important physiological function in augmenting post-prandial insulin secretion in response to ingestion of a meal. GLP-1 has a glucose dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose (PG) levels are above normal) [10]. Liraglutide is the active ingredient used in the authorised product Victoza® pen-injector approved in more than 70 countries including EU, US, Canada, Japan and China for the treatment of T2DM in adults to achieve glycaemic control, in combination with metformin and/or metformin and sulphonylurea or a thiazolidinedione or insulin. Using the liraglutide pen-injector, the start dose is 0.6 mg and the dose is increased in 0.6 mg increments to a maximum of 1.8 mg. In brief, in healthy subjects and patients with T2DM the most prominent treatment effects of Victoza® are:

a) glucose-dependent insulin synthesis and secretion
b) decreased glucagon secretion in a glucose-dependent manner,

c) delay in gastric emptying,
d) decreased appetite and food intake.

Also, liraglutide does not seem to have an independent impact on renal clearance as assessed by eGFR in a clinical phase 3 setting [11].

In T1DM, the effect on glucose-dependent insulin synthesis and secretion may be limited by the pathophysiological nature of T1DM.

Please refer to the current version of the NN9211 IB, edition 3, 07 August 2013, and any updates hereof for further information about non-clinical data.

For an assessment of benefits and risks of the trial, see section 18.1.

3.2 Rationale for the trial

T1DM is caused by a chronic autoimmune response against the pancreatic beta-cells, which results in life-long exogenous insulin dependence. The precise aetiology of T1DM is currently unknown. Genetically susceptible individuals can, following a putative environmental trigger, seroconvert and develop islet autoantibodies. It is assumed, but has never been formally proven in man, that beta-cell mass continuously decreases in an otherwise silent fashion before diagnosis. At clinical diagnosis, most patients still harbour a functional beta-cell mass as evidenced by their C-peptide levels and histology data from organ donors. It is hypothesized that a relatively modest recovery of beta-cell mass could re-establish a pre-diabetic state. Moreover, the Diabetes Control and Complications Trial firmly established that preservation of small amounts of endogenous insulin secretory capacity confers protection against long-term diabetic complications [12].

Targeting the autoimmune component of the disease in order to protect the beta-cells and preserve endogenous insulin secretion is a viable approach, provided that this can be done with an acceptable benefit/risk profile. Indeed, successful reversal to insulin independence has been achieved with potent immuno-suppressants such as cyclosporine or non-myeloablative stem cell therapy [13,14]. Unfortunately, these treatments have considerable systemic side effects and therefore cannot be applied as a generalized intervention [15,16]. Furthermore, the disease has a tendency to recur after treatment discontinuation. The latter is due to the accumulation of beta-cell antigen-specific memory T-cells, which can expand and react more efficiently, as soon as beta-cells are being augmented or re-introduced. Inhibition of IL-21 with NNC0114-0006 in T1DM may be beneficial by restoring the balance between effector T-cells and T_{reg} cells.

Current literature on exendin-4, a GLP-1 receptor agonist, suggest that combination with an immunomodulatory therapy may be a viable approach for preserving beta-cell function in T1DM since the combination of the two treatments appear to result in additive or synergistic effects [17-19]. To this end, Novo Nordisk has conducted nonclinical studies to investigate the effect of NNC0114-

0008 and liraglutide in late pre-diabetic and established diabetes and acute diabetes mouse models. Nonclinical data from the (non-obese-diabetic) NOD mouse model and the Rat-Insulin-Promoter-Lymphocytic-Choriomeningitis-Glyco-Protein (RIP-LCMV-GP) mouse model for T1DM showed that when liraglutide was administrated as monotherapy, a significant but temporary decline in blood glucose (BG) levels was observed. After combined treatment with NNC0114 0006 and liraglutide, BG values were lowered and many treated mice remained normoglycemic when treatment with liraglutide was stopped, suggesting expansion or recovery of functional beta-cell mass. In summary, literature evidence and in-house in vivo studies provide a rationale for targeting both IL 21 and GLP 1 receptors through the combined use of NNC0114-0006 and liraglutide to preserve beta cell function in patients with T1DM.

4 Objectives and endpoints

4.1 Objectives

Primary objective

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)

Secondary objectives

- Objectives related to treatment period (from baseline to week 54):
    - To assess safety and tolerability of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess effect on glycaemic parameters (including insulin usage and insulin regimen) of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess pharmacokinetic (PK) properties of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To explore biomarkers relevant for the effect of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess disease burden and health status in subjects with newly diagnosed T1DM treated with NNC0114-0006 and liraglutide in combination and alone
- Objectives related to the post-treatment observation period (from week 54 to week 80):
    - To assess post-treatment safety and tolerability of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess post-treatment effect on preservation of beta-cell function of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM
    - To assess post-treatment effect on glycaemic parameters (including insulin usage and insulin regimen) of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM

- To explore biomarkers relevant for the post-treatment effect of NNC0114-0006 and liraglutide in combination and alone in subjects with newly diagnosed T1DM

- To assess post-treatment development of disease burden and health status in subjects with newly diagnosed T1DM treated with NNC0114-0006 and liraglutide in combination and alone

4.2 Endpoints

4.2.1 Primary endpoint

The primary endpoint is $AUC_{0\text{-}4h}$ for a mixed meal tolerance test (MMTT) stimulated C-peptide concentration-time curve at week 54 relative to baseline (defined as the MMTT performed at Visit 2).

- $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$

4.2.2 Supportive secondary endpoints

4.2.2.1 Supportive secondary efficacy endpoints

- $AUC_{0\text{-}4h}$ for MMTT stimulated C-peptide concentration time curve at week 80 relative to baseline*
- $AUC_{0\text{-}2h}$ for MMTT stimulated C-peptide concentration time curve at week 54 and week 80 relative to baseline*
- Maximum MMTT stimulated C-peptide concentration ($C_{max,\ C\text{-}peptide}$) at week 54 and week 80 relative to baseline*
- $AUC_{0\text{-}4h}$ for MMTT stimulated plasma glucose concentration time curve at week 54 and week 80 relative to baseline
- $AUC_{0\text{-}2h}$ for MMTT stimulated plasma glucose concentration time curve at week 54 and week 80 relative to baseline
- Maximum MMTT stimulated plasma glucose concentration ($C_{max,\ glucose}$) week 54 and week 80 relative to baseline
- Total daily insulin dose in units per kg (three day average) at week 54 and week 80*
- Number of insulin injections per day (three day average) at week 54 and week 80
- Change in HbA_{1c} from baseline to week 54 and week 80*
- Change in fasting plasma glucose from baseline to week 54 and week 80*
- Change in fasting C-peptide from baseline to week 54 and week 80*
- Change in fasting glucagon from baseline to week 54 and week 80
- 7-point self-measured plasma glucose (SMPG) profiles. The following endpoints will be derived:
    - 7-point profiles at week 54 and week 80

- Change in postprandial glucose (PPG)/prandial increment (breakfast, lunch, dinner and average over the three meals) from baseline to week 54 and week 80
- Change in mean of 7-point profiles from baseline to week 54 and week 80

- Before breakfast SMPG at week 54 and week 80
- Change in patient reported outcome (PRO) scores (SF36, Experience of Treatment Benefits and Barriers, Diabetes Treatment Satisfaction Questionnaire (DTSQ)) from baseline to week 54 and week 80

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

4.2.2.2 Supportive secondary safety endpoints

- Number of treatment emergent adverse events reported
  - from first dose of trial product to week 54
  - from week 54 to week 80
- Number of treatment emergent hyperglycaemic episodes
  - from first dose of trial product to week 54
  - from week 54 to week 80
- Number of treatment emergent episodes of diabetic ketoacidosis (DKA)
  - from first dose of trial product to week 54*
  - from week 54 to week 80
- Number of subjects experiencing treatment emergent injection/infusion site reactions from first dose of trial product and during treatment period (54 weeks) caused by:
  - NNC0114-0006/liraglutide/placebo injection/infusion
- 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*
  - from week 54 to week 80
- Change in body weight from baseline to week 54 and week 80
- Diabetes complications (retinopathy and estimated glomeruli filtration rate) from baseline to week 54 and week 80
- Change in laboratory safety variables (haematology, biochemistry, coagulation, lipids, IgE, urine dipsticks, cytokine panel, and hormones), vital signs, electrocardiograms (ECGs), eye-examination and outcome of physical examination from baseline to week 54 and week 80
- Change in anti-NNC0114-0006 antibodies from baseline to week 54 and week 80
- Change in anti-liraglutide antibodies from baseline to week 54 and week 80

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

4.2.2.3 Supportive secondary biomarker endpoints

- Change in biomarker parameters from baseline to week 54 and week 80
  - T-cell profiling including islet-specific auto reactive CD8+ T-cells
  - IL-21
  - islets autoantibodies against glutamic acid decarboxylase (GAD), zinc-transporter 8 (ZnT8), islet antigen-2 (IA2), insulin autoantibody (IAA), isotypes of IAA and GAD
- Change in differential methylated INS DNA in plasma from baseline to week 54 and week 80
- Change in serum vitamin D (1,25 dehydroxy-calciferol) from baseline to week 54 and week 80

Differential methylated INS DNA and IL-21 will be analysed only if a functioning assay will be available in due time allowing to incorporate the analyses results in the database prior to database lock.

4.2.2.4 Supportive secondary pharmacokinetic endpoints

NNC0114-0006:

- $AUC_{\tau, NNC0114-0006}$, area under the NNC0114-0006 time-concentration curve over a dosing interval at steady state (SS) (defined as after last dose)
- Terminal half-life ($t_{½}$) after last dose of NNC0114-0006
- $V_{ss, NNC0114-0006,}$ the apparent volume of distribution of NNC0114-0006 at steady-state
- $CL_{ss, NNC0114-0006}$, clearance of NNC0114-0006 at steady state
- $MRT_{, NNC0114-0006,}$ the mean residence time of NNC0114-0006
- $R_{A,AUC, NNC0114-0006}$, accumulation ratio of NNC114-0006 defined as $AUC_{48\text{-}54\ weeks}/AUC_{0\text{-}6\ weeks}$
- $C_{trough, NNC0114-0006}$, observed NNC0114-0006 concentration prior to dosing of NNC0114-0006 at steady state
- $C_{1h, NNC0114-0006}$, observed NNC0114-0006 concentration 1 hour after dosing of NNC0114-0006 at steady state

The following pharmacokinetic endpoints for liraglutide will be derived after the last dose administered at week 54:

- $C_{liraglutide}$, liraglutide concentration at steady state

5 Trial design

5.1 Type of trial

The trial is a randomised, multi-centre, multinational, placebo-controlled, double-dummy, double-blind, efficacy, safety and PK CPOP trial in subjects with newly diagnosed T1DM with residual beta-cell function. The trial includes four parallel treatment groups, one with NNC0114-0006 12 mg/kg i.v. every 6 week and liraglutide 1.8 mg s.c. daily, one with NNC0114-0006 12 mg/kg i.v. every 6 week, one with liraglutide 1.8 mg subcutaneously (s.c.) daily and, one placebo arm randomised in a even ratio. The randomisation will take place not more than 4 weeks from start of screening (V1). The exposure period for NNC0114-0006 and liraglutide in combination or alone is 54 weeks. The primary endpoint (C-peptide) is at week 54 as defined per U.S. FDA and EMA requirements [20,21] followed by a 26 weeks observation period. All groups will receive insulin treatment according to a treat-to-target (T-T-T) regimen throughout the entire trial. See Figure 5–1 for the schematic trial design.

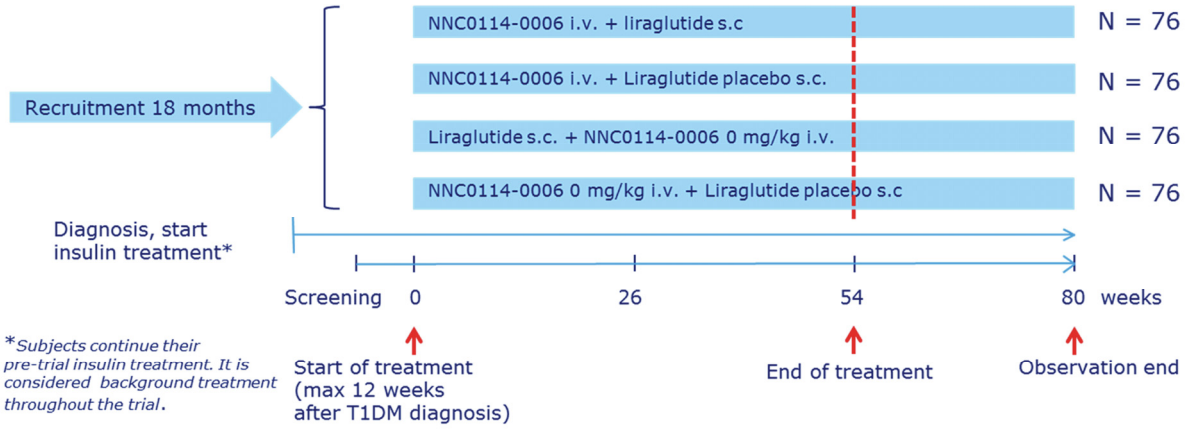


Figure 5–1 Trial design

5.2 Rationale for trial design

The rationale for the trial design, is to investigate the effect of NNC0114-0006 and liraglutide in combination on preservation of beta-cell function compared to placebo at week 54 in adult subjects with newly diagnosed T1DM with residual beta-cell function. In addition to the effect of the combination of NNC0114-0006 and liraglutide on preservation of beta-cell function, the trial will also generate data of treatment with either NNC0114-0006 or liraglutide compared to placebo on preservation of beta-cell function. The duration of the trial with 54 weeks of exposure of NNC0114-0006 and/or liraglutide has been chosen to align with the regulatory requirements from FDA and EMA. The length of the observation period of 26 weeks is chosen to give guidance for the further development program for the combination therapy of NNC0114-0006 and liraglutide. The FDA and

EMA guidelines advice that studies of products aimed at preservation of beta-cell function in recent-onset T1DM with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as stimulated C-peptide levels. Therefore the MMTT stimulated AUC_{0-4h} C-peptide concentration has been chosen as the primary efficacy parameter.

The randomisation will be stratified according to non-fasting C-peptide level. The stratification factor has two levels according to C-peptide value: ≥0.2 nmol/l to ≤0.6 nmol/l and >0.6 nmol/l. There is no cap on the size of the strata. The effects of NNC0114-0006 on preservation of beta-cell function may depend on the level of the residual beta-cell function. The fasting C-peptide level is a marker of the residual beta-cell function and by stratifying for non-fasting C-peptide, the treatment arms are balanced with regards to the residual beta-cell function.

Clinical meaningful endpoints have been included such as number of treatment emergent hypoglycaemic episodes, insulin injections per day, and change in HbA_{1c}. Furthermore, other secondary end-points e.g. total insulin usage and fasting values of glucose, insulin, glucagon and C-peptide have been included to describe effect of treatments on the glucose metabolism and insulin usage.

A multi-centre and multinational design has been chosen to ensure that the results are applicable for subjects with different demographic characteristics.

5.3 Treatment of subjects

The subjects in the trial will be randomised in a blinded manner to receive one of the following treatment arms:

Table 5–1 Treatment arms

Treatment arms	Treatment start (V3)	1st dose escalation (V7) liraglutide	2nd dose escalation (V10) liraglutide
1	NNC0114-0006 12 mg/kg[1] i.v. + liraglutide 0.6 mg s.c.	NNC0114-0006 12 mg/kg i.v. + liraglutide 1.2 mg s.c.	NNC0114-0006 12 mg/kg i.v. + liraglutide 1.8 mg[2] s.c.
2	NNC0114-0006 12 mg/kg i.v. + liraglutide placebo s.c.	NNC0114-0006 12 mg/kg i.v. + liraglutide placebo s.c.	NNC0114-0006 12 mg/kg i.v. + liraglutide placebo s.c.
3	Liraglutide 0.6 mg s.c. + NNC0114-0006 C 0 mg/ml i.v.	Liraglutide 1.2 mg s.c. + NNC0114-0006 C 0 mg/ml i.v.	Liraglutide 1.8 mg s.c. + NNC0114-0006 C 0 mg/ml i.v.
4	NNC0114-0006 C 0 mg/ml i.v. + liraglutide placebo s.c.	NNC0114-0006 C 0 mg/ml i.v.+ liraglutide placebo s.c.	NNC0114-0006 C 0 mg/ml i.v. + liraglutide placebo s.c.

1. The dose is fixed so the dose is both the maximum and the minimum dose.
2. The maximum dose after dose escalation is 1.8 mg however if this is not tolerated it is allowed to reduce the dose to 1.2 mg. This is the lowest accepted dose.

5.3.1 NNC0114-0006

NNC0114-0006 C 100 mg/ml and NNC0114-0006 C 0 mg/ml will be administered as an i.v. infusion every 6 weeks (first administration Week 0 and last administration Week 48) at the trial sites. The i.v. infusion of NNC0114-0006 C 100 mg/ml or NNC0114-0006 C 0 mg/ml will be administered according to instructions as detailed in the Trial Materials Manual (TMM). Subjects will remain at the clinical trial site for at least 2 hours after completion of NNC0114-0006 C 100 mg/ml or NNC0114-0006 C 0 mg/ml administration to be observed for AEs. On days with MMTT the administration of NNC0114-0006/placebo, may be done during the MMTT.

Dosing day exclusion criteria

The infusion of NNC0114-0006 must be postponed if there are symptoms or signs of infection, which in the opinion of the investigator are clinically significant (e.g. fever, pneumonia or tonsillitis or unspecific viral infection).

If NNC0114-0006 cannot be given within 2 weeks after the scheduled visit this should be recorded as a missed dosing in the electronic case report form (eCRF). The next NNC0114-0006 dose will be given as planned.

5.3.2 Liraglutide

Liraglutide and liraglutide placebo will be self-administered s.c. either in the abdomen, thigh or upper arm daily with a pen-injector around the same time of the day, when the most convenient time of the day has been chosen. The last dose of liraglutide will be administered at the day prior to the Visit 63 (week 54).

Liraglutide and insulin should not be injected in close physical proximity.

Initiation and escalation of liraglutide/liraglutide placebo

All subjects will initiate 0.6 mg liraglutide or 0.1 ml liraglutide placebo[1] treatment on the day of randomisation. As the target dose is 1.8 mg liraglutide or 0.3 ml liraglutide placebo, the dose will be escalated in increments of 0.6 mg liraglutide or 0.1 ml liraglutide placebo every 2 weeks until 1.8 mg liraglutide or 0.3 ml liraglutide placebo has been reached. In case of in-tolerable liraglutide side effects related to the dose escalation, it is acceptable to reduce the dose to the previous dose level for up to an additional 2 weeks. If 1.8 mg liraglutide or 0.3 ml liraglutide placebo is not tolerated due to side effects, the dose can be reduced to 1.2 mg liraglutide or 0.2 ml liraglutide placebo, which is considered to be the lowest acceptable dose. If 1.2 or 0.2 ml liraglutide placebo is not tolerated, the subject must be withdrawn (see Section 6.5).

[1] The pen-injector has a dose scale of 0.6, 1.2 and 1.8 mg which will equal 0.1,0.2 and 0.3 ml liraglutide placebo on the dose scale.

Missed doses of liraglutide/liraglutide placebo before target dose is reached

If any dose is missed by the subject ≤ 3 consecutive days before reaching the target dose of 1.8 mg or 0.3 ml placebo (1.2 mg or 0.2 ml placebo, if higher dose is not tolerated), it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. After having missed liraglutide doses for ≤ 3 days the subject must be re-initiated on the dose the subject was taking prior to the missed doses. The dose escalation should be performed as originally planned.

If any dose is missed by the subject > 3 consecutive days at any time point it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. The subject must be re-initiated on 0.6 mg liraglutide/placebo and dose escalation should be every 2 weeks.

Missed doses of liraglutide/liraglutide placebo after target dose is reached

After reaching the target dose of 1.8 mg or 0.3 ml placebo (1.2 mg or 0.2 ml placebo, if higher dose is not tolerated), dose and dose frequency should not be changed at any time during the treatment period.

If any dose is missed by the subject ≤ 3 consecutive days it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. After having missed liraglutide doses ≤ 3 days the subject must be re-initiated on the target dose.

If any dose is missed by the subject > 3 consecutive days at any time point it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. The subject must be re-initiated on 0.6 mg liraglutide/placebo and dose escalation should be every 2 weeks.

5.3.3 Insulin treatment

Subject will continue on their current insulin treatment after they have been randomised. Subjects will be trained in diabetes self-care including carbohydrate counting before and at randomisation and whenever needed during the course of the study in order to achieve the most optimal diabetes control.

During the trial subjects will receive insulin treatment in order to achieve metabolic control according to the insulin titration guideline (Appendix A). This insulin treatment will be handled by the local trial sites in collaboration with Novo Nordisk's Insulin Titration Group. It is acceptable to pause or stop insulin treatment if the investigator assesses that the subject is in remission.

Glucagon can be used as rescue medication for the treatment of severe hypoglycaemia. The investigator or designee will ensure training has been conducted.

Insulin reduction on the day of liraglutide/ liraglutide placebo initiation and escalation

As it is a blinded trial, when liraglutide/ liraglutide placebo is initiated, the total daily pre-randomisation insulin dose should be reduced by 25 % for a minimum of 24 hours after the initiation of liraglutide/ liraglutide placebo. The reduction in the total daily insulin dose may come from reduction in basal and/or bolus insulin dose. The advice is to maintain the ratio between basal and bolus insulin when reducing insulin on the day of liraglutide/ liraglutide placebo initiation and escalation. A change of the ratio should be based on reaching the pre-meal SMPG targets. The pre-randomisation dose is the average of the previous three consecutive day's insulin dose. Thereafter the insulin dose should be adjusted according to the glucose target in Table 5–2.

When escalating to 1.2 mg and 1.8 mg liraglutide/ liraglutide placebo, the total daily insulin doses should be reduced by 10 % for a minimum of 24 hours after the escalation of liraglutide/ liraglutide placebo dose. The total daily dose is the average of the previous three consecutive days' insulin dose. The reduction in the total daily insulin dose may come from reduction in basal and/or bolus insulin dose. Thereafter, the insulin dose should be adjusted according to the glucose target in Table 5–2.

Table 5–2 Pre-meal SMPGs

Pre-breakfast/pre-meal SMPG	
mmol/L	mg/dl
4.0-6.0	71-108

5.3.4 Prohibited medication

The following medications must not be used during the treatment period (week 0-54):

1. Systemically corticosteroids, monoamine oxidase (MAO) inhibitors, systemic non-selective beta-blockers and growth hormone

2. Medications or herbal products that can influence the glucose homeostasis (except for insulin) and/or the immune system. It is up to the investigator to judge which herbal products influence on the glucose homeostasis

3. Treatment with any medication for the indication of diabetes or obesity other than insulin and trial medication.

The following medications must not be used during the trial period (week 0-80):

1. Live vaccines

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the subject will continue their usual insulin treatment at the discretion of the investigator.

5.5 Rationale for treatment

The concept of combining immunotherapy with another agent was recently tested in the NOD recent onset diabetes model using a combination regimen of anti-IL-21 (NNC0114-0008) and liraglutide. These experiments used a two-week course of 5 injections at 25 mg/kg of NNC0114-0008 combined with daily liraglutide administration. In the spontaneous NOD mouse model, the first experiment resulted in potent remission from hyperglycaemia in established T1DM, with statistically better efficacy as compared to each respective monotherapy. In a repeat study, however, the efficacy of NNC0114-0008 monotherapy was equivalent to the combination therapy, and an additive effect could not be demonstrated. Finally, in the induced RIP-LCMV-GP mouse model the combination treatment outperformed both monotherapies. All together the animal data suggest that a combination regimen of NNC0114-0006 and liraglutide may preserve beta-cell function synergistically in T1DM patients. The non-clinical data from the NOD mice and RIP-LCMV-GP model suggest that more than two doses of NNC0114-0006 need to be administered to get a clinical significant effect.

The intravenous route for administration of NNC0114-0006 has been chosen to ensure the beta-cells are adequately exposed to NNC0114-0006. The dosage of 12 mg/kg i.v. every 6 weeks (2 doses in total) has in the NN8828-3842 trial in patients with RA shown efficacy and an acceptable safety profile. The efficacy was only established on the primary endpoint. The trial will generate data for beta-cell function every 12 weeks, which will allow to evaluate when an effect will start. Measurement of the effect by doing a MMTT has been chosen to comply with FDA [20] and EMA [21] guidelines, where primary endpoint should be measured after one year. The length of the observation period of 26 weeks is chosen to give guidance for the further development program for the combination therapy of NNC0114-0006 and liraglutide.

Liraglutide is the active ingredient used in the authorised product Victoza® for the treatment of T2DM. Liraglutide is given subcutaneously once daily at a starting dose of 0.6 mg daily, and the therapeutic dose is 1.2 mg or 1.8 mg. 1.8 mg liraglutide is the maximal approved dose, and therefore this dose has been chosen as the preferred one.

Due to the nature of the development of T1DM and the progressive decline in beta-cell function and non-fasting C-peptide over time, only a randomised parallel-group design will make comparison to the natural course of the disease development (placebo) possible during the administration period.

There is currently no approved comparator available for beta-cell function preservation after onset of T1DM. Thus placebo is the relevant comparator.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened: 600

Number of subjects planned to be randomised: 304

Maximum number of subjects to be randomised: 314

Number of subjects expected to complete the trial (defined as reaching primary endpoint): 240

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes".

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Type 1 diabetes mellitus (as diagnosed clinically*) ≤ 12 weeks prior to randomisation
3. Male or female, aged 18-45 years (both inclusive) at the time of signing informed consent
4. Non-fasting C-peptide ≥0.2 nmol/l
5. BMI ≥18.5 kg/m^2
6. Presence of one or more islet specific auto antibodies (glutamic acid decarboxylase (GAD), islet antigen-2 (IA2) or zinc-transporter 8 (ZnT8)) at screening
7. Insulin dependence unless in temporary spontaneous remission (honeymoon period).

*See Section 6.8 for the clinical diagnosis.

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial products or related products
2. Previous participation in this trial. Participation is defined as signed the informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential not using adequate contraceptive methods (adequate contraceptive measures, as required by local regulations or practice)
   For Ireland: Adequate contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, IUD or intrauterine system or consistent use of barrier methods together with the use of spermicide and sexual abstinence.
   For Sweden: Adequate contraceptive measures are: oral (except low-dose gestagen

(lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives, intrauterine device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For United Kingdom: Adequate contraceptive measures are defined as established use of oral, injected or implanted hormonal methods of contraception, sterilisation, IUD or intrauterine system, or consistent use of barrier methods together with the use of spermicide, and sexual abstinence.

4. Male of reproductive age who or whose partner(s) is not using adequate contraceptive methods (adequate contraceptive measures, as required by local regulation or practice)
5. Participation in another interventional clinical trial within 5 half-life of the product(s) and if unknown then 3 months before randomisation (V3)
6. Severe diabetic ketoacidosis (defined as confirmed blood pH below 7.2) within 2 weeks prior to randomisation (V3)
7. Daily insulin usage > 1 U/kg per day at screening (V1) or use of continuous subcutaneous insulin infusion (CSII)
8. History of recurrent (e.g. several times a year) of severe (e.g. pneumonia) or chronic infections or conditions predisposing to chronic infections (e.g., bronchiectasis and chronic osteomyelitis)
9. History of severe systemic fungal infection within the past 12 months prior to screening (V1) unless treated and resolved with appropriate documented therapy
10. Vaccination within 4 weeks before randomisation (V3)
11. Requiring a vaccine during treatment or within 60 days after last dose of NNC0114-0006 with the exception of influenza vaccination according to local diabetes treatment requirements. The influenza vaccine can be given 3 weeks after a dose of NNC0114-0006 and 2 weeks before next dose of NNC0114-0006
12. Evidence of herpes zoster resolved less than 2 months prior to screening (V1)
13. History of disseminated or complicated herpes zoster
14. Evidence of or cytomegalovirus infection (CMV) resolved less than 2 months prior to screening (V1)
15. Serologic evidence of acute infection with CMV, defined as a positive CMV IgM
16. A positive QuantiFERON®-TB Gold test (test may be repeated if result is inconclusive) throughout the trial
17. A history of active tuberculosis (TB) within the last 3 years from screening even if treated effectively
18. History of active TB more than 3 years prior to screening if there is no documentation that the prior anti-TB treatment was appropriate in duration and type
19. Household contact with a person with active TB, unless appropriate isoniazid prophylaxis for TB was previously given
20. Positive serology for hepatitis B documented by any of the following:

- Positive test for hepatitis B surface antigen (HBsAg)
- Positive test for hepatitis B core antibody (HBcAb)

– Note: Hepatitis B surface antibody (HBsAb) positivity without HBcAb positivity indicates vaccination against hepatitis B and is not exclusionary with prior history of vaccination

21. Positive test results for hepatitis C virus (HCV) as documented by any of the following:
    - Anti-HCV antibody positivity (as assessed by an enzyme immunoassay)
    - Presence of HCV ribonucleic acid (RNA) in serum
22. Positive test for current Epstein-Barr virus (EBV) infection as documented by :
    - Presence of IgM EBV antibodies
23. Human immunodeficiency virus (HIV) 1 or 2 antibodies
24. Subjects presently classified as being in NYHA Class IV (New York Heart Association (NYHA))
25. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (Systolic≥160mmHg or diastolic ≥100 mmHg) in accordance with National High Blood Pressure Education Program, 7th Joint National Committee and ESH/ESC 2013 guidelines
26. Within the past 180 days prior to screening (V1) any of the following: Myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack
27. Renal impairment estimated glomerular filtration rate (eGFR) <60ml/min as per (Chronic Kidney Disease Epidemiology Collaboration) CKD-EPI [22]
28. History of pancreatitis (acute or chronic)
29. Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN2) or Medullary Thyroid Carcinoma (MTC)
30. Impaired liver function, defined as alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) ≥ 2.5 times upper limit of normal at screening (V1)
31. One or more screening (V1) laboratory values as stated:
    - Haemoglobin <6.2 mmol/l (10.0 g/dl)
    - Neutrophils $<2x10^9$/l
    - Leucocytes $<3.5x10^9$/l
    - Thrombocytes $<100x10^9$/l
    - Alkaline phosphatase (ALP) >2 times the UNL
    - Creatinine >2 times the UNL
    - Bilirubin >1.5 times the UNL
    - Calcitonin ≥ 50 ng/l
    - Any other laboratory abnormality that might, in the judgment of the investigator, place the subject at unacceptable risk for participation in this trial
32. Proliferative retinopathy or maculopathy requiring acute treatment as verified by dilated fundoscopy or fundus photography performed within 90 days prior to randomisation (V3)

33. Current treatment with any of the following: Systemically corticosteroids, MAO inhibitors, systemic non-selective beta-blockers or growth hormone
34. Receipt of any other concomitant medications or herbal products that can influence the immune system within 90 days prior to screening (V1)
35. Treatment with any medication for the indication of obesity in a period of 90 days before screening (V1)
36. Currently planned surgical procedures which may impair the subjects eligibility to participate
37. Currently planned coronary, carotid or peripheral artery revascularisation
38. Any past or current diagnosis of malignant neoplasms
39. Known impairment of the immune system, except for T1DM
40. Donation or loss of >400 ml of blood within 8 weeks prior to randomisation or longer, if required by local regulation
41. History of alcohol or drug abuse within the last 5 years or abuse that, in the investigator's opinion, might compromise the subject's compliance or safety while participating in the trial and/or ability to complete the trial.

All laboratory parameters listed in the in- and exclusion criteria will be analysed at a central laboratory.

6.4 Randomisation criteria

1. Absence of major bacterial infections within 4 weeks prior to randomisation (V3), (e.g., pneumonia and meningitis)
2. Absence of any symptoms or signs of an infection, which in the opinion of the investigator is clinically significant

To be randomised, all randomisation criteria must be answered "yes".

If one or more randomisation criteria are answered "no", the subject should be offered to have the randomisation visit re-scheduled not later than 12 weeks after the diagnosis of T1DM.

6.5 Temporary discontinuation of trial product

If the investigator suspects acute pancreatitis, trial products should be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. If tests reveal that a subject does not have acute pancreatitis, re-initiation of liraglutide should be managed according to Section 5.3.

Furthermore the subject can be temporarily discontinued of the NNC0114-0006 in case of an infection which is considered by the investigator to cause a safety concern.

Temporary discontinuation of treatment with investigational product will not lead to withdrawal from the trial. However if 2 consecutive NNC0114-0006 doses are missed the subject should be withdrawn from the trial.

6.6 Withdrawal criteria

The subject may withdraw at will at any time. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures. Furthermore Novo Nordisk may decide to stop the trial, part of the trial or a trial site at any time.

The subject must be withdrawn if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation criteria
2. Participation in another clinical trial throughout the trial
3. If 2 consecutive NNC0114-0006 doses are missed
4. Subjects switching to an insulin pump at any time point during trial participation
5. If, during the trial, the randomised liraglutide/ liraglutide placebo dose of 1.2 mg/day or corresponding placebo volume after dose escalation is not tolerated
6. Hypoglycaemia and/or hyperglycaemia with ketosis during the treatment period posing a safety concern, as judged by the investigator
7. Acute pancreatitis. Subjects that are diagnosed with acute pancreatitis during the trial (as a minimum 2 of the following diagnostic criteria)
    1. Severe acute upper abdominal pain,
    2. Amylase and/or lipase >3x UNL or
    3. Characteristic findings on ultrasound/computerised axial tomography (CT)/magnetic resonance imaging (MRI)
8. Initiation of any prohibited medication (see Section 5.3.4).
9. Calcitonin ≥ 50 ng/l before week 54
10. Pregnancy
11. Intention of becoming pregnant
12. Unintended weight loss before week 54 posing a safety issue as judged by the investigator
13. Acute EBV or CMV infection before week 54 confirmed by central laboratory
14. Hepatitis B infection before week 54 confirmed by central laboratory

If a subject is withdrawn from the trial please see Section 8.1.7 for which visits the subject should attend.

6.7 Subject replacement

Subjects who are withdrawn will not be replaced.

6.8 Rationale for trial population

T1DM is a disease affecting all age groups with the highest incidences seen in children and adolescent below 19 years of age [23]. A large proportion of the target population includes children and adolescents with newly diagnosed T1DM as well as young adults (below 30 years of age). Data from Sweden indicate that newly diagnosed patients with T1DM from18 years of age to 35 years of age and patients with LADA above 35 years of age are expected to outnumber patients with T1DM younger than 18 years of age at least by a factor of three in the future [24]. Since NNC0114-0006 has not previously been administered to subjects below the age of 18 years or in subjects with newly diagnosed T1DM and the FDA and EMA recommends testing in adults prior to testing in a pediatric population, the first clinical trial will include subjects with newly diagnosed T1DM from 18 to 45 years of age. The reason for excluding subjects >45 years is to minimize the risk of including subjects with LADA. The destruction of beta-cells in LADA subjects progresses more slowly than in other types of T1DM. The decline of beta-cell function occurs more rapid in young versus older newly diagnosed T1DM subjects. The high age limit has been chosen as a trade-off between being able to recruit subjects to the trial and the lower decline of beta-cell function with increasing age.

As stated above, the functional beta-cell mass continuously decreases in an otherwise silent fashion before clinical diagnosis of T1DM. However, most patients still have functional beta-cell mass as evidenced by their C-peptide level at diagnosis [25]. It is therefore hypothesized that a relatively modest recovery of beta-cell mass could re-establish a pre-diagnostic 'silent' state of T1DM. In order to ensure that patients with a residual beta-cell mass potentially can achieve a clinically meaningful improvement in glucose control, the peak or mean non-fasting C-peptide level needs to be above 0.2 nmol/l [26] within 12 weeks after onset of T1DM and that the subjects are metabolic stable (defined as no severe DKA, (confirmed pH below 7.2) within the last 2 weeks prior to screening).

The clinical diagnosis of T1DM is defined by the following two paragraphs:

1. One or more of the following:

- HbA1c ≥ 6.5% or
- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or
- a 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test with a glucose load of 75 grams anhydrous glucose in water or
- classical symptoms of hyperglycaemia and a random plasma glucose ≥ 11.1 mmol/l (200 mg/dl)[1]
  In the absence of unequivocal hyperglycamia, results should be confirmed by repeat testing.

2. In order to:

- ensure that the aetiology is autoimmune, the clinical diagnosis needs to be confirmed by the presence of islet-specific auto-antibodies
- exclude T2DM and LADA the subjects should be without severe insulin resistance (i.e. total daily insulin dose larger than 1 U/kg per day at screening).

7 Milestones

Planned duration of recruitment period (i.e. FPFV – LPFV): 18 month

End of trial is defined as LPLV.

For United Kingdom:

Planned date for LPLV: 27-Nov-2018

Recruitment:

Recruitment will be monitored on an ongoing basis by the sponsor. Prior to the initiation visit all trial sites should have a recruitments mitigation plan in place detailing how many subjects they can recruit within a certain period. If a trial site has not enrolled the number of subjects according to the recruitment mitigation plan, the remaining subjects may be reallocated.

The screening and randomisation rate will be followed closely via the interactive voice/web response system (IV/WRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment periods ends, after which no further subjects may be screened and the IV/WRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure [27], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE) [28], the Food and Drug Administration Amendment Act (FDAAA) [29], European Commission Requirements [30,31] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

Throughout the trial the investigator should ensure working in accordance with (ICH GCP) [2] and local regulations. The investigator must ensure that trial procedures are performed as described in the protocol. Any discrepancies will result in protocol and/or GCP deviations and the investigator must take appropriate action to avoid recurrence of the detected discrepancies.

The following sections describe the assessments and procedures that must be performed during this trial. The timing of the assessments and procedures are specified in the flow chart Section 2.

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from the IV/WRS.

In addition the investigator must keep a log of staff and delegations of task(s) at the site. The investigator must sign the log of staff and the delegation of task(s) at site at the time of delegation.

8.1.1 Informed consent

Before screening takes place, subjects must be provided with oral and written information about the trial and the procedures involved. Subjects will be fully informed, orally and in writing about their responsibilities and rights while participating in the trial, as well as about the possible advantages and disadvantages when participating in the trial. Subjects will have the opportunity to ask questions and have ample time to consider participation. The informed consent process may take place before the screening visit (Visit 1).

Subjects who wish to participate in the trial must sign and date the subject information/informed consent for the trial before any trial related procedures (see Section 18.2). All subjects must be provided with a copy of their own signed and dated informed consent form.

8.1.2 Screening

At screening (V1), subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

8.1.3 Screening failures

If any inclusion criteria are answered no or any exclusion criteria are answered yes, the subject is a screening failure.

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up of serious adverse events (SAEs) must be carried out according to Section 12.3. A screening failure session must be made in the IV/WRS. The case book must be signed after all queries are closed.

8.1.4 Re-screening/re-sampling

Re-sampling or re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria related to laboratory parameters.

However if the **tuberculosis screening test** at Visit 1 is inconclusive re-tests can be performed. The repeat test results must be available for evaluating the subject's eligibility before Visit 3.

8.1.5 Investigator's assessment

It is the responsibility of the investigator or delegated staff to review the e-diaries, PROs, ECGs, eye examinations (fundoscopy/ fundus photography), laboratory reports etc. This must be documented with the investigator or delegated staff's dated signature either on the front page of the documents and/or in the subject's medical records. The signed documents must be retained at the investigator site as source documentation.

8.1.6 Missed visits and unscheduled visits

If a visit is missed every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to the visit schedule.

If the investigator asks to subject to have a test described in the protocol re- done (e.g extra blood sample if some of the blood sample values are out of range) this should be recorded as an unscheduled visit and an unscheduled visit form must be completed.

If the subject attends the clinic and some of the tests have to be re-scheduled (e.g. in a non-fasting state at a fasting visit) the re-scheduled tests should NOT be recorded as an unscheduled visit. In this case blood samples will have a different date of collection than the rest of the assessments. Likewise re-scheduling of the MMTT and dosing of NNC0114-0006/placebo should not be recorded as an unscheduled visit. Temporary discontinuation of trial product

A temporary discontinuation is when the subject temporarily discontinues trial product after randomisation see Section 6.5

8.1.7 Withdrawn subjects

If a subject is withdrawn from the trial during the treatment period (week 0-54), the investigator must aim to undertake procedures similar to those for Visit 63 as soon as possible and perform the safety follow up visit (Visit 90) 15 ±1 weeks after last dose of NNC0114-0006. Subjects will be instructed to use appropriate pregnancy prevention until 15 weeks after last dose of NNC0114-0006. The end-of-trial form must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A withdrawal session must be made in the IV/WRS. The case book must be signed after all queries have been closed.

If a subject is withdrawn from the trial during the observation period (week 55-80), the investigator must aim to undertake procedures similar to those for Visit 89 as soon as possible and the safety follow up visit (Visit 90) 15 ±1 weeks after last dose of NNC0114-0006. Subjects withdrawn 14 weeks or more after last dose of NNC0114-0006 should not attend Visit 90. The end-of-trial form must be completed. A withdrawal session must be made in the IV/WRS. The case book must be signed after all queries have been closed.

Additional follow-up of subjects due to adverse events (AEs) or pregnancy is described in Section 12.3 and 12.5.

If subjects fails to return for these visits or is unable to do so, every effort should be made by the investigator to contact him/her by phone or by sending appropriate correspondence (i.e., certified letter) that will become part of the investigators' file to record that efforts were made to reach the subject.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the eCRF.

If new information becomes available which the safety committee at Novo Nordisk concludes would compromise the safety of the subjects, the trial will be permanently discontinued. In such cases, the subjects will still need follow-up visits as described above, i.e. at discontinuation and at 15 weeks ± 1 week after last dosage of NNC0114-0006 dosage for safety reasons.

8.1.8 Fasting visits

The subject should attend selected visits fasting (see Section 2).

Fasting is defined as no food or drink intake for at least 6 hours, except water. Trial products and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood sampling and body weight measurements have been performed.

If the subject is not fasting as required on days where fasting blood sampling should be drawn all blood samples (both fasting and non-fasting) must be re-scheduled within the visit window and the date for the fasting blood samples must be recorded in the eCRF. All other assessments can be performed even though the subject is not fasting. Re-scheduling of fasting blood samples is not considered as an unscheduled visit.

8.2 Subject related information

The timing of the assessments is specified in the flow chart Section 2.

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the screening visit (V1)) or found as a result of a screening procedure. The disease under investigation (T1DM) should not be entered as it is captured under diagnosis of diabetes.

Medical history is a medical event that the subject has experienced in the past. Only relevant medical history should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than the NNC0114-0006, liraglutide and insulin, which is taken during the trial, including the screening and follow-up periods. Information on insulin treatment is recorded in diabetes treatment history see Section 8.2.7 and in the e-diary see Section 8.6.3.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

For restrictions regarding concomitant medication, please refer to Section 5.3.

8.2.3 Smoking status

Details of smoking status must be recorded at the first visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

8.2.4 Abuse of alcohol and/or drugs

Subject will be asked if he/she has a history of alcohol and/or drug abuse or is currently abusing alcohol and/or drugs. In case of a history of alcohol and/or drug abuse, duration of abuse in years and the year of end of abuse should be recorded in the eCRF.

8.2.5 Demography

The following information has to be recorded:

- Date of birth, unless not permitted by local regulations
- Age
- Sex
- Race, unless not permitted by local regulations
- Ethnicity, unless not permitted by local regulations

8.2.6 Diagnosis of diabetes

The following information has to be recorded:

- Date of diagnosis of T1DM

8.2.7 Diabetes treatment history

The following information has to be recorded:

- Start date of current diabetes treatment
- Number of severe hypoglycaemic episodes since diagnosis

8.2.8 Family history of diabetes

The following information has to be recorded:

- Is there a family history of diabetes (Y/N)
- Indicate the relation to the subject
- Type of diabetes

8.2.9 Diabetes complications

The following information has to be recorded (Y/N):

- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Other

8.3 Assessments for efficacy

The timing of the assessments and procedures are specified in the flow chart Section 2.

8.3.1 Mixed meal tolerance test

The subject will have a MMTT performed at certain visits, as outlined in Section 2.

Instructions prior to MMTT visits

The subject should be instructed to:

- Follow normal routine on the days prior to the MMTT visit regarding eating however the subject should attend the MMTT visit fasting
- Follow normal exercise and refrain from hard exercise (comparable to and exceeding 5 km running or weightlifting) 24 hours prior to the MMTT
- Minimise physical activity in the morning of the MMTT to the extent possible
- Refrain from intake of alcohol and use of medications that affect motility (i.e. prokinetics, anticholinergic, tricyclic antidepressants) 24 hours prior to the MMTT
- Not to take their basal insulin after 22.00 the evening before the MMTT visit
- Subjects who normally take basal insulin in the morning should bring their basal insulin to the MMTT
- Not to take any bolus insulin later than 2 hours prior to the MMTT
- Remember to bring their bolus insulin to the MMTT visits (to be given after MMTT)
- Take liraglutide/liraglutide placebo at the same time as usual both the day before the MMTT visit and on the day of the MMTT
- Remember to bring their liraglutide/liraglutide placebo to the MMTT visits, if applicable
- Remember to bring their BG meter provided for this trial
- Remember the importance of having BG on target

Preparation and conduct of the MMTT

The MMTT will be initiated in the morning after fasting for at least 6 hours. The NNC0114-0006/placebo may be given during the MMTT.

Subjects will be instructed not to take basal insulin after 22.00 the evening before the MMTT. Receipt of insulin boluses is allowed until 2 hours prior to the MMTT.

The plasma glucose value measured at the site before the MMTT must be ≤9.0 mmol/l (162 mg/dl) in order to avoid hyperglycaemia during the MMTT. Therefore if the plasma glucose value measured at the site is > 9.0 mmol/l (162 mg/dl) the subject may receive bolus insulin and the MMTT can be performed after 2 hours if a plasma glucose value ≤ 9.0 mmol/l (162 mg/dl) is confirmed. The MMTT may also be re-scheduled within 1-10 days. Re-scheduling of the MMTT is not considered as an unscheduled visit. Two rescheduling's are allowed per MMTT visit. If this is not possible the MMTT must be reported as not done. All other assessments at the visit should be conducted as planned including dosing of NNC0114-0006/placebo.

If plasma glucose value measured at the site before the MMTT is ≤3.9 mmol/l (70 mg/dl), the MMTT will be rescheduled within 1-10 days. Re-scheduling of the MMTT is not considered as an unscheduled visit. Two rescheduling's are allowed per MMTT visit. If this is not possible the MMTT must be reported as not done. All other assessments at the visit should be conducted as planned including dosing of NNC0114-0006/placebo.

All plasma glucose values to be measured at site must be measured with a validated BG instrument. The BG meters handed out to the subjects should not be used for this purpose.

The subject's body weight must be measured before intake of the standardised liquid meal. The standardised liquid meal will be provided by Novo Nordisk. The subject must consume 6 ml/kg (maximum 360 ml) of the standardised liquid meal as quickly as possible and within 12 minutes. The investigator should confirm that the subject consumed the required amount in the eCRF.

Blood samples (11-point profile) will be collected 10 minutes prior to the meal (-10) at meal start (0), and at 15, 30, 60, 90, 120, 150, 180, 210 and 240 minutes after meal start. The blood samples will be assayed for C-peptide and plasma glucose. During the MMTT plasma glucose will be monitored on a validated plasma glucose instrument. If the glucose level exceeds 16.7 mmol/l (300 mg/dl) plasma ketones (betahydroxybutyrate) should be measured on a BG meter.

The subject is allowed to go to the toilet. The number of visits to the toilet should be limited. The subjects are allowed to drink water 2 hours after start of the MMTT. The amount of ingested water should be limited.

Precautions during the MMTT

In case the plasma glucose exceeds 16.7 mmol/l (300 mg/dl) and plasma ketones > 0.6 mmol/l and ≤ 1.5mmol/l (only measured if plasma glucose is above 16.7 mmol/l (300 mg/dl)), the MMTT can be stopped at the discretion of the investigator and rescue insulin treatment may be initiated if deemed necessary.

If the plasma ketone level is above 1.5 mmol/l presenting a risk of ketoacidosis, the MMTT **must** be stopped and appropriate treatment should be initiated. The plasma ketone level should be controlled as long as it is above 1.5 mmol/l.

In case of hypoglycaemia during the MMTT (plasma glucose value <3.9 mmol/l (70 mg/dl)), the MMTT can be stopped at the discretion of the investigator and rescue treatment according to local practice can be initiated.

After the MMTT

The subjects may have a meal after the last blood sample has been taken.

It is up to the discretion of the investigator to decide if subjects who normally takes basal insulin in the morning should take their basal insulin after the MMTT. Bolus insulin will be allowed jointly with the post-test meal, as applicable.

Documentation of the MMTT

The following has to be recorded:

- Date of mixed meal tolerance test
- Was the subject fasting prior to intake of liquid meal (Y/N)
- Did the subject withhold the insulin treatment as required prior to the MMTT (Y/N)
- Was the last SMPG measurement at the site before start of the meal within the acceptable range (4.0-9.0 mmol/l)
- Code number(s) of the liquid meal
- Meal time. Actual time for the start and stop
- How much volume of the liquid meal was ingested (ml)
- Actual time points for the blood samples
- Was the MMTT stopped prematurely and reason for stopping

8.3.2 Self-measured blood glucose

At Visit 2, subjects will be provided with a BG meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use (control solutions will only be provided if they are needed, requested or required according to local requirements or procedures). The subjects will be instructed in how to use the device, the instruction will be repeated as necessary during the trial.

The blood glucose meter use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

Subjects will be instructed in how to record the results of the self-measured blood glucose (SMBGs) in the e-diaries. The record of each SMBG will include date, time point (e.g. before breakfast, before lunch, etc.) and value. BG should always be measured when a hypo- or hyperglycaemic episode is suspected. Hypoglycaemic and hyperglycaemic episodes will be recorded by the subject in the e-diary (see Section 8.6.3). The investigator may ask the subject to perform additional SMPG measurements if needed for any safety reason.

8.3.3 4-point self-measured plasma glucose profiles

Subjects will be instructed to perform SMPG measurements before breakfast, before lunch, before dinner and at bedtime daily to allow optimal insulin titration. The plasma glucose levels, the date and the time point of all measurements will be recorded for each time point stated in the e-diary.

8.3.4 7-point profile

Subjects will be instructed to perform SMPG measurements before and 90 minutes after the start of breakfast, lunch, dinner and at bedtime. Measurements will be performed according to the flowchart in Section 2. The plasma glucose levels, the date and the time point for all measurements will be recorded for each time point stated in the e-diary.

The 7-point plasma glucose profile includes one before breakfast measurement, one before lunch, one before dinner and one at bedtime measurement. These measurements are the same needed for the 4-point profile.

8.3.5 Insulin doses

Subjects will be instructed in how to record the insulin doses in the e-diaries. Each record should include date, time point (e.g. before breakfast, before lunch etc.), value, units and type (basal or bolus) of insulin.

Insulin doses will be collected on a daily basis to allow optimal insulin titration.

If a subjects reports an actual bolus insulin dose that deviates from the prescribed bolus insulin dose the subject will be asked to report a reason for this deviation in the e-diary.

8.3.6 Carbohydrate intake per meal

Subjects who will be titrated according to the principle of flexible insulin therapy (see Appendix A) will be instructed in how to record the carbohydrate intake in the e-diary. Each record should include date, time point (e.g. breakfast lunch etc.) and grams of carbohydrate. The carbohydrate intake will be collected on a daily basis, if applicable to allow optimal insulin titration.

8.3.7 Patient reported outcomes (PROs)

The following questionnaires will be used in the trial to investigate the impact of the treatment on subject's overall health related quality of life and their treatment experience and satisfaction:

- 36-Item Short Form Health Survey version 2 (SF-36v2)
- Diabetes-Specific Health Beliefs: Experience of Treatment Benefits and Barriers – Type 1 (ETBB)
- Diabetes Treatment Satisfaction Questionnaire - status (DTSQs)

The questionnaires have to be completed by the subjects at selected visits (see Section 2).

The questionnaires must be completed by the subject him/herself on paper and should preferably be completed after conclusion of all fasting activities but before any other visit-related activities. It will take the subject approximately 15 minutes to answer all the questions.

The questionnaires will be supplied in a linguistically validated version for all languages relevant for this trial.

It is the responsibility of the investigator or delegated staff to review the completed PRO questionnaires for (and ensure reporting of) any potential AEs. Review of PROs must be documented on the designated signature sheet on the documents and/or in the subject's medical record.

If clarification of entries or discrepancies in the PRO is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject

Data from the questionnaires will be transferred into the eCRF by the investigator or delegated staff.

8.4 Assessments for safety

The timing of the assessments and procedures are specified in the flow chart Section 2.

8.4.1 Adverse events

AEs must be recorded at each visit in accordance with the procedures outlined in Section 12.2 and 12.3.

8.4.2 Adverse Events requiring special forms in the eCRF

For some AEs the investigator must fill in special forms in the eCRF. The AEs that require special forms in the eCRF are

- Pancreatitis

- Thyroid disease
- Neoplasm
- Hypersensitivity reactions
- Injection/Infusion site reactions

If the subject experiences a hyperglycaemic or hypoglycaemic episode the subject should report this in the e-diary.

Hyperglycaemia and hypoglycaemia will only be reported on an AE form if they fulfil the criteria of a SAE.

In case any of these events fulfil the criteria for a SAE, please report accordingly (see Section 12.1)

Some events may require additional assessments as described in the following section.

8.4.2.1 Pancreatitis

If an event of pancreatitis (or clinical suspicion of pancreatitis) is observed during the trial, this must be recorded as an AE and on a specific Pancreatitis event form in the eCRF. The following information must be reported if available:

- Signs and symptoms of pancreatitis
- Specific laboratory test supporting a diagnosis of pancreatitis:
  - Amylase
  - Lipase
  - ALAT and ASAT
  - Bilirubin
  - Alkaline Phosphatase
- Imaging performed and consistency with pancreatic disease
- Complications to the event
- Relevant risk factors for pancreatic disease including
  - History of gall-stones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

8.4.2.2 Thyroid disease

If an event of thyroid disease, including any thyroid neoplasms is observed during the trial, this must be recorded as an AE and on a specific thyroid disease event form in the eCRF. The following information must be reported if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing Thyroid function including :
  - Thyroid-stimulating hormone (TSH)
  - Total and free T3 and T4 and Free Thyroid Index
  - Calcitonin
  - Thyroid Peroxiodase antibodies
  - Thyroglobulin and Thyroglobulin antibody
  - Thyroid Stimulating Hormone receptor antibody
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

Thyroidectomy and genetic testing

For Israel: the following is not applicable.

In case a subject is to undergo a thyroidectomy (partial or total) for any reason during the trial, the subject will be asked to inform the investigator prior to the operation. Prior to the thyroidectomy, the subject will be asked to consent to the following:
If assessment of the thyroid gland confirms C-cell pathology (i.e., hyperplastic or neoplastic thyroid C-cells) a blood sample is collected and analysed to identify germline *RET* gene mutations associated with MEN2 syndrome if allowed by local law. The blood sample should be collected at the first visit to the clinic after the confirmation of C-cell pathology. The identification of the gene mutations will be performed by the central laboratory (for details please see Attachment I).
The blood sample will be destroyed after analysis.

8.4.2.3 Neoplasm

All events of neoplasm (excluding thyroid neoplasm which should be recorded according to Section 8.4.2.2) must be reported including malignant neoplasm, in situ neoplasm and benign neoplasm observed during the trial. This must be recorded as an AE and on a specific neoplasm event form in the eCRF. The following information must be reported if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event

8.4.2.4 Hypersensitivity reactions

If suspicion of a hypersensitivity reaction occurs the subjects should be instructed to contact the site staff as soon as possible for further guidance.

All events of hypersensitivity reactions must be reported as an AE and on a specific hypersensitivity reaction event form in the eCRF. The following information must be obtained:

- Signs and symptoms associated to the event
- Time of appearance after administration of trial drug
- If any relevant immunological tests has been performed and type and result of test
- If any treatment was given for the reaction
- Any previous history of similar reactions
- Any relevant risk or confounding factors identified

Treatment should be according to local practice.

In the event of a severe immediate hypersensitivity reaction to trial product, blood sampling for special laboratory assessment of anti-NNC0114-0006 and anti-liraglutide IgE antibodies and anti-NNC0114-0006 and anti-liraglutide binding antibodies should be conducted at 2 weeks and between 3 and 6 month after the event.

In the event of an immediate systemic hypersensitivity reaction to trial product it is recommended locally to test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. Moreover, a baseline tryptase measurement is necessary ~1 week after the immediate severe hypersensitivity reaction due to individual to individual variation in tryptase baseline concentration.

Tryptase concentrations (if measured) as well as anti-NNC0114-0006 and anti-liraglutide IgE antibodies will not be reported to the trial database but be reported to Novo Nordisk Safety Operations for inclusion in the ARGUS Safety database. Results will be included in the narratives.

8.4.2.5 Injection/Infusion site reactions

All events of injection site/Infusion site reactions caused by NNC0114-0006 and liraglutide must be reported as an AE and on a specific injection site reaction event form in the eCRF. The following information must be obtained:

- Type of reaction – local or generalised
- Symptoms associated to the event
- Treatment for the event
- Association with the trial product(s)
- Risk factors associated to the event

Treatment should be according to local practice.

8.4.2.6 Hyperglycaemic episodes

A hyperglycaemic episode is defined as, and confirmed by PG values >16.7 mmol/l (300 mg/dl).

PG should always be measured when there is a suspicion of a hyperglycaemic episode. Multiple (>1) hyperglycaemic values of SMPG >16.7 mmol/l (300 mg/dl) are considered as one hyperglycaemic episode until the SMPG is <16.7 mmol/L (300 mg/dl). One episode is set to a maximum of 24 h for the first SMPG >16.7 mmol/l (300 mg/dl).

All PG values >16.7 mmol/l (300 mg/dl) should be recorded by the subject in the e-diary from visit 2 to visit 89.

The recording should include the following information (layman-language will be used in the e-diary to phrase the respective questions ensuring that subjects understand the questions):

- Date and time of hyperglycaemic episode
- The PG level before treating the episode
- Blood ketone value before treating the episode
- Date, time and dose of last liraglutide/placebo administration prior to the episode
- Date, time and dose of last basal insulin administration prior to the episode
- Date, time and dose of last bolus insulin administration prior to the episode
- Whether the episode was symptomatic
- Where there any factors contributing to the hyperglycaemic episode?
    - Recent changes in diet
    - Concomitant infection
    - Recently missed or reduced dose of insulin
    - Other
    - Unknown

The subject should measure his/her plasma ketones when plasma glucose values >16.7 mmol/l (300 mg/dl). Subjects will be instructed in how to record the results of the ketone values in the provided e-diaries and should only record the ketone values based on the glucometer measurements.

If the hyperglycaemic episode fulfils the criteria for an SAE then an AE form and a SIF must also be completed in the eCRF.

Assessments in case of suspicion of treatment emergent hyperglycaemia and diabetic ketoacidosis

Inadequate dosing or discontinuation of insulin treatment may lead to hyperglycaemia and DKA. Usually the first symptoms of hyperglycaemia develop gradually over a period of hours or days. Symptoms may include: increased thirst, dry mouth, increased frequency of urination, headache, fatigue, blurred vision, or even nausea, vomiting, abdominal pain, drowsiness, flushed dry skin, loss of appetite, flushing, confusion, difficulty breathing as well as acetone odour of breath. Untreated hyperglycaemia eventually lead to DKA, which is potentially lethal. Illness, such as infections and fever may lead to increased insulin requirement.

If a subject suspects hyperglycaemia, the subject must perform plasma glucose measurement immediately. If SMPG > 16.7 mmol/l (300 mg/dl), plasma ketones should be measured.

Normally, ketone levels are expected to be less than 0.6 mmol/l. Ketone levels may increase if a person fasts, exercises vigorously or has diabetes and becomes ill. If plasma ketone levels are higher than 1.5 mmol/l, subjects will be instructed to contact the site staff immediately for advice and assistance.

If the investigator suspects DKA, confirmatory tests and appropriate treatment should be initiated. A DKA is confirmed if at a minimum three of the following 5 diagnostic criteria are present [32]:

1. PG > 13.9 mmol/l (250 mg/dl)
2. Arterial pH < 7.30
3. Serum Bicarbonate < 18 mEq/l
4. Serum Ketones: Positive. If available, measurement of plasma hydroxybutyrate may be useful for diagnosis 3-hydroxybutyrate > 1.5 mmol/l
5. Urine Ketones: Positive

Confirmed cases of DKA must be reported as SAEs by completion of an AE and SIF in the eCRF and should be followed-up with investigations of potential precipitating causes of DKA (i.e. infection/stroke/acute myocardial infarction/pancreatitis).

8.4.2.7 Hypoglycaemic episodes

Blood glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- ≤ 3.9 mmol/l (70 mg/dl) or
- > 3.9 mmol /l (70 mg/dl) occurring in conjunction with hypoglycaemic symptoms

should be reported according to the instructions below throughout the trial from visit 2 to visit 89. Upon onset of a hypoglycaemic episode the subject is recommended to measure blood glucose every 15 minutes in accordance to current guidelines [33].

A SMPG ≤3.9 mmol/l (70 mg/dl) or hypoglycaemic symptoms must trigger a hypoglycaemic episode form to be completed by the subject. Repeated SMPG measurements and/or symptoms will per default be considered as one hypoglycaemic episode until a succeeding measurement is >3.9 mmol/l (70 mg/dl) or symptoms have been resolved. One hypoglycaemic episode form is to cover these measurements and/or symptoms. However, each hypoglycaemic episode form will cover a period of maximum 60 minutes after onset of a hypoglycaemic episode.

In case of several low SMPG values within the 60 minute interval, the lowest value is the one that will be reported as the SMPG value for the hypoglycaemic episode but the start time of the episode will remain as the time for the first SMPG value and/or symptom.

If a new low SMPG value is measured or the subject still has symptoms more than 60 minutes after the first reported low SMPG value it is considered as a new episode and a new hypoglycaemic episode form is to be filled in.

The record should include the following information (layman-language will be used in the e-diary to phrase the respective questions ensuring that subjects understand the questions):

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available) and any follow up measurements. (The lowest value measured during the hypoglycaemic episode will be reported as the SMPG value for the episode, the remaining values will be kept as source data).
- Whether the episode was symptomatic (Yes/No). (A hypoglycaemic episode starting as non-symptomatic should be updated to symptomatic if the subject experiences symptoms later during the episode. The subjects are therefore to be prompted whether there are changes to symptoms for each low SMPG value within the 60 minutes period).

- Whether the subject was able to treat him/herself (If the severity of a hypoglycaemic episode aggravates, only one hypoglycaemic episode should be reported reflecting the most severe condition. The subjects are therefore to be prompted whether they are able to self-treat (Yes or No) for each low SMPG value within the 60 minutes period).
- Date, time and dose of last liraglutide/placebo administration prior to the episode
- Date, time and dose of last basal insulin administration prior to the episode
- Date, time and dose of last bolus insulin administration prior to the episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease
- Whether the subject was asleep when the episode occurred
  If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration [33].

Oral carbohydrates should not be given if the subject is unconscious.

If the question "Was the subject able to treat him/herself?" is answered "No", the following information should be recorded:

- Who helped manage the episode (medical person or non-medical person)
- Where the treatment was administered (in clinic/ emergency room/ hospital or other. If the subject was treated in clinic/ emergency room/ hospital whether they were transported in an ambulance or not)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other)
- Were symptoms alleviated after administration of treatment?
- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), miscalculation of insulin dose, other or unknown)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms 34:
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination

  - General malaise: headache or malaise
- Did the subject experience other symptoms?

The Investigator must review the e-diary data for correct reporting of SMPGs and hypoglycaemic episodes at each contact. If the investigator experiences missing data in the diary, the subject must be questioned whether there have been any severe hypoglycaemic episodes since the last visit i.e. any hypoglycaemic episodes where the subject was not able to self-treat. Any severe hypoglycaemic episodes must be reported on a hypoglycaemic episode form.

Non-severe hypoglycaemic episodes not having a hypoglycaemic episode form completed within 7 days since the SMPG measurement will not be reported retrospectively and missing data points for non-severe hypoglycaemic episodes will generally not be questioned by the investigator or queried by Novo Nordisk due to subject's short recall of non-severe hypoglycaemic episodes [35,36] .

The subject must be re-trained in how to report hypoglycaemic episodes if the investigator identifies unreported hypoglycaemic episodes.

If the hypoglycaemic episode fulfils the criteria for an SAE and/or a medical event of special interest (MESI) then an AE form and a safety information form must also be filled in, see section 12.1.

8.4.3 Technical complaints

Technical complaints must be recorded in accordance with the procedures outlined in Section 12.4. The following information has to be recorded:

- Product
- Code no
- DUN
- Onset date of technical complaint
- Description of the technical complaint

8.4.4 Body measurements

8.4.4.1 Height

Height without shoes should be measured in meters (m) or inches (in) and recorded with two decimals at screening (V1).

8.4.4.2 Body weight

Body weight should be measured and recorded according to Section 2.

Body weight should be measured in kilograms (kg) or pounds (lb) and should be recorded with one decimal in the eCRF. The body weight should be measured with an empty bladder, without shoes and only wearing light clothes.

Body weight should be measured using a calibrated scale. The same scale should preferably be used throughout the trial.

8.4.4.3 BMI

BMI will be calculated at the first visit by the eCRF using the equation:

BMI kg/m^2 = Body weight (kg)/ (Height (m) x Height (m)) or (kg/m^2 = (lb/in^2 x 703))

8.4.5 Electrocardiogram

A 12-lead ECG must be performed locally by the investigator or delegated staff at the time points specified in Section 2. The ECG print out must be interpreted, signed and dated by the investigator.

The evaluation must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

A baseline ECG performed for any reason unrelated to the trial within 30 days prior to Visit 1 is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime. If the ECG is performed before the subject has signed the informed consent form, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

Any abnormal, clinical significant findings at screening visit (Visit 1) must be recorded as concomitant illness.

Any clinical significant worsening from Visit 1 must be recorded as an AE (see Section 12.1)

In the treatment period of the trial the following information has to be recorded:

- Overall interpretation
- Heart rate
- PR interval
- QRS duration
- QTc interval
- RR interval

In the observation period of the trial the following information has to be recorded:

- Overall interpretation

8.4.6 Eye examination

Dilated fundoscopy or fundus photography should be performed by the investigator, a local ophthalmologist or an optometrist according to local practice at the visits specified in Section 2. Result of the dilated fundoscopy/ fundus photography will be interpreted locally by the investigator in relation to the trial. The evaluation must be documented, signed and dated.

The evaluation must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

Any abnormal, clinical significant findings at randomisation visit (Visit 3) must be recorded as concomitant illness.

Any clinical significant worsening from Visit 3 must be recorded as an AE (see Section 12.1)

If an eye examination has been performed within 90 days prior to Visit 3 as part of routine practice, and if the results are available prior to randomisation (Visit 3), the procedure does not have to be repeated, provided no worsening of visual function has occurred in the meantime. The investigator must still interpret, sign and date the fundoscopy/ fundus photography results. If the fundoscopy/ fundus photography is performed before the subject has signed the informed consent form, it must be documented in the subjects medical records that the reason for performing the procedure was not related to this trial. At Visit 63 the fundoscopy/ fundus photography may be performed in a time window of 2 weeks prior and 2 weeks after the visit and at Visit 89 the fundoscopy/ fundus photography may be performed 2 weeks prior to the visit.

8.4.7 Physical examination

Physical examination will be performed at selected visits according to Section 2. The examination will include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation
- Thyroid gland

Any abnormal, clinically significant findings at screening visit (Visit 1) must be recorded as concomitant illness.

Any clinically significant worsening from Visit 1 must be reported as an AE (see Section 12).

8.4.8 Vital signs

The following vital signs will be assessed at selected visits according to Section 2:

- Systolic and diastolic blood pressure (mmHg). Subjects should rest in a sitting position for 5 minutes
- Pulse. Subjects should rest in a sitting position for 5 minutes
- Body temperature, ear
- Respiratory rate (breath/minutes)
- Overall interpretation of vital signs

Any abnormal, clinically significant findings at screening visit (Visit 1) must be recorded as concomitant illness.

Any clinically significant worsening from Visit 1 must be reported as an AE (see Section 12.1).

8.5 Laboratory assessments

The timing of the blood samples are outlined in the flow chart (see Section 2). Laboratory assessments can be done at another day than on the day of the actual visit as long as it is within the visit window.

Review of laboratory reports must be documented either on the document and/or in the subject's medical record.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory

standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

In the case of an 'abnormal, clinically significant' finding, the investigator must comment in the subject notes and, if it occurs at screening visit (Visit 1), record this on the concomitant illness/medical history form.

Any clinically significant worsening after Visit 1 must be reported as an AE (see Section 12.1).

All blood samples will be sent to the central laboratory. Instructions for obtaining samples, handling conditions including coding in order to keep subject identity confidential, storage, blood sampling, storage and shipping will be described in a trial specific laboratory manual supplied by the central laboratory. Some samples will be shipped to the central laboratory, from where they will be shipped to specialised laboratories for analysis. It will be specified below if samples are analysed at site or at a specialised laboratory, all other samples will be analysed at the central laboratory.

8.5.1 Laboratory assessments for efficacy

8.5.1.1 Glucose metabolism

The following will be analysed:

- HbA_{1c} will be measured according to Section 2, except at Visit 1.
- Fasting plasma glucose (FPG) will be measured according to Section 2, except at Visit 1. For the measurement of FPG the subject must be fasting according to Section 8.1.8.
- Fasting glucagon will be measured according to Section 2, except at Visit 1. For the measurement of fasting glucagon the subject must be fasting according to Section 8.1.8.
- Fasting C-peptide will be measured according to Section 2, except at Visit 1. For the measurement of C-peptide the subject must be fasting according to Section 8.1.8.
- PG (non-fasting) will be measured at Visit 1.
- C-peptide (non-fasting) will be measured at Visit 1.

8.5.1.2 Mixed meal tolerance test

Please refer to Section 8.3.1 for details on the samples for the 11 points C-peptide and glucose profiles.

8.5.1.3 Biomarkers

Differentially methylated INS DNA

Minimally invasive methods to determine episodes of beta-cell death could be a valuable tool for patient stratification in clinical trials, assessing clinical response to therapy, and directing patient

care. When beta-cells die, they release insulin (INS) DNA that can be measured in serum. Though the INS gene can be detected in cells other than beta-cells, the methylation status of this gene is tissue-dependent, e.g., beta-cell-derived INS is hypomethylated. The differentially methylated INS DNA assay is hypothesized to identify waves of beta-cell death by measuring the ratio of methylated to unmethylated insulin DNA, thus providing a method of assessing beta-cell loss.

Samples will be drawn according to Section 2. This hypothesis-testing assay will be used by a specialised lab if a functioning assay is available in due time to ensure analysis and results ready for data base lock. If no functional assay is available the samples will be destroyed.

Antibodies (autoantibodies) & isotypes

The autoantibodies are used to confirm the clinical diagnosis of TD1M at screening and the assessments during the trial will give information of disease development. Further during the trial, isotypes of anti-insulin (IAA) and of anti-GAD autoantibodies will also be determined. Isotypes will change over time as the diabetes-associated immune response progresses or is modified by therapy. Therefore, autoantibody isotypes will provide information regarding the immune and disease status of an individual.

Autoantibodies will be drawn according to Section 2. The following autoantibodies will be analysed:

- Anti-GAD
- Anti-ZnT8
- Anti-IA2
- Anti-IAA, excepted at Visit 1

Additionally, isotypes for anti-IAA and –GAD will be evaluated, excepted at Visit 1.

Anti-IAA and –GAD isotypes will be analysed at a specialised laboratory and only if the sample is positive for anti-IAA or anti-GAD antibodies. These results will be reported to the investigator at the end of the trial.

Immunology

T1DM is mediated by immune destruction of the islets, characterised by T-cell infiltrate and detectable autoantibodies in the periphery. Additionally, IL-21 is an important immune-modifying cytokine that has been demonstrated to impact B- and T-cell compartments. The assays proposed will assess the disease- and treatment-associated effects on the immune response mediating T1D.

Samples will be drawn according to Section 2. The investigator must record the date and the exact time for sampling the blood.

The following will be analysed:

- T-cell profiling including islet-specific auto reactive CD8+ T-cells
- IL-21, excepted at Visit 2

The blood sampling for assessment of T-cell profiling including islet-specific auto reactive CD8+ T-cells should preferably be performed at about the same time of day for a given subject.

Blood sampling for the assessment of Il-21 should be taken pre-dose of the NNC0114-0006 administration. IL-21 will be analysed at a specialised laboratory only if a functioning assay is available in due time to ensure analyses and results are ready for data base lock. The investigator will receive the results of the immunology assessments at the end of the trial. If no functional assay is available the samples will be destroyed.

The periphery blood mononuclear cells (PBMCs) used for the analyses of the T-cell profiling including islet-specific auto reactive CD8+ T-cells will be stored for up to 15 years for potential future assessments if the subject has consented to it (see Section 24.2).

8.5.1.4 Vitamin D (1,25 dehydroxy-calciferol)

Samples for Vitamin D (1,25 dehydroxy-calciferol) will be drawn according to Section 2.

8.5.2 Laboratory assessments for safety

8.5.2.1 Pregnancy test

A human chorionic gonadotropin serum pregnancy test will be performed at Visit 1 and 63 on all women where childbearing potential has not been ruled out by for example measuring FSH levels.

Urine pregnancy test will be performed for females of childbearing potential at any time during the trial if a menstrual period is missed or required by local law. If a subject during a phone contact reports missing menstrual period, an unscheduled visit should be scheduled as soon as possible to have a urine pregnancy test performed. Urine pregnancy kits will be supplied by the central laboratory. The test will be performed at site.

For Austria: A monthly urine pregnancy test is mandatory for female subjects of childbearing potential.

8.5.2.2 Anti-drug antibodies

Assessment of antibodies against liraglutide and NNC0114-0006 (anti-drug antibodies) in serum will be performed at specialised laboratories according to Section 2.

Samples for the determination of anti-drug antibodies must be drawn in a fasting state to minimise interference of endogenous GLP-1. During the treatment period samples must be drawn prior to administrating trial products.

The investigators will not receive the results until the trial is completed and unblinded. A detailed description of the assay methods will be included in the antibody analysis report at the end of the study.

Antibody samples may be retained until drug approval by FDA and/or EMA. The retained antibody samples may be used for further characterisation for antibody responses towards drug if required by health authorities or for safety reasons. At end of trial the specialised laboratories responsible for the anti-drug antibodies analysis will arrange the transfer of samples to Novo Nordisk for storage. Anti-drug antibodies are stable for many years when stored frozen (e.g. -20 degrees Celsius), and further characterisation is therefore possible. Samples will only be used for further characterisation if required by the authorities (FDA and/or EMA) or for safety reasons.

Anti-liraglutide antibodies

The screening analysis of serum samples for antibodies against liraglutide will be done in the two arms dosed with liraglutide at Visit 3, 19, 31, 43, 63, 69, and 89 or 90. However all subjects will have blood samples drawn to avoid unblinding. The assay is a validated RIA. Samples positive for anti-liraglutide antibodies will furthermore be characterised for cross-reactivity to native GLP-1.

At Visit 69, 89 and 90 positive anti-liraglutide antibody samples from the screening analysis will in addition be analysed for in vitro neutralising effect by comparison to Visit 3 (before drug exposure) in a cell-based assay. Furthermore, antibody positive samples from the screening analysis that cross-react with native GLP-1 will be analysed for in vitro neutralising effect towards native GLP-1 in a cell-based assay.

Anti-NNC0114-0006 antibodies

The screening analysis of serum samples for antibodies against NNC0114-0006 will be done in the two arms dosed with NNC01114-0006 at Visit 3, 19, 31, 43, 63, 89 and 90. However all subjects will have blood samples drawn to avoid unblinding. The assay is a validated bridging antibody assay. Samples positive for anti-NNC0114-0006 antibodies will furthermore be characterised for specificity to the constant region with mutations and the variable region.

The neutralising effect of anti-NNC0114-0006 antibodies will be evaluated by correlating results to PK data and the specificity of anti-drug antibodies (towards the constant region with mutations and the variable region).

8.5.2.3 Total IgE

Total IgE will measured according to Section 2.

8.5.2.4 Biochemistry

The following will be analysed according to Section 2:

- ALAT
- Albumin
- Alkaline phosphatase
- Amylase
- ASAT
- Bilirubins, total
- Calcium (albumin corrected)
- Chloride
- Creatinine kinase
- Creatinine
- Gamma glutamyltransferase
- CRP
- Estimated GFR, only at Visit 1, 63 and 89
- Lactate dehydrogenase
- Lipase
- Magnesium
- Phosphate
- Potassium
- Sodium
- Total proteins
- Urea (blood urea nitrogen)
- Uric acid

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation as this indirect measurement of GFR has a median difference with direct measurement of GFR of 2.5 ml/min [37].

8.5.2.5 Coagulation parameters

The following will be analysed according to Section 2:

- INR
- D-dimer

8.5.2.6 Haematology

The following will be analysed according to Section 2:

- Erythrocytes
- Haematocrit
- Haemoglobin
- Leucocytes
- Mean corpuscular haemoglobin
- Mean corpuscular haemoglobin, conc.
- Mean corpuscular volumen
- Thrombocytes
- Differential count:
    - Eosinophils
    - Neutrophils
    - Basophils
    - Lymphocytes
    - Monocytes

8.5.2.7 Cytokines

The following will be analysed according to Section 2:

- Cytokine panel (IL-6, IL-10, IL-17, IFNγ, TNF-α)

The investigators will not receive the results until the trial is completed.

8.5.2.8 Urine dipstick

Urinalysis will be performed from a sample of mid-stream urine by means of a stick at the trial site. The following will be assessed according to Section 2 and result reported in the eCRF:

- Erythrocyte
- Glucose
- Ketone
- Leucocyte
- Nitrite
- pH
- Protein
- Specific gravity

The urine sticks provided by the central laboratory may include more parameters than requested for this protocol. Such data will not be recorded in the eCRF. The investigator must review all results on the urine stick for concomitant illnesses and AEs and report these according to Section 8.2.1 and 12.

8.5.2.9 Virus screen for hepatitis B and C

The following assessments will be performed according to Section 2:

- HBcAb
- HBsAb
- HBsAg
- Anti-HCV antibody, assessed by an enzyme immunoassay
- HCV-RNA

8.5.2.10 Tuberculosis screening test

A QuantiFERON®-TB Gold test will be performed at Visit 1.

If the test is inconclusive retests can be performed. The repeat test results must be available for evaluating the subject's eligibility before Visit 3.

8.5.2.11 Virus screen for Epstein-Barr virus

Blood samples will be drawn according to Section 2 for assessment of:

- IgM EBV antibodies
- IgG EBV nuclear antigen

8.5.2.12 Virus screen for cytomegalovirus infection

The following will be analysed according to Section 2:

- CMV IgM
- CMV IgG

8.5.2.13 HIV

The following will be analysed at Visit 1:

- HIV_1 antibodies
- HIV_2 antibodies

8.5.2.14 Hormones

The following will be analysed according to Section 2:

- TSH, excepted at Visit 19, 43 and 55
- Calcitonin

For actions to be taken if calcitonin is ≥ 10 ng/L, please refer to Appendix B.

8.5.2.15 Lipids

The following will be analysed according to Section 2:

- Cholesterol
- Free fatty acids
- HDL cholesterol
- LDL cholesterol
- Triglycerides

8.5.3 Other laboratory assessments

8.5.3.1 Genotype (optional)

For Israel: the following is not applicable.

Blood samples for genotyping will be collected and analysed for human leucocyte antigen (HLA) class I, provided the subject has given separate written informed consent. The samples will be stored as described in Section 24.2.

8.5.3.2 Blood samples for long term retention (optional)

For Israel: the following is not applicable.

Provided the subject has given a separate written informed consent, specific blood samples will be collected and serum stored for up to 15 years for potential future assessments see Section 24.2. Since new biomarkers related to TD1M and/or to safety, efficacy, or mechanism of action of NNC0114-0006 and liraglutide may evolve during the conduct of the trial, potential future

assessment on stored samples may be related to safety, e.g. infections, efficacy or mode of action of NNC0114-0006 and liraglutide as well as to TD1M.

8.5.3.3 Serum concentration of NNC0114-0006 for pharmacokinetics

PK samples will be taken according to Section 2. At Visit 3 and 55, samples will be taken pre-dose (up to 60 min before) and 1 hour after start of the infusion. At NNC0114-0006 dosing visits, the sample should be taken pre-dose. The investigator must record the date and the exact time for sampling the blood.

Serum will be analysed by use of an enzyme-linked immunosorbent assay (ELISA) specific for NNC0114-0006. The ELISA is validated for human serum samples.

All samples from subjects receiving active treatment with NNC0114-0006 will be analysed for NNC0114-0006. For subjects receiving placebo or liraglutide treatment only, the samples taken 1 hour after the start of infusion at Visit 3 will be analysed in order to verify the placebo treatment. If the NNC0114-0006 concentration in this sample is above the lower limit of quantification (LLOQ), all samples from that subject will also be analysed. A copy of the subject treatment allocation report will be forwarded to the laboratory before any analyses are started.

The analysis will be performed by a specialised laboratory. Investigators will not receive the results until the trial is completed and unblinded.

The PK samples will be retained until the clinical trial report (CTR) has been finalised. The samples will be stored at the specialised laboratory.

8.5.3.4 Plasma concentration of liraglutide for pharmacokinetics

A single blood sample for PK will be drawn and assayed for plasma concentrations of liraglutide at the visits specified in Section 2. The investigator must record the date and the exact time for sampling the blood. The sample can be taken at any time during the visit. Plasma will be analysed by use of an enzyme-linked immunosorbent assay (ELISA) specific for liraglutide. The ELISA is validated for human plasma samples

All samples from subjects receiving active treatment with liraglutide will be analysed for liraglutide. For subjects receiving placebo treatment or NNC0114-0006 only, samples taken at Visit 6 will be analysed in order to verify the placebo treatment. If the liraglutide concentration in this sample is above the lower limit of quantification (LLOQ), all samples from the subject will also be analysed.

A copy of the subject treatment allocation report will be forwarded to the laboratory before any analyses are started.

The analysis will be performed by a specialised laboratory. Investigators will not receive the results until the trial is completed and unblinded.

The PK samples will be retained until the CTR has been finalised. The samples will be stored at the specialised laboratory.

8.6 Other assessments

8.6.1 Trial product administration NNC0114-0006

Investigators must report the exact volume of NNC0114-0006 in the eCRF after each infusion. Each record should also include date and start and stop time of the infusion.

8.6.2 Liraglutide/liraglutide placebo

Subjects will be instructed to report the dose (0.6, 1.2 or 1.8 mg) as indicated on the pen in their e-diary on a daily basis. Each record should also include date, time and injection site.

8.6.3 Subject e-diaries

The subjects will be provided with an e-diary at Visit 2. The investigator or delegated will train the subject in the use of the e-diary according to the provided instructions.

The following information will be collected in the e-diaries:

- Liraglutide/placebo doses (see Section 8.6.2)
- 4-point profiles (see Section 8.3.3)
- 7-point profiles (see Section 8.3.4)
- Insulin doses (see Section 8.3.5)
- Reasons for deviating from the prescribed bolus insulin dose
- Carbohydrate (CHO) intake per meal (CHO-counting subjects only) (see Section 8.3.6)
- Hypoglycaemic episodes (see Section 8.4.2.7)
- Hyperglycaemic episodes including ketone data (see Section 8.4.2.6)

Review of e-diaries must be documented. Please refer to Section 13.3.

8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed. Substantial failure to comply with the prescribed dose regimen can lead to withdrawal at the discretion of the investigator.

Treatment compliance:

Throughout the trial the treatment compliance will be assessed by monitoring of drug accountability as specified in Section 9.4. The unused/used liraglutide pens code numbers will be assessed against the dispensed code numbers and in case of discrepancies the subject must be asked.

The target dose of liraglutide or placebo is 1.8 mg. If 1.8 mg per day is not tolerated, the subject can stay on 1.2 mg per day.

Subjects are asked to report the actual daily dose in the e-dairy. Prior to or during each visit/phone contact the investigator or delegated staff should review the subject's compliance with regards to liraglutide/placebo treatment. If the subject has missed a dose completely or not administered the expected dose the investigator or delegated staff should ask the subject for the reason for non-compliance and discuss the importance of treatment compliance.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the TMM.

Trial products must not be dispensed to any person not included in the trial.

9.1 Trial products

The following IMPs for treatment at site will be provided by Novo Nordisk A/S Denmark:

- NNC0114-0006 C 100 mg/ml, 3 ml cartridges
- NNC0114-0006 C 0 mg/ml, 3 ml cartridges

Trial cartridge will be packed blinded and will appear similar.

NNC0114-0006 C 100 mg/ml /NNC0114-0006 C 0 mg/ml appear clear to slightly opalescent and colourless/slightly yellow essentially free from visible particles. If this is not the case or the liquid is cloudy it must not be used.

The following IMPs for treatment at home will be provided by Novo Nordisk A/S Denmark:

- Liraglutide 6.0 mg/ml, 3 ml pre-filled pen-injector
- Liraglutide placebo, 3 ml pre-filled pen-injector

Liraglutide /Liraglutide placebo will be packed blinded and are visually identical.

Liragutide 6 mg/ml /Liragutide placebo appear clear and colourless or almost colourless. If this is not the case the liquid must not be used.

The following trial products will be provided by Novo Nordisk A/S, Denmark:

<table>
<tr><th>Trial product</th><th>Strength</th><th>Dosage form</th><th>Route of administration</th><th>Container/ delivery device</th></tr>
<tr><td>NNC0114-0006 C 100 mg/ml</td><td>100 mg/ml</td><td rowspan="2">3 ml cartridge</td><td rowspan="2">i.v.</td><td rowspan="2">Cartridge</td></tr>
<tr><td>NNC0114-0006 C 0 mg/ml</td><td>0 mg/ml</td></tr>
<tr><td>Liraglutide 6.0 mg/ml</td><td>6.0 mg/ml</td><td rowspan="2">3 ml pre-filled pen</td><td rowspan="2">s.c.</td><td rowspan="2">3 ml pre-filled pen/pen-injector</td></tr>
<tr><td>Liraglutide placebo</td><td>0 mg/ml</td></tr>
</table>

The following non-IMPs are used in this trial:

- Insulin:
  During the trial subjects will receive insulin treatment in order to achieve a metabolic control according to the insulin titration guideline. Subjects will continue their pre-trial insulin treatment. Thus treatment will be considered background treatment. Preferably the type and/or brand of basal and bolus insulin should not be changed throughout the trial. Insulin will not be provided by Novo Nordisk.

- Glucagon
  Glucagon will be used as rescue medication for the treatment of severe hypoglycaemia. Glucagon will not be provided by Novo Nordisk.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13 [38], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Dispensing unit numbers (DUNs) will be distributed to the trial sites according to enrolment and randomisation.

For NNC0114-0006 C 100 mg/ml / NNC0114-0006 C 0 mg/ml i.v. infusion, an instruction for handling will be described in the TMM.

For Liraglutide 6.0 mg/ml/Liraglutide placebo a direction for use (DFU) will be provided to the sites. The investigator must document that direction for use is given to the subject orally and in writing at the first dispensing visit (Visit 3). The investigator may give the DFU to the subject at subsequent visits, if needed.

9.3 Storage

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
NNC0114-0006 C 100 mg/ml	Store in a refrigerator (2°C to 8°C) Protect from light Do not freeze	Below 30°C Protect from light Do not freeze	For 6 hours
NNC0114-0006 C 0 mg/ml			

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time**
Liraglutide 6.0 mg/ml, 3 ml pre-filled pen	Store in a refrigerator (2°C to 8°C)	Store below 30°C US: 15-30° or in a refrigerator (2°C-8°C) CA: At room temperature not above 30°C or in a refrigerator (2°-8°C) Protect from light Do not freeze	1 month US: For 30 days CA: For 30 days
Liraglutide placebo 3 ml pre-filled pen			

*In-use time starts after removal from the refrigerator at site. The dosing should be performed within 6 hours after the trial product is removed from the refrigerator.

** In-use time starts when first dose is taken

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range).

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product.

The trial products will be dispensed to each subject as required according to treatment group. The IWRS will allocate trial product to the subject at randomisation and each dispensing visit. The correct dispensing unit number(s) (DUN(s)) must be dispensed to the subject. The investigator or delegated person is responsible for ensuring that:

- Drug accountability for NNC0114-0006 C 100 mg/ml / NNC0114-0006 C 0 mg/ml is performed on a cartridge level using the IWRS drug accountability module
- Drug accountability for Liraglutide 6.0 mg/ml/Liraglutide placebo is performed on a pen level using the IWRS drug accountability module
- Subjects are instructed to return all used, partly used and unused trial product including empty packaging material at each dispensing visit and at end of treatment visit

Due to the formulation of NNC0114-0006 C 100 mg/ml, NNC0114-0006 C 0 mg/ml, Liraglutide 6.0 mg/ml, Liraglutide placebo it is not possible for the monitors to verify drug accountability on a volume level.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies and other deliveries

The following auxiliary supplies will be provided by Novo Nordisk and specified in the TMM:

- Needles for pre-filled pen injector
- BG meters to measure plasma glucose levels and to measure blood ketone levels, when needed including
    - lancets, plasma-calibrated test strips and control solutions
    - control solutions will only be provided if they are needed, requested or required according to local requirements or procedures.
- Mixed meals
- Set for the infusion of NNC0114-0006

10 Interactive voice/web response system

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons.

IV/WRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Withdrawal
- Completion
- Code break
- Drug accountability
- Data change

IV/WRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

This trial is double-blind. A randomisation session will be carried out for all subjects using the IV/WRS. At the randomisation visit (Visit 3) subjects meeting all inclusion and randomisation criteria and none of the exclusion criteria will be centrally randomised to one of the 4 parallel treatment groups in a 1:1:1:1 manner to:

- NNC0114-0006 C 100 mg/ml 12 mg/kg i.v. every 6 weeks and liraglutide 1.8 mg s.c. daily
- NNC0114-0006 C 100 mg/ml 12 mg/kg i.v. every 6 weeks and liraglutide placebo 0 mg s.c. daily
- NNC0114-0006 C 0 mg/ml i.v. every 6 weeks and liraglutide 1.8 mg s.c. daily
- NNC0114-0006 C 0 mg/ml i.v. every 6 weeks and liraglutide placebo 0 mg s.c. daily

The randomisation will be stratified according to non-fasting C-peptide levels:

- non-fasting C-peptide ≥ 0.2 nmol/l to ≤0.6 nmol/l
- non-fasting C-peptide >0.6 nmol/l

11.1 Breaking of blinded codes

The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IV/WRS, record the reason, and sign and date the document.

When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS helpdesk should be contacted. Contact details are listed in Attachment I.
If the code has been broken the subject must be withdrawn from the trial and a withdrawal session must be completed in IV/WRS.

12 Adverse events, and technical complaints and pregnancies

12.1 Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see Section 8.4.2.7.
- Non-serious hyperglycaemia is an AE, but is reported on a hyperglycaemic episode form instead of on an AE form, see Section 8.4.2.6.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild** - no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** - considerable interference with the subject's daily activities; unacceptable.

- **Causality**

Relationship between an AE and the relevant trial product(s):

  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.

- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the trial product.

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].
  Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

[a]. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

[b]. The term "hospitalisation" is used when a subject:
- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

[c]. A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d]. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Severe infections should be reported as SAEs (i.e. should be reported as an “important medical event”, if not fulfilling other SAE criteria like “hospitalisation”).

Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

Adverse Events requiring additional information

In this trial the following AEs require the completion of an additional eCRF page:

1. Hypersensitivity reactions
2. Injection/Infusion site reaction
3. Neoplasm
4. Pancreatitis
5. Thyroid Disease

The following events should be reported on in the e-diary by the subjects. They should only be reported on an AE form if they fulfil the criteria of an SAE.

1. Hyperglycaemic episodes
2. Hypoglycaemic episodes

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:
   - Administration of wrong drug or use of wrong device. Note: Use of wrong DUN is not considered a medication error
   - Wrong route of administration, such as intramuscular instead of subcutaneous.
   - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
   - Accidental administration of a lower or higher dose than intended. However the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although they did not necessarily occur.

Note: A drug pause should not be reported as a medication error.

Trial specific AEs.

Severe infections should be reported as SAEs (i.e. should be reported as an "important medical event", if not fulfilling other SAE criteria like "hospitalisation").

Any infection requiring hospitalisation and/or which based upon appropriate medical judgement, is considered to be:

i. More severe, longer-lasting or harder-to-treat than generally expected (e.g. for ear infections, pneumonia, meningitis, bronchitis, sinusitis or skin infections)
ii. An infection with unusual localization
iii. Re-activation of a latent infection (e.g. JC polyomavirus (progressive multifocal leukoencephalopathy), Epstein-Barr virus, varicella-zoster virus (herpes zoster), herpes-simplex virus)
iv. An opportunistic infection defined as an infection caused by an organism that does not normally cause disease but may occur in people with weakened immune systems. These micro-organisms may (but not exclusively) include:
    - Acinetobacter baumanni
    - Aspergillus sp.
    - Blastoschizomyces capitatus
    - Candida albicans
    - Clostridium difficile
    - Cryptococcus neoformans
    - Cryptosporidium
    - Cytomegalovirus

- Geomyces destructans
- Histoplasma capsulatum
- Isospora belli
- Kaposi's Sarcoma caused by Human herpesvirus 8 (HHV8), also called Kaposi's sarcoma-associated herpesvirus (KSHV)
- Legionnaires' Disease (Legionella pneumophila)
- Microsporidium
- Mycobacterium Tuberculosis
- Mycobacterium avium complex (MAC) (Nontuberculosis Mycobacterium)
- Pneumocystis jirovecii, previously known as Pneumocystis carinii f. hominis
- Pseudomonas aeruginosa
- Staphylococcus aureus
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Trichosporon beigelii
- Toxoplasma gondii

Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent[2] until the end of the post-treatment follow-up period (26 weeks after the end of treatment). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?"

[2] With the exception of hyperglycaemic and hypoglycamic episodes for which reporting starts at V2.

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- NN9211 IB, edition 3, 07 August 2013 and updates thereto
- NN9828 IB, edition 1, 2015 and updates thereto

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form and an MESI form. The MESI form is a form tailored to collect specific information related to the individual MESI.

The AE form for a non-serious AE not fulfilling the MESI criteria should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.
  Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

- **For SAEs with additional data collection:** in addition also the specific event form within 14 calendar days of the investigator's first knowledge of the AE.
- **Non-serious AEs with additional data collection:** The AE form and the specific event form within 14 calendar days of the investigator's first knowledge of the event

- **SAEs fulfilling the MESI criteria:** In addition to above, the MESI form **within 14 calendar days** of the investigator's first knowledge of the AE.
- **Non-serious AE fulfilling the MESI criteria:** The AE form, and safety information form and MESI form **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the

eCRF becomes available again, the investigator must enter the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

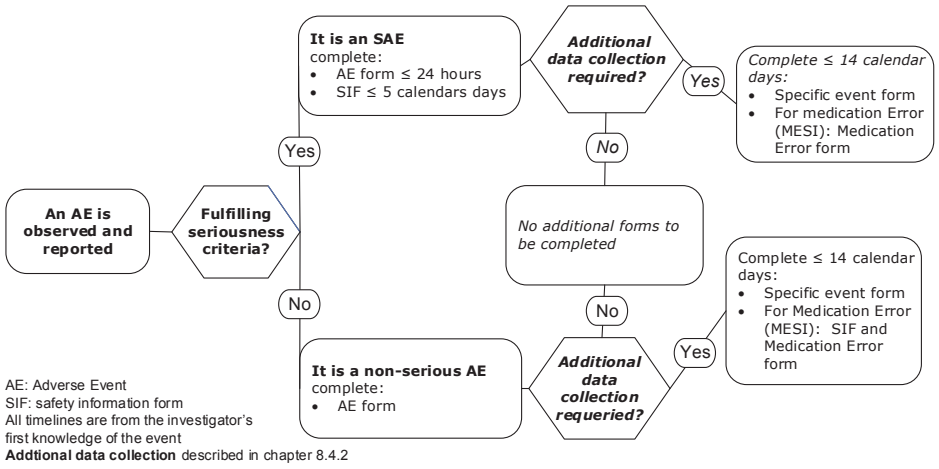


Figure 12–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by Novo Nordisk:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP [2]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and GCP [2], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:
If a SAE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow up information must be reported to Novo Nordisk according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

- **Non-serious AE fulfilling the MESI criteria:** Non-serious AE fulfilling the MESI criteria must be followed as specified for non-serious AEs. Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- NNC0114-0006 C100 mg/ml, 3 ml cartridges
- NNC0114-0006 C 0 mg/ml, 3ml cartridges
- Liraglutide 6.0 mg/ml, 3 ml pre-filled pen-injector
- Liraglutide placebo 3 ml pre-filled pen-injector
- Needles

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each code or lot number or for each DUN must be completed.

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the code number and, if available, the DUN.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see Section 9).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s).

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**

The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:
Non-serious AEs:

- Paper AE form* **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- Paper AE form* **within 24 hours** of the investigator's first knowledge of the SAE.
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.5.2 Pregnancies in female partners of male subjects

Male subjects must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period. At the last scheduled visit, male subjects must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male subject and assess, if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the subject's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax:

1. Reporting of pregnancy information

Information from the male subject has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. Reporting of AE information

The following AEs in the foetus and newborn infant have to be reported:

- Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s).
- SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus).

Forms and timelines for reporting AEs:

Please see Section 12.5.1, point 2, "Forms and timelines for reporting AEs:".

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

12.6.1 NNC0114-0006

Because of the early stage of clinical development of NNC0114-0006, no special warnings or precautions can be formulated at present. No clinically relevant safety findings have been observed in the non-clinical studies, or by the limited clinical safety data emerged to date, that would conclude any specific recommendations, e.g. on AE or laboratory monitoring.

Administration of NNC0114-0006 must take place in an environment where access to resuscitation equipment (i.e. ventilation balloon and medication for treatment of hypersensitivity reactions) is available in case of an acute reaction/or development of other unpredicted, serious or life-threatening reactions. Written emergency procedures must be in place, and the clinical staff responsible for dosing and monitoring the subjects must be adequately trained in emergency procedures.

To date, no subjects have accidentally been overdosed with NNC0114-0006, as no subjects have received doses of NNC0114-0006 exceeding the dose level of any planned dose ranges in the FHD trial. The highest dose level tested in the FHD trial was 25 mg/kg administered i.v. and this dose level was well tolerated in both healthy subjects, subjects with RA and subjects with Crohn's Disease. In case of an overdose, treatment with NNC0114-0006 should be suspended and appropriate medical supportive treatment of clinical signs should be given.

For further information, please refer to the current version of the NN9828 IB.

12.6.2 Liraglutide

When initiating treatment with liraglutide, the subject may in some cases experience loss of fluids/dehydration, e.g. in case of vomiting, nausea or diarrhoea, sometimes with a decrease in kidney function. It is important to avoid dehydration by drinking enough fluids.

From clinical trials and marketed use overdoses have been reported up to 40 times the recommended maintenance dose (72 mg). Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients recovered without complications.

For further information, please refer to the current version of the NN9211 IB.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal NN9828 safety committee to perform ongoing safety surveillance of clinical trials with NNC0114-0006, including this trial.

The safety committee will conduct on-going monitoring of blinded safety data (all reported adverse events, selected safety laboratory parameters, including calcitonin, amylase and lipase).

If safety signals are observed either based on immediate review of serious adverse events reported, or based on periodic review of all other adverse events and above mentioned laboratory parameters collected during the trial, the safety committee will take appropriate measures to safeguard the subjects.

The NN9828 safety committee may recommend unblinding of any data for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms, safety information forms and technical complaint forms will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

For eCRFs:

Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

For paper CRFs

Corrections to the data in CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary).

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes. Queries will be generate in the eCRF on an ongoing basis, and the investigator should solve these queries preferable **within 3 business days.**

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF **no later than 24 hours** after the last visit at the trial site to ensure the planned lock of the database. In addition queries must be solved immediately in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

When access to update the AE form in the eCRF application is removed, the investigator must record any AE follow-up information, if required, on the paper CRFs provided.

Laboratory reports will be retained at the sites.

13.3 E-diaries

At visit 2 the subjects will be provided with an e-diary device for electronic recording of data as specified in Section 8.6.3 after subjects have been trained in the use of the device. The e-diary device will be returned by the subjects at the EOT visit. The e-diary and related support services will be supplied by a vendor that will be working under the direction and supervision of Novo Nordisk.

The e-diary will contain built in edit checks, to ensure that all relevant questions are answered. All data entered will be transferred automatically from the device to the database, where they are kept as a certified copy of source data.

The e-diary device is not intended to support the subsequent review and modification of completed entries. If corrections to transferred data are needed, a query flow will be initiated. Data in the e-diary will be viewable to relevant sites and Novo Nordisk personnel on a secure, password protected web portal. Data will be transferred to the Novo Nordisk trial database at defined intervals.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks.

14.1 Source data verification

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the eCRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element. The investigator should make a reasonable effort to obtain additional information from external sources e.g. primary physician and other hospitals/departments to collect information required to evaluate all in- and exclusion criteria if not available in the subject’s medical record at the trial site and if not part of the screening assessments performed.

Considering the electronic source data environment, it is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore transcription to the e-diary from glucometer is considered the source document for recordings of glucometer.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original PROs must not be removed from the trial site.

Data recorded in the subject’s e-diary is considered source data with respect to:

- Date, time, dose and injection site of liraglutide
- 4-point profiles
- 7-point profiles
- Date, time point (e.g. before breakfast, before lunch etc.), value, units and type (basal or bolus) of insulin doses
- Reasons for deviating the prescribed insulin dose
- Carbohydrate intake per meal (CHO-counting subjects only)
- Hypoglycaemic episodes
- Hyperglycaemic episodes including ketone data

The monitor will ensure that the eCRFs are completed on an ongoing basis and within agreed timelines and that paper CRFs are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Screen failure reason

Monitors must review the subject's medical records and other source data to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

14.2 Titration Surveillance

Surveillance of insulin titration will be performed centrally by an independent Novo Nordisk Titration Group not otherwise involved in the conduct of the trial. Surveillance will be performed on an ongoing basis throughout the trial. Details are described in Appendix A.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation (CRO).

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data. Novo Nordisk will collect information on practical use of these systems within the conduct of this trial.

The e-diary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11[39]. After trial finalisation, each trial site will be supplied with electronic media containing site-specific subject records including the subjects' diaries and audit trail including any data additions and corrections made. Novo Nordisk will furthermore retain and securely store copies of all archived documents and data.

17 Statistical considerations

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Based on the statistical model, treatment means or geometric means (LSMeans) and treatment comparisons (i.e. treatment differences or treatment ratios) will be presented with 95% confidence intervals (CI) and p-values for the two-sided test of no treatment difference. A significance level of 5% will be used. All pairwise treatment differences (or ratios) will be presented. No adjustment for multiple testing will be performed.

Some endpoints will be summarised for the treatment period, for the observation period and for the entire trial period (i.e. the treatment period together with the observation period)

The treatment period and the observation period will be derived for completed subjects as

- The start of the treatment period will be the date of first trial product administration
- The end of the treatment period will be the day before the visit at week 54 (i.e. the day before visit 63)
- The start of the observation period will be the day after the end of the treatment period
- The end of the observation period will be the date of the last visit

For withdrawn subjects the date of last contact will be the maximum of the date of the last visit and the withdrawal date. The treatment period and the observation period will be derived for withdrawn subjects as

- The start of the treatment period will be defined as described for completed subjects
- The end of the treatment period will be as defined for competed subjects if this date is before or on the date of last contact. Otherwise the end of the treatment period will be the date of last contact
- An observation period will only be defined if the date of last contact is after the end of the treatment period
  - The start of the observation period will be defined as for completed subjects
  - The end of the observation period will be the date of last contact

For endpoints evaluated as change from baseline and/or for baseline adjustment in the statistical analyses, baseline will be defined as the information recorded at the Visit 3 (randomisation). If no measurement is available at Visit 3, then the information recorded at Visit 2 will be used as the baseline. Furthermore, if no measurement is available at Visit 2, then the information recorded at Visit 1 will be used as the baseline.

As there is no previous experience with NNC0114-0006 in subjects with T1DM, the defined endpoints and analyses may be supplemented with additional endpoints or analyses such that a better evaluation of the effect and safety of NNC0114-0006 can be obtained.

17.1 Sample size calculation

This is a phase 2 trial and the first Novo Nordisk trial of NNC0114-0006 in subjects with newly diagnosed T1DM. Therefore the knowledge on treatment effects and on the standard deviation of the primary endpoint is limited.

The statistical power calculations have been done under the following assumptions

- The primary endpoint is $AUC_{0\text{-}4h}$ for a MMTT stimulated C-peptide concentration-time curve at week 54 relative to baseline, i.e. $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$. The primary endpoint will be log-transformed in the statistical analysis and this will be denoted $\ln(AUC_{0\text{-}4h,C\text{-}peptide,\Delta 54w})$. Thus, $AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta 54w}$ is the proportion of $AUC_{C\text{-}peptide}$ that is preserved after 54 weeks relative to the level at baseline. E.g. a reduction of $AUC_{C\text{-}peptide}$ of 35% corresponds to a preservation of 65% and value of the $\ln(AUC_{0\text{-}4h,C\ \text{-}peptide,\Delta 54w})$ is $\ln(0.65)=-0.431$.
- The residual standard deviation of $\ln(AUC_{0\text{-}4h,\ C\text{-}peptide,\ \Delta 54w})$ in the model described above may depend on the treatment. Based on the results of Herold et al. [40] the standard deviation is assumed to be 1 in the placebo group and 0.5 in the group treated with NNC0114-0006 in combination with liraglutide.
- The expected preservation in the placebo treated patients is 65%, based on the results of Herold et al. [40] who found a mean of 70% decline in $AUC_{C\text{-}peptide}$ over a 24-months period. Assuming a linear decline, the mean 12-months decline would be 35%, i.e. a preservation of 65%. The statistical power calculations have been done assuming three levels of treatment effects for NNC0114-0006 in combination with liraglutide; a preservation of 85% and 95% and 98%, respectively.

Table 17–1 shows the statistical power for the test of no treatment effect if the true mean preservation is 85%, 95% or 98% in the group treated with NNC0114-0006 in combination with liraglutide and 65% in the placebo group when the numbers of completers are 40, 60 or 80, respectively using a two-sided test and 5% level of significance. The rows corresponding to the chosen number of (completing) subjects are highlighted.

Table 17–1 Power calculations

True treatment effect (preservation)	N (completers per group)	Statistical power
85%	40	0.320
85%	**60**	**0.451**
85%	80	0.566
95%	40	0.561
95%	**60**	**0.740**
95%	80	0.854
98%	40	0.628
98%	**60**	**0.804**
98%	80	0.903

Assuming a preservation of 98% and a SD of 0.5 for NNC0114-0006 in combination with liraglutide and a preservation of 65% and a SD of 1 for placebo, then the power will be 80.4% with 60 subjects completing the trial in each of the two treatment arms.

17.2 Definition of analysis sets

The following analysis sets are defined in accordance with the ICH-E9 [41] guidance:

- The full analysis set (FAS) will include all randomised subjects. Only in exceptional cases subjects may be excluded from the FAS. In such cases the reason for exclusion will be justified and documented. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation ‘as treated’.
- The PK analysis set will include all randomised subjects with at least one valid PK measurement. Subjects in the PK analysis set will contribute to the evaluation ‘as treated’.
- The safety analysis set will include all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set will contribute to the evaluation ‘as treated’.

Analyses of efficacy and biomarker endpoints will be based on the FAS. Analyses of the PK endpoints will be based on the PK analysis set. Analyses of safety endpoints will be based on the safety analysis set.

Before the database is locked and ready for statistical analysis a review of all data will take place. Extreme values and outliers will be identified by the study group during programming and data review according to ICH-E9 [41] using a fake randomisation. In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from analysis.

Obviously erroneous data points may be excluded from the analyses or re-analysed (in case of e.g. serum concentrations). The decision to re-analyse or exclude data points from the statistical analysis is the joint responsibility of the study group. Furthermore, the individual PK profiles with fake subject numbers and the individual profiles for C-peptide and plasma glucose from the MMTT will be examined prior to database lock to establish whether it is possible to calculate all endpoints. If samples are missing that are important for the derivation of the endpoints, certain endpoints will not be calculated and they will be excluded from the analysis. In these cases, the subjects, observations or endpoints to be excluded and the reason for their exclusion will be documented prior to database lock. The subjects and observations excluded from analysis and the reason for exclusion will also be described in the clinical trial report.

The impact of protocol deviations and outliers may be investigated further in sensitivity analyses, if deemed relevant.

17.3 Primary endpoint

The primary endpoint is $AUC_{0\text{-}4h}$ for a MMTT stimulated C-peptide concentration-time curve at week 54 relative to baseline: $AUC_{0\text{-}4h,\ C\text{-}peptide,\ 54w}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$.

More specifically, $AUC_{0\text{-}4h,\ C\text{-}peptide,\ t}$ at time 't' will be determined as the area from 0 to 4 hours under the C-peptide concentration profile after a MMTT using the trapezoidal method based on observed concentration values and actual measurement times. If the MMTT is stopped before 4 hours due to hyperglycaemia or hypoglycaemia, the last measured C-peptide concentration will be carried forward for calculation of the primary endpoint. If the MMTT is stopped before 4 hours it will most likely be due to hyperglycaemia as hypoglycaemia is not expected when a high amount of carbohydrates are ingested. Using LOCF will result in an overestimated AUC since the C-peptide response is expected to be at the maximum level during hyperglycaemia. Furthermore, the risk of hyperglycaemia during MMTT will be higher in the placebo group if the active treatments have an effect on beta-cell preservation. Thus, LOCF is considered as a conservative approach.

The $AUC_{0\text{-}4h}$ for MMTT stimulated C-peptide is derived at baseline and at 12, 24, 36, and 54 weeks and is denoted $AUC_{0\text{-}4h,\ C\text{-}peptide,\ t}$, where t is the time of the assessment. Thus, t=54 weeks corresponds to the primary endpoint.

Let y_{it} denote the value of $AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta t}$ evaluated relative to baseline at time *t* for subject *i*, i.e.

$$y_{it} = AUC_{0\text{-}4h,\ C\text{-}peptide,\Delta t} = AUC_{0\text{-}4h,\ C\text{-}peptide,\ t}/AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline}$$

y_{it} will be analysed using a multiplicative repeated measurements model including all available assessments over time with treatment, stratum and sex as factors and $\ln(AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline})$ and age at baseline as covariates (see Table 17–2). The interaction between all variables and visit (week) will be included in the model.

Table 17–2 Model terms for the statistical model for the primary endpoint

Model term	Description
$\ln(y_{it})$	dependent variable, subject i, time t
$\ln(AUC_{0\text{-}4h,\ C\text{-}peptide,\ baseline})$	fixed effect covariate with a visit dependent coefficient
Visit	fixed effect factor corresponding to time t=12w, 24w, 36w, 54w
Treatment	fixed effect interaction term between treatment and visit (i.e. the treatment effect is not assumed the same for all visits), with treatment as a factor with 4 levels: NNC0114-0006 in combination with liraglutide, NNC0114-0006, liraglutide and placebo
Stratum	fixed effect interaction term between stratum and visit, with stratum as a factor with two levels according to non-fasting C-peptide measurement at screening: 0.2-0.6 nmol/l and >0.6 nmol/l
Age	fixed effect covariate with a visit dependent coefficient
Sex	fixed effect interaction term between sex and visit

The variance-covariance matrix for the repeated measurements for each subject will be unstructured and may depend on treatment, if an assumption of equal variance-covariance matrix between treatments turns out not to be reasonable.

From the model, least square means (LSMeans) for each treatment group at selected time points, including week 54 will be estimated, and mean differences between treatment groups in log-transformed $AUC_{0\text{-}4h,\ C\text{-}peptide,At}$ at these time points will be estimated. These estimates will be back-transformed to the original scale to represent treatment (geometric) means and treatment (geometric mean) ratios with 95% CIs.

The primary endpoint will be summarised using descriptive statistics and presented graphically.

Sensitivity analyses

The following sensitivity analyses will be made

- To assess the impact of the subjects for whom the MMTT is stopped before 4 hours due to hyperglycaemia or hypoglycaemia, a sensitivity analysis will be performed excluding these subjects
- An analysis using last observation carried forward (LOCF) of the primary endpoint. The analysis will be made using a normal linear regression model for the log-transformed primary endpoint with treatment, stratum and sex as fixed factors and age and baseline value (log-transformed) as covariates
- An analysis based on the subjects completing the treatment period (i.e. completing the visit at week 54). The analysis will be made using a normal linear regression model for the log-

transformed primary endpoint with treatment, stratum and sex as fixed factors and age and baseline value (log-transformed) as covariates

Exploratory analyses

An exploratory analysis will be made to investigate a potential interaction between treatment and stratum for the primary endpoint. The analysis will be made by adding the interaction between stratum, treatment and visit as a factor in the mixed model for repeated measurements (MMRM) described for the primary endpoint. The treatment means and the treatment ratios at selected time points including week 54 will be presented with 95% CIs for each stratum separately.

The effect of the biomarkers at baseline and high resolution HLA (class I) genotyping on the primary endpoint will be explored one variable at a time.

For continuous variables, the analysis will be made by adding the biomarker at baseline (log-transformed) as a fixed effect covariate with a coefficient that depends on visit and treatment to the MMRM described for the primary endpoint. The estimated effect of the variable at selected time points including week 54 will be presented with a 95% CI for each treatment.

For categorical variables, the analysis will be made by adding a fixed effect interaction term between the variable, treatment and visit to the MMRM described for the primary endpoint. The treatment means and the treatment ratios at selected time points including week 54 with 95% CIs will be presented for each category of the variable.

An exploratory analysis will be made to investigate a potential effect of the concentration of liraglutide on the primary endpoint using data from the two groups of subjects treated with liraglutide. This analysis will be made by adding the log-transformed concentration of liraglutide measured on the visit corresponding to the last MMTT as a covariate in the analysis using LOCF for the primary endpoint.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Efficacy endpoints

Endpoints derived from the mixed meal tolerance test

The endpoints based on the mixed meal tolerance test will be derived from the individual C-peptide concentration-time curves and from the individual plasma glucose concentration-time curves. The AUC endpoints will be derived using the same approach as described for the primary endpoint. The C_{max} endpoints will be derived as the ratio between the C_{max} at the relevant time points.

The endpoints will be analysed using a similar model as applied for the primary endpoint except that the corresponding value at baseline will be included as a covariate.

The endpoints will be summarised using descriptive statistics and presented graphically. The C-peptide concentration-time curves and the plasma glucose concentration-time curves will be presented graphically.

Insulin dose

The total daily insulin dose will be derived as the average of the doses reported on the three days prior to the visit.

The endpoints will be analysed using a similar model as applied for the primary endpoint except that the dose at baseline will be included as a covariate. The analysis will be made on the original scale (i.e. without log-transformation). Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

The endpoints will be summarised using descriptive statistics and presented graphically.

Number of insulin injections

The number of insulin injections will be derived as the average of the reported number on the three days prior to the visit. The endpoints will be summarised using descriptive statistics.

HbA_{1c}, FPG, fasting C-peptide and fasting glucagon

The HbA_{1c} and FPG endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale (i.e. without the log-transformation). Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

The fasting C-peptide and fasting glucagon endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate. The values will be log-transformed prior to analysis, i.e. the change will be calculated for the log-transformed data and the log-transformed value at baseline will be included as a covariate.

The endpoints will be summarised using descriptive statistics and presented graphically.

Self-measured plasma glucose profiles

The 7-point SMPG profile will include a pre-meal measurement and a measurements 90 minutes after start of meal for breakfast lunch and dinner as well a measurement at bedtime.

The 4-point SMPG profile will be used for titration of the insulin dose and will include a pre-meal measurement for breakfast, lunch and dinner and a measurement at bedtime.

7-point profiles at week 54 and week 80

A normal linear mixed effect model will be fitted to the 7-point SMPG profile data at week 54. The model will include treatment, time-point, the interaction between treatment and time-point, sex and stratum as fixed factors, age as a covariate and subject as a random effect. The variance-covariance matrix will be unstructured and may depend on treatment if an assumption of equal variance-covariance matrix between treatments turn out not to be reasonable. From this model the treatment differences at each time-point will be estimated and explored.

The same analysis will be made using the 7-point SMPG profile data at week 80.

The 7-point SMPG profiles will be summarised using descriptive statistics and presented graphically.

Change in prandial increment and change in mean of 7-point profile

The prandial increment at a meal will be calculated as the post-meal measurement minus the pre-meal measurement. The prandial increment will be calculated for breakfast, lunch and dinner separately. The average over the three meals will also be calculated. The mean of the 7-point SMPG profile will be calculated as the mean of all 7 points.

The endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

The endpoints will be summarised using descriptive statistics and presented graphically.

Before breakfast SMPG

The within-subject variability will be evaluated using the before breakfast measurements from 4-point SMPG profiles at week 54 and week 80.

A normal liner mixed effect model will be fitted to the before breakfast SMPG values at week 54. The model will include treatment, sex and stratum as fixed factors, age as a covariate and subject as a random effect. The model will assume independent within- and between-subject error variances depending on treatment. The within-subject variance will be presented for each treatment with the 95% CI. The 95% CI will be calculated using the delta method.

The same analysis will be made for the before breakfast SMPG values at week 80.

PRO endpoints

Data collected with the PRO questionnaires (SF-36v2, Experience of Treatment Benefits and Barriers, and DTSQ (status)) will be scored according to the instruments' respective scoring algorithms into the following endpoints (domains)

- For Experience of Treatment Benefits and Barriers:
  - 'Perceived benefits'
  - 'Perceived barriers'
- For Diabetes Treatment Satisfaction Questionnaire (status):
  - 'Treatment satisfaction'
  - 'Perceived frequency of hypoglycaemia'
  - 'Perceived frequency of hyperglycaemia'
- For SF-36v2:
  - 'Physical Component Summary' score
  - 'Mental Component Summary' score
  - 'Physical functioning'
  - 'Role-physical'
  - 'Bodily pain'
  - 'General health'
  - 'Vitality'
  - 'Social functioning'
  - 'Role-emotional'
  - 'Mental health'

The PRO endpoints will be summarised using descriptive statistics.

Biomarker endpoints

The biomarker endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs. If the model assumptions are not fulfilled then transformations of the data will be considered, e.g. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

The biomarker endpoints will be summarised using descriptive statistics and presented graphically.

17.4.1.2 Safety endpoints

Adverse events, DKA episodes and infusion/injection site reactions

All adverse events (including DKA episodes and infusion/injection site reactions) will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). An adverse

event will be defined as treatment emergent if the onset of the adverse event occurs on or after the first day of trial product administration.

Treatment emergent adverse events will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. Separate summaries will be made for treatment emergent DKA episodes and for treatment emergent infusion/injection site reactions. The summaries will be made for the treatment period, for the observation period and for the entire trial period.

Additional information will be recorded on special eCRF pages for selected adverse events. This information will be listed.

All adverse events will be listed and separate listings will be made for DKA episodes and infusion/injection site reactions.

Hyperglycaemic episodes

Hyperglycaemic episodes will be defined as treatment emergent if the onset occurs on or after the first day of trial product administration.

The number of treatment emergent hyperglycaemic episodes will be summarised by treatment. The summaries will be made for the treatment period, for the observation period and for the entire trial period.

Hypoglycaemic episodes

Classification of Hypoglycaemia:

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset of the episode occurs on or after the first day of trial product administration, and no later than 1 day after the date of last contact.

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

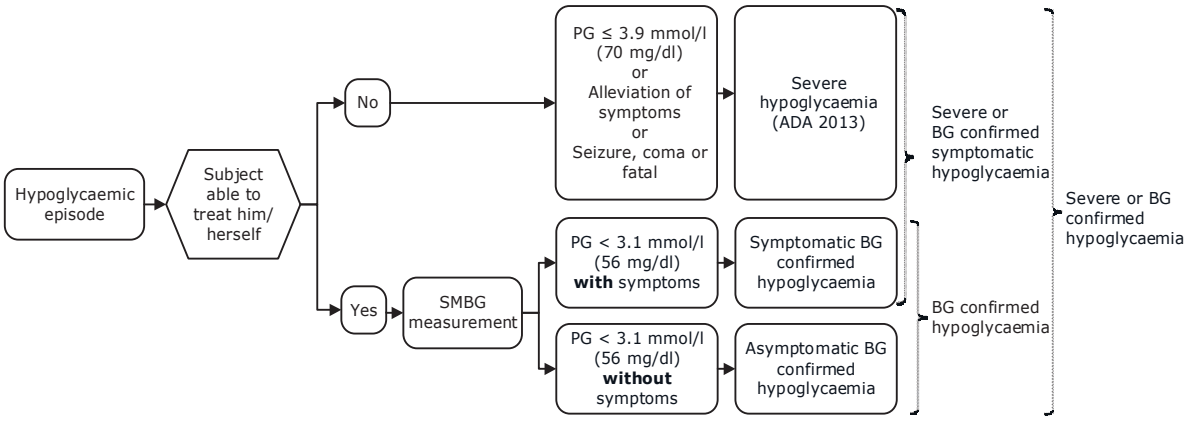
Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–1) and the ADA classification of hypoglycaemia (see Figure 17–2).

Novo Nordisk classification of hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/l (56 mg/dl) [42].Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of blood glucose (BG) confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–1) in addition to the ADA classification:

- Severe hypoglycaemia according to the ADA classification [33].
- Symptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/l (56 mg/dl) **with** symptoms consistent with hypoglycaemia.
- Asymptomatic BG confirmed hypoglycaemia: An episode that is BG confirmed by plasma glucose value <3.1 mmol/l (56 mg/dl) **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification [33] or BG confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl) **with** symptoms consistent with hypoglycaemia.
- BG confirmed hypoglycaemia: An episode that is BG confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl) **with** or **without** symptoms consistent with hypoglycaemia.
- Severe or BG confirmed hypoglycaemia: An episode that is severe according to the ADA classification [33] or BG confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl) **with** or **without** symptoms consistent with hypoglycaemia.

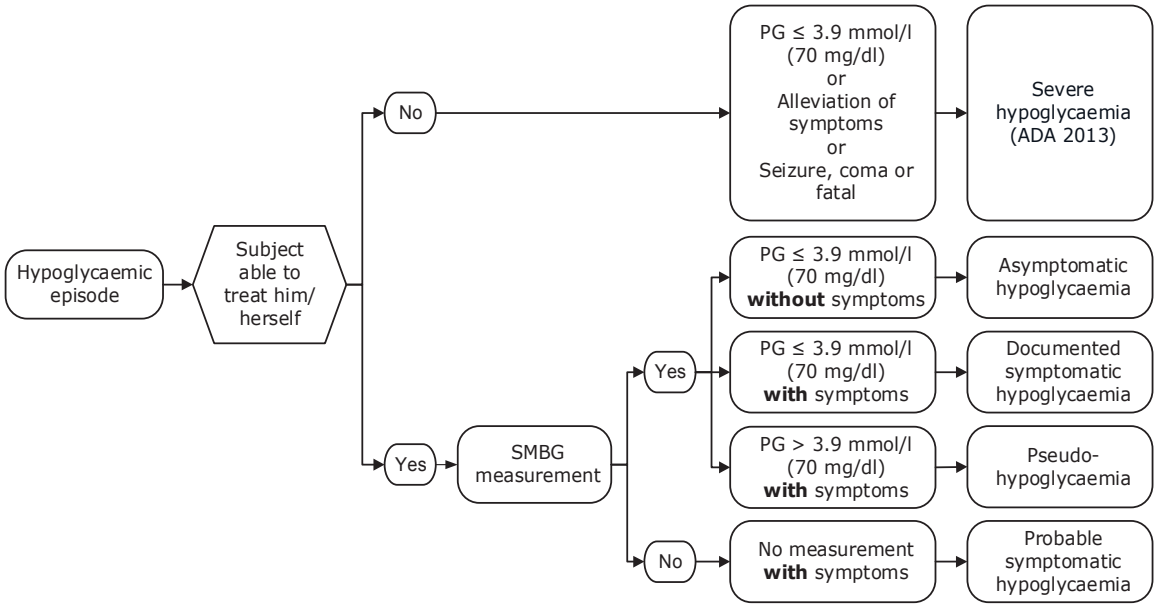


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–1 Novo Nordisk classification of hypoglycaemia

ADA classification [33] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/l (70 mg/dl).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/l (70 mg/dl).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/l (70 mg/dl) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/l (70 mg/dl).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–2 ADA classification of hypoglycaemia

Analysis of hypoglycaemic episodes

The number of treatment emergent hypoglycaemic episodes will be summarised by treatment. Separate summaries will be made for the Novo Nordisk and for the ADA classifications and for nocturnal episodes. The summaries will be made for the treatment period, for the observation period and for the entire trial period.

The total number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binominal regression model with a log link function, and the logarithm of the exposure time as an offset. The model will include treatment, stratum and sex as factors and age as a covariate. The treatment ratio will be estimated and the corresponding two-sided 95% CI will be calculated. The analysis will be made for the treatment period, for the observation period and for the entire trial period.

The total number of treatment emergent nocturnal severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using the same model as above. The analysis will be made for the treatment period, for the observation period and for the entire trial period.

To the extent that data allows, additional analyses may be performed for the other classes of hypoglycaemic episodes using the same model as described above.

Sensitivity analyses will be made (for each analysed class of hypoglycaemia) comparing number and individual rates of hypoglycaemic episodes, respectively, using the Wilcoxon-Mann-Whitney method. This will be made for all different pairs of treatments.

Body weight

The body weight endpoints will be analysed using a similar model as described for the primary endpoint except that the body weight at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

Body weight endpoints will be summarised using descriptive statistics and presented graphically.

Diabetes complications, eye examination and physical examination

The endpoints for eGFR will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs. If the model assumptions are not fulfilled then transformations of the data will be considered, e.g. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

The endpoints will be summarised. The endpoints for eGFR will be presented graphically.

Laboratory safety variables (haematology, biochemistry, coagulation, lipids, IgE, urine dipsticks, cytokine panel and hormones)

The laboratory safety variables will be flagged if outside the reference range and abnormal values will be listed.

The endpoints for the laboratory safety variables will be summarised and the numerical variables will be presented graphically.

The endpoints for amylase and lipase will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate. The individual values will be log-transformed prior to analysis, i.e. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

The endpoints for TSH, IgE and cytokine panel will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs. If the model assumptions are not fulfilled then transformations of the data will be considered, e.g. the change will be calculated on the log-transformed data and the log-transformed value at baseline will be included as a covariate.

Vital signs and ECG

The systolic blood pressure, diastolic blood pressure and pulse endpoints will be analysed using a similar model as described for the primary endpoint except that the corresponding value at baseline will be included as a covariate and the analysis will be made on the original scale. Consequently, treatment means (LSMeans) and treatment differences will be presented with 95% CIs.

The endpoints will be summarised. The numerical endpoints will be presented graphically.

Anti-NNC0114-0006 antibodies and anti-liraglutide antibodies

The endpoints will be summarised and presented graphically.

17.4.1.3 Pharmacokinetic endpoints

The PK endpoints described in Table 17–3 will be derived from the individual NNC0114-0006 concentration-time curves after the first dose and after the last dose of NNC0114-0006.

Furthermore, the trough concentration prior to dosing and the concentration 1 hour after dosing will be determined for NNC0114-0006 and the liraglutide concentration will be determined for liraglutide at the visits specified in Section 2.

Table 17–3 Definition and calculation of PK endpoints

Endpoint	Description	Calculation
$AUC_{\tau, NNC0114-0006}$	Area under the NNC0114-0006 concentration-time curve over a dosing interval at steady state (SS) (defined as after last dose)	$AUC_{\tau, NNC0114-0006}$ will be derived as the area under the concentration-time curve using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 6 weeks (after the last dose). Missing values will be imputed using linear interpolation, possibly using measurements after 6 weeks. If the end time of the interval (i.e. 6 weeks) is after the time of the last quantifiable concentration, t_z, and the terminal rate constant, λ_z, can be determined then $AUC_{\tau, NNC0114-0006}$ will be derived as the sum of $AUC_{0-tz, NNC0114-0006}$ and $AUC_{tz-6\ weeks, NNC0114-0006,}$ where $AUC_{tz-6\ weeks,NNC0114-0006}$ will be approximated using estimated values from the linear regression model applied for estimation of λ_z. If λ_z cannot be determined, then $AUC_{0-tz, NNC0114-0006}$ will be used instead of $AUC_{\tau, NNC0114-0006}$.

Endpoint	Description	Calculation
λ_z	Terminal rate constant for NNC0114-0006 (this is not an endpoint but it is used for calculation of some endpoints)	The terminal rate constant λ_z will be determined through linear regression with the logarithm to concentration as the response variable and actual measurement time as the explanatory variable. Valid observations from the terminal part of the curve, which is approximately linear, will be used for the determination.
$t_{½}$	Terminal serum half-life after last dose of NNC0114-0006	Calculated as $\log(2)/\lambda_z$
$V_{ss,\ NNC0114-0006}$	The apparent volume of distribution of NNC0114-0006 at steady-state	Calculated as $MRT_{NNC0114-0006} * CL_{SS,\ NNC0114-0006}$
$CL_{ss,\ NNC0114-0006}$	Clearance of NNC0114-0006 at steady state	Calculated as dose/$AUC_{\tau,\ NNC0114-0006}$
$MRT_{NNC0114-0006}$	The mean residence time of NNC0114-0006	Calculated as $MRT = \frac{AUMC_\tau + \tau * AUC_{\tau-\infty}}{AUC_\tau}$ where $AUC_{\tau-\infty} = AUC_{0-tz} + AUC_{tz-\infty} - AUC_{0-\tau}$ and $AUMC_{0-\tau} = \sum_{i=2}^{n}(t_i - t_{i-1})(t_i C_i + t_{i-1} C_{i-1})$
$R_{A,AUC,\ NNC0114-0006}$	Accumulation ratio of NNC114-0006 defined as $AUC_{48-54\ weeks}/AUC_{0-6\ weeks}$	$AUC_{48-56\ weeks}$ will be calculated as described for $AUC_{\tau,\ NNC0114-0006}$. $AUC_{0-6\ weeks}$ will be calculated using a similar approach except that extrapolation using λ_z will not be made

The PK endpoints will be summarised using descriptive statistics. The PK data will be presented graphically.

17.5 Interim analysis

No formal interim analysis has been planned.

17.6 Pharmacokinetic and/or pharmacodynamic modelling

PK data for anti-IL-21, PD data for C peptide (reflecting beta cell function) from the Meal Tolerance Tests, and other pharmacodynamic markers may be used for population PK and PK/PD modelling if relevant to support dose selection and trial design of potential future trials. This exploratory analysis will not be reported in the Clinical Trial Report.

17.7 Health economics and/or patient reported outcomes

Please refer to Section 17.4.1.1 for a description of the PRO endpoints. The results will be included in the clinical trial report.

18 Ethics

18.1 Benefit-risk assessment of the trial

NNC0114-0006 has been developed for treatment of chronic inflammatory and autoimmune diseases. A total of approximately 158 healthy subjects and subjects with RA, SLE, and Crohn's Disease have received active treatment, either as single doses or multiple doses (up to 4 doses in total). The safety profile generated by non-clinical safety studies and the clinical trials conducted have not raised any safety concerns. For the completed trials in subjects with RA (including at total of 114 subjects) and in subjects with Crohn's Disease (including a total 53 subjects), a tendency towards an increased risk of mild infections when treated with NNC0114-0006 compared to placebo was observed. No pattern in time to onset or duration of these events has been identified; however a potential risk of mild infections in relation to treatment with NNC0114-0006 is present.

Theoretical risks when treating with NNC0114-0006 include immunogenicity, local infusion reactions, hypersensitivity reactions and AEs associated with the inhibition of IL-21-mediated signalling such as other (severe and opportunistic) infections and malignancies. As with other anti-inflammatory therapies, suppression of the immune system may carry an inherent risk of compromising host immunity. In the non-clinical safety studies in cynomolgus monkeys, a decreased antibody response to immunisation with specific antigens has been observed in accordance with the expected pharmacology of NNC0114-0006. Therefore a decreased response to vaccinations cannot be excluded. In alignment with labels of other immune-modulatory compounds, administrations of live vaccines are excluded during clinical trials.

The concept of combining immunotherapy with another agent was recently tested in the NOD recent onset diabetes model using a combination regimen of anti-IL-21 (NNC0114-0008) and liraglutide. These experiments used a two-week course of 5 injections at 25 mg/kg of NNC0114-0008 combined with daily liraglutide administration. In the spontaneous NOD mouse model, the first experiment resulted in potent remission from hyperglycaemia in established T1DM, with statistically better efficacy as compared to each respective monotherapy. In a repeat study, however, the efficacy of NNC0114-0008 monotherapy was equivalent to the combination therapy, and an additive effect could not be demonstrated. Finally, in the induced RIP-LCMV mouse model the combination treatment outperformed both monotherapies. This suggest that combination treatment with liraglutide and NNC0114-006 may preserve beta-cell functions in humans.

The safety profile of liraglutide is well characterised for use in T2DM, for which indication it has been approved and marketed as Victoza®. Liraglutide is generally well tolerated by both healthy subjects, obese subjects and subjects with T2DM. AEs related to the gastrointestinal organ system were found to be the most common, with nausea being the most frequently reported AE in subjects treated with liraglutide. In the clinical development program 42% had one or more gastrointestinal related event. The gastrointestinal AEs were most frequent in the early part of the treatment period.

Episodes of hypoglycaemia were infrequent due to the glucose-dependent mode-of-action of liraglutide. There have been few reported events of acute pancreatitis. Subjects should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, liraglutide, and other potentially suspect medicinal products should be discontinued. If the diagnosis of pancreatitis is confirmed the subject must be withdrawn as described in Section 6.6. If a pancreatitis can be excluded all previously discontinued treatments can be re-initiated.

Novo Nordisk is currently investigating the safety and potential benefits of liraglutide as adjunct treatment to insulin in subjects with established T1DM. The emerging safety data generated during these ongoing clinical trials with liraglutide in T1DM is being reviewed on an ongoing basis.

Relevant precautions have been implemented in the design and planned conduct of this trial in order to minimise the risks. Patient safety will be monitored closely by recording adverse events, measuring safety laboratory parameters, local tolerability and antibody development against NNC0114-0006 and liraglutide. Adverse events will be evaluated with respect to seriousness, severity, time of onset, duration, frequency and outcome, and all safety data generated during the present trial will be reviewed on an ongoing basis.

There will be benefits from a public health point of view and from an individual point of view.

Public health point benefits:
Despite great advances in diabetes care, T1DM is still associated with considerable morbidity and premature mortality. T1DM develops when the immune system destroys the insulin-producing pancreatic beta-cells. NNC0114-0006 in combination with liraglutide administered to subjects with T1DM is expected to provide a new, attractive treatment option for newly diagnosed T1DM subjects aiming at sustained preservation of endogenous insulin production. Patient benefits could consequently include a decrease or elimination of the requirement for administration of exogenous insulin and a reduction of both short and long term diabetes complications while improving the quality of life.

Individual benefits:
Subjects will get a state-of-art metabolic control during the trial. Subjects will be trained in diabetes self-care including carbohydrate counting before and around randomisation and whenever needed in order to achieve the most optimal diabetes control. During the trial subjects will receive insulin treatment in order to achieve a metabolic control according to the insulin titration guideline.

It is concluded that the potential benefits from participating in the trial outweighs the potential risks. The safety profiles of NNC0114-0008 and liraglutide generated from the non-clinical studies and clinical trials have not revealed any safety issues that should prohibit administration of either NNC0114-0006 or liraglutide to subjects with early onset ofT1DM. The results from this trial are

assumed to contribute to the development of new improved treatments for subjects with newly diagnosed T1DM.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP [2] and the requirements in the Declaration of Helsinki [3].

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

If the subject agrees to have blood samples taken for genotyping (see Section 8.5.3.1) a separate signed informed consent form will be obtained from the subject.

Furthermore if the subject agrees to have a blood sample taken for long term storage of human samples (see Section 8.5.3.2) and/or to have some of the blood stored from the T-cell profiling islet-specific auto reactive CD8+ T-cells samples (see Section 8.5.1.3) a separate signed informed consent form will be obtained from the subject.

In case a subject undergoes a thyroidectomy, a separate informed consent will be obtained for collection of a blood sample for genetic testing (see Section 8.4.2.2)

In case of abnormal outcome of a pregnancy a separate informed consent will be obtained (see Section 12.5.1 and 12.5.2.

18.3 Data handling

If the subject is withdrawn from the trial or lost to follow up, then the subject's data will be handled as follows:

- Data already collected and data collected at the end-of-trial visit and the last safety follow-up visit (Visit 90) will be retained by Novo Nordisk, entered into the database and used for the trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subject during trial

The site will be offered a communication package to the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject may receive letters or other material during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the clinical database.

Documentation on protocol deviations must be kept in the investigator's trial master file and sponsor trial master file.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochures
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol, each investigator agrees to comply fully with ICH GCP [2], applicable regulatory requirements and the Declaration of Helsinki [3].

By signing the protocol, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications [43].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure [27].

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors [43] (ICMJE) (sometimes referred to as the Vancouver Criteria).

At the end of the trial, one or more publications (abstracts, posters manuscripts) will be prepared for submission to scientific congresses and peer-reviewed journals in collaboration between Novo Nordisk and investigator(s) appointed by Novo Nordisk. These investigator(s) must meet the ICMJE authorship criteria to be named authors on publications.

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation and human biospecimens

24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of biospecimens

The trial will involve collection of biospecimens to be stored in central archives. Blood samples for genotyping (see Sections 8.5.3.1), long term storage (see Section 8.5.3.2) and PBMCs (see Section 8.5.1.3) will be stored for up to 15 years for potential future assessments. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of trial products may evolve during the conduct of the trial, the analyses of the stored biospecimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. After the end of trial the central laboratory will arrange the transfer of samples to an appointed storage facility. Novo Nordisk will have access to the samples.

None of the data will be identified by name. Blood samples will be identified only by a subject number, a visit number and a trial identification number. The trial staff is responsible for

maintaining a code list which links to the subject number. The code list must be kept for at least 15 years. The code list may be reviewed by Novo Nordisk staff including auditors or representatives from regulatory authorities, but no copies will be made of this list.

Potential consequences for the subject and their relatives

The results of the potential additional genotyping (other than HLA) and of potential analysis of long term storage samples and PBMCs will not have any medical consequences for the subjects or their relatives and the results will be reported in separate documents, hence will therefore not be included in the CTR.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochures, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with:

For Austria: Arzneimittelgesetz (BGBL Nr. 185/1983) last amended with BGBl. I Nr. 48/2013

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Appendix A: Insulin Titration Guideline

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

Trial phase: 2

Table of Contents

1 Introduction

The goal of insulin therapy is to achieve near normoglycaemia, i.e. to reach a pre-defined HbA_{1c} level with a low rate of hypoglycaemic episodes and as little weight gain as possible. Several trials have shown that this is difficult to achieve, unless plasma glucose (PG) values are intensively monitored and the insulin dose(s) frequently adjusted [1-6].

To ensure treatment uniformity between the sites, as well as to ensure that subjects receive an optimal treatment, titration algorithms have been developed specifying recommended dose adjustments at different PG levels.

It is recognised that treatments differ between different regions and countries. Likewise, specific titration guidelines may not be applicable in certain clinical situations. It is important that other information, such as symptoms of hypo/hyperglycaemia, previous response to dose adjustments, other glucose measurements and other indicators of the subject's level of glycaemic control, is taken into consideration when decisions on dosing are made. The investigator should always use his clinical judgement to avoid safety hazards. The investigator is responsible for the treatment of the subjects and can therefore overrule the guideline.

To optimise and maintain glycaemic control, the investigator should, throughout the trial be at least in weekly contact with the subjects to assist the subjects in adjusting insulin doses and to ensure the subject's welfare.

2 Treatment regimens

There are no maximum or minimum insulin doses defined (see section 5.3.3 of the protocol).

2.1 Injection area

The insulin types used in this trial should be injected subcutaneously in accordance with local labelling. The chosen region should be the same throughout the trial. Rotation of injection sites within a given region is recommended.

2.2 Time of injection

Bolus insulin (regular human insulin or fast-acting insulin analogues) should be administered with the main meals (2-4 times daily) according to local labelling.

Basal insulin, neutral protamine Hagedorn (NPH) insulin or long-acting insulin analogues, should be administered once or twice daily in accordance with local labelling. Please note that insulin glargine and insulin degludec should only be administered once daily.

3 Initiation and titration

Please note the request for insulin reduction during the liraglutide/placebo dose escalation period described in section 3.5.

3.1 Insulin at trial initiation

All subjects will continue their current insulin regimen after randomisation.

3.2 Titration of basal insulin (not applicable on liraglutide/placebo initiation and escalation days)

After the liraglutide/placebo dose initiation and escalation days, basal insulin will be adjusted weekly by the investigator in connection with the scheduled visit/phone contacts.

For subjects receiving basal insulin once daily the dose should be *increased* based on the mean pre-breakfast SMPG values measured on the day of the contact and 2 days prior to the contact in accordance with Table 1. If one of the SMPG values < 4.0 mmol/l (< 71 mg/dl) the dose should be reduced according to Table 2.

For subjects receiving basal insulin twice daily the evening dose should be adjusted according to pre-breakfast SMPG values measured on the day of the contact and 2 days prior to the contact and the morning dose should be adjusted according to the pre-dinner SMPG values measured 3 days prior to the contact according to

Table 1 and Table 2.

Table 1 Basal insulin increase

Mean pre-breakfast/pre-dinner SMPG		Dose adjustment
mmol/l	mg/dl	U
4.0 – 6.0	71 – 108	No adjustment
6.1 – 10.0	109 – 180	+ 2
10.1 – 15.0	181 – 270	+ 4
> 15.0	> 270	+ 6

Table 2 Basal insulin reduction

Lowest pre-breakfast/pre-dinner SMPG		Dose adjustment
mmol/l	mg/dl	U
3.1 – 3.9	56 – 70	- 2
<3.1	< 56	- 4

3.3 Initiation of a second basal insulin dose during the trial

It is recommended that basal insulin is not changed from a once daily to a twice daily regimen during the liraglutide dose escalation period. Thereafter a second dose can be initiated at the investigator's discretion except for insulin glargine and insulin degludec which should only be dosed once daily. Adjustment of the second dose should be done in accordance with the principles described in section 3.2.

3.4 Titration of bolus insulin (not applicable on liraglutide/placebo initiation and escalation days)

Bolus insulin (mealtime) should be adjusted according to section 3.4.1, if the subject follows the principles of flexible insulin therapy and according to section 3.4.2, if the subject follows the bolus algorithm. It is left to the discretion of the investigator to decide which method the subject uses. Furthermore, the subjects are allowed to change the method at any time point during the trial if agreed with the investigator.

3.4.1 Carbohydrate counting - subjects following principles of flexible bolus insulin therapy

Bolus insulin should be dosed in accordance with principles of flexible dosing whereby the meal carbohydrate content and pre-prandial plasma glucose value are used to determine bolus insulin dose.

Using this method, bolus insulin dose adjustment is conducted several times daily in accordance with the Insulin:Carbohydrate (I:Carb) ratio and the plasma glucose correction factor (sensitivity factor). Bolus insulin dose consists of meal bolus to cover for carbohydrates consumed in the meal and, if required, a correction dose (to supplement or reduce the dose based on the difference between the SMPG and the target). This method is applicable to subjects with prior hands-on experience using this method of determining bolus insulin doses. It is the responsibility of the investigator to ensure that the subject is comfortable with this method. If more training is needed this should be carried out according to local practice.

The I:Carb ratio expresses the amount of carbohydrate (in grams) for which 1U of bolus insulin would effectively minimise postprandial plasma glucose excursions. The plasma glucose correction

factor (sensitivity factor) expresses the expected reduction in plasma glucose per 1U of bolus insulin. The I:Carb ratio and the correction factor (sensitivity factor) per type of meal should be recorded at trial start and should, if needed, be adjusted at the discretion of the investigator during the weekly contacts based on the reviewed SMPGs.

In this trial the target pre-prandial plasma glucose range is 71−108 mg/dl (4.0−6.0 mmol/l).

In the following, an example on how to cover a subject's prandial insulin dose is provided. In case of hypoglycaemic episodes, the dose will be reduced at the investigator's discretion.

Example 1 – Carbohydrate coverage of a meal and plasma glucose correction dose:

A subject has pre-prandial plasma glucose of 180 mg/dL (10.0 mmol/l) and intends to eat a meal containing 60 g of carbohydrates. The I:Carb ratio has been estimated to 1U:10g.

The meal coverage dose is calculated as follows:

Total carbohydrate in meal * I:Carb ratio = 60 g * (1U/10g) = 6U.

The plasma glucose correction factor (sensitivity factor) has been estimated to be 36 mg/dl per 1U (2.0 mmol/l per 1U). The pre-prandial plasma glucose target range is 71-108 mg/dl (4.0-6.0 mmol/l). The subject was advised to correct to the target plasma glucose of 108 mg/dl (6.0 mmol/l) at this meal.

The correction dose can be calculated as follows:

(Pre-prandial plasma glucose – target plasma glucose) ÷ plasma glucose correction factor = (180 mg/dl – 108 mg/dl) ÷ 36 mg/dl/U = 2U or (10.0 mmol/l – 6.0 mmol/l) ÷ 2.0 mmol/l/U = 2U

Thus this subject needs 8U of rapid-acting insulin to cover for the meal and correct for hyperglycaemia before the meal.

3.4.2 Bolus dosing - subjects using the algorithm

Bolus titration should take place once weekly in relation to the visits/phone contacts. Bolus insulin will be adjusted according to Table 3.

- Breakfast dose will be adjusted according to the pre-lunch SMPG values obtained the previous 3-4 days
- Lunch dose will be adjusted according to the pre-dinner SMPG values obtained the previous 3-4 days
- Dinner dose will be adjusted according to the bedtime SMPG values obtained the previous 3-4 days.

Table 3 Bolus insulin dose adjustment

Pre-prandial/bedtime SMPG		Dose adjustment	Rules for dose adjustment
mmol/l	mg/dl	U	
< 4.0	< 71	- 1	≥ 1 SMPG below target
4.0 – 6.0	71 -108	0	0-1 SMPG above target No SMPGs below target
> 6.0	> 108	+ 1	≥ 2 SMPGs above target No SMPGs below target

Additional bolus dosing is allowed at the investigator's recommendation. These additional doses will be documented in the diary.

3.5 Insulin reduction on the days of liraglutide/placebo initiation and dose escalations

When liraglutide/placebo is initiated, the total daily insulin dose should be reduced by 25% for a minimum of 24 hours after the initiation of liraglutide/ liraglutide placebo. Thereafter the doses should be adjusted according sections 3.2 and 3.3. On the dose escalation days the total daily insulin dose should be reduced by 10% on each occasion for a minimum of 24 hours after the escalation of liraglutide/ liraglutide placebo dose and thereafter adjusted according to sections 3.2 and 3.4.

3.6 Deviations from the algorithm

It is recommended that the algorithm is followed. However, it is also important that the decision to adjust the insulin doses are based on all relevant information as described in Section 1. A reason for deviating from the algorithm should be documented.

4 Data collection

The following data should be available for Novo Nordisk's Insulin Titration Group for all subjects within 24 hours (on weekdays) after a site visit/phone contact:

- SMPG values
- Carbohydrate intake per meal (CHO-counting subjects only)
- Date and insulin doses taken (daily)
- New insulin doses prescribed after titration
- Reason for deviation between the recommended and the prescribed basal insulin dose
- Reason for deviation between the recommended and actual bolus insulin doses
- Hypoglycaemic episodes

Furthermore the investigator should provide the following from the CHO-counting subjects:

- I:CHO ratio per meal (initial and any changes)
- Plasma glucose correction factor per meal (initial and any changes)

5 Review procedure

Surveillance of titration data will be performed centrally by Novo Nordisk in an unbiased manner. It is important that data regarding hypoglycaemic episodes is entered into the respective system within 24 hours (on weekdays). If delays occur, action cannot be taken in due time before the subject's next site visit/phone contact. The aim is to reduce the time periods in which a subject may receive suboptimal treatment.

The data listed in section 4 will be reviewed by Novo Nordisk within 24 hours (on weekdays). The reviewer may contact the investigator to get clarification regarding the reason for deviation or to request entry of missing data.

When the investigator receives an inquiry, a response should be received at Novo Nordisk within 24 hours (on weekdays).

During the trial HbA_{1c} will be monitored by Novo Nordisk for additional surveillance of the glycaemic control. Novo Nordisk may be in contact with sites (visit or phone contact) to discuss progress in glycaemic control and titration of individual subjects based on SMPGs and HbA_{1c}. This will be done in an unbiased and whenever possible in a blinded manner.

6 References

1 Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008; 51(3):408-416.

2 Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006; 29(6):1269-1274.

3 Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; 28(10):1569-1581.

4 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26(11):3080-3086.

5 Garber AJ, King AB, Del PS, Sreenan S, Balci MK, Munoz-Torres M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825):1498-1507.

6 Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825):1489-1497.

Appendix B:Monitoring of Calcitonin

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

Trial phase: 2

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1 Background

Treatment with GLP-1 receptor agonists has shown to be associated with thyroid C-cell changes in rodents but not in non-human primates. The human relevance of this finding is unknown. However, based on the findings in rodents, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) is currently being performed in clinical trials with liraglutide.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (greater than 100 ng/l) as likely indicative of C-cell neoplasia, the interpretation of values between upper normal range (5.0 and 8.4 ng/l for women and men, respectively) and 100 ng/l can become challenging.

There are several known confounding factors affecting calcitonin levels, namely renal dysfunction, smoking, autoimmune thyroiditis and several drug classes (e.g. proton pump inhibitors, beta-blockers, H_2-blockers and glucocorticoids). Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e. with various co-morbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

2 Calcitonin and C-cell abnormalities - evaluation and follow-up

Subjects with a personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2) or with a screening calcitonin ≥ 50 ng/l will be excluded from the trial.

A blood sample will be drawn at pre-specified trial visits for measurement of calcitonin. In case a subject has an increased calcitonin value ≥ 10 ng/l the algorithm outlined below should be followed. The algorithm applies for all calcitonin values including screening values.

The summary for the rationale for the use of specific calcitonin values to trigger medical evaluation and an overview of the algorithm is provided below:

2.1 CT ≥ 100 ng/l

The subject (even if a screen failure) should immediately be referred to a thyroid specialist for further evaluation and the subject must be withdrawn from the trial if the measurement is during the treatment period of the trial. If the calcitonin level is ≥ 100 ng/l during the observation period the subject should be referred to a thyroid specialist for further evaluation but can remain in the trial.

These values were found in 0.15% of a population with thyroid nodular disease published by Costante et al[1] and in one subject (on active comparator) in the liraglutide development program. For a calcitonin value of ≥100 ng/l, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid. Diagnostic evaluation should consist of thyroid ultrasound, fine needle aspiration of any nodules >1 cm and potentially surgery with neck dissection. Family history of MTC or MEN2 should be evoked and a RET proto-oncogene analysis should be performed.

2.2 CT ≥ 50 and < 100 ng/l

The subject (even if a screen failure) should be referred to a thyroid specialist for further evaluation and the subject must be withdrawn from the trial if the measurement is during the treatment period of the trial. If the calcitonin level is ≥50 and <100 ng/l during the observation period the subject should be referred to a thyroid specialist for further evaluation but can remain in the trial.

These values were found in 0.14% of the population with thyroid nodular disease published by Costante et al[1]. Diagnostic evaluation will likely include ultrasound examination and if available and if there is no contraindication, subjects should undergo a pentagastrin stimulation test. Subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. In the US and other countries where pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery.

2.3 CT ≥ 20 and <50 ng/l

The subject can continue in the trial. Repeat testing of calcitonin at next protocol scheduled calcitonin visit. If the subject is a screen failure or if the value is the last one taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

These values are expected to be found in up to 1% of subjects. Based on data from Costante et al[1], the predictive value of calcitonin levels ≥ 20 and < 50 ng/l for clinically significant C-cell disease begins to fall. However, up to 25% of these subjects had a positive pentagastrin stimulation test. The likelihood of having a medullary carcinoma >1 cm with calcitonin in this range is extremely low.

2.4 CT ≥ 10 and < 20 ng/l

The subject can continue in the trial. Repeat testing of calcitonin at next protocol scheduled calcitonin visit. If the subject is a screen failure or if the value is the last one taken in the trial, the subject should be referred to a thyroid specialist for further evaluation.

Costante et al [1] had 216 (3.7%) patients in this category. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin of 33 ng/l, and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cut-off of CT > 10 ng/l to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT >10 and <20 ng/l to allow conclusions [2,3].

3 References

1 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007; 92(2):450-455.

2 Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C et al. Sporadic hypercalcitoninemia: clinical and therapeutic consequences. Endocr Relat Cancer 2009; 16(1):243-253.

3 Verga U, Ferrero S, Vicentini L, Brambilla T, Cirello V, Muzza M et al. Histopathological and molecular studies in patients with goiter and hypercalcitoninemia: reactive or neoplastic C-cell hyperplasia? Endocr Relat Cancer 2007; 14(2):393-403.

Protocol Amendment

no 1.0
to Protocol, final version 2.0
dated 07 May 2015

Trial ID: NN9828-4150

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

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

Department: ClinOps 1, Insulin, GH & Devices

Table of Contents

1 Introduction including rationale for the protocol amendment

The rationale for this protocol amendment is divided into two categories:

- Updates due to requirement from the Voluntary Harmonisation Procedure (VHP)
- Clarification of minor inconsistencies and clarifications in the protocol and the subject information

1.1 Rationale for protocol updates due to requirements from VHP

6.3 Exclusion criteria 3

Exclusion criteria 3 and 4 have been updated to reflect Clinical Trial Facilitation Group (CTFG) guideline for highly effective contraception

8.5.2.1 Pregnancy test

Updated to reflect requirement for Ireland that female of childbearing potential must have a urinary pregnancy test done at each visit

11.1 Breaking of blinded codes

It has been specified that Investigators are responsible for all trial related medical decisions

1.2 Rational for clarification of minor inconsistencies and clarifications in the protocol and the subject information

The rationale for this part of the amendment is to correct some minor inconsistencies and clarifications in the protocol and subject information.

5.3.3 Insulin treatment

It has been clarified that it is preferred that subjects continue on their pre-trial insulin treatment in order to minimise “noise” from different insulin treatments.

6.2 Inclusion criteria

It has been clarified what is considered as the date of the diagnosis of T1DM

6.3 Exclusion criteria

Exclusion criteria 14 has been updated due to a typing error

Exclusion criteria 39 has been updated to ensure not to exclude subjects that we do not believe have any safety concerns by participating in this trial

6.8 Rationale for the trial population

It has been clarified that the presence of islet-specific auto-antibodies should be confirmed at screening

8.1 Visit procedures

It has been clarified that the investigator should keep a pre-screening log so that the sponsor can react if it is shown that some in and exclusion criteria are resulting in many subjects being unable to participate in the trial.

8.2.6 Diagnosis of diabetes

It has been clarified what is considered the date of the diagnosis of T1DM.

8.3.1 Mixed meal tolerance test

It has been clarified that no special BG meter is required for the mixed meal tolerance test (MMTT) as all blood glucose (BG) meters are validated.

8.4.2.7 Hypoglycaemic episodes

It has been clarified that all hypoglycaemic episodes should be reported in the e-diary by the subject.

8.5.1.3: Biomarker

Lab sampling for Il-21 have been added for additional 3 visits in order to ensure understanding of the synthesis rate of IL-21

9.3 Storage

The storage conditions for in-use conditions has been corrected as there was a minor error in this section

Master SI/IC

The archiving period of the data has been updated as this was incorrect. Furthermore some minor corrections to the schematic overview of the trial have been made.

2 Changes

In this protocol amendment:

Any new text is written in *italics*.

Any text deleted from the protocol is written using ~~strike through~~.

2.1 Changes to protocol due to requirements from VHP

2.1.1 Section 2 Flowchart

Visit 1 to 37 procedures

Foot note:

2. For woman of childbearing potential only. Blood sample at V1. For all subsequent visits a urine stick must only be measured for females of childbearing potential if a menstrual period is missed or as required by law. Austria: Urine-stick pregnancy test will be performed monthly ~~at all visits to the clinic~~. *Ireland: Urine-stick pregnancy test will be performed at all visits to the clinic*.

Visit 38-90 procedures

Foot note:

3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. Austria: Urine-stick pregnancy test will be performed monthly ~~at all visits to the clinic~~. *Ireland: Urine-stick pregnancy test will be performed at all visits to the clinic*

2.1.2 Section 6.3 Exclusion criteria 3

Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential not using *highly effective* ~~adequate~~ contraceptive methods *for the duration of the trial* (*highly effective*~~adequate~~ contraceptive measures, as required by local regulations or practice, *i.e. a measure that results in less than 1% per year failure rate when used consistently and correctly)*

For Ireland: *Highly effective* ~~Adequate~~ contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, IUD or intrauterine system ~~or consistent use of barrier methods together with the use of spermicide~~ ~~*and*~~ *or true* sexual abstinence.*

For Sweden: *Highly effective* ~~Adequate~~ contraceptive measures are: oral (except low-dose gestagen (lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives, intrauterine

device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate).

For United Kingdom: *Only highly effective methods of birth control for the duration of the trial are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly*). *Highly effective* ~~Adequate~~ contraceptive measures are defined as established use of oral, ~~injected or implanted~~ *intravaginal, transdermal combined estrogen and progestogen* hormonal methods of contraception; *oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence*(when in line with preferred and usual lifestyle)*.~~sterilisation, IUD or intrauterine system, or consistent use of barrier methods together with the use of spermicide,and sexual abstinence.~~

**Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods),declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception*

2.1.3 Section 6.3 Exclusion criteria 4

Male of reproductive age who or whose partner(s) is not using *highly effective* ~~adequate~~ contraceptive methods *for the duration of the trial* (*highly effective*~~adequate~~ contraceptive measures, as required by local regulation or practice**,** *i.e. a measure that results in less than 1% per year failure rate when* **used consistently and correctly**)

2.1.4 Section 8.5.2.1 Pregnancy test

A human chorionic gonadotropin serum pregnancy test will be performed at Visit 1 and 63 on all women where childbearing potential has not been ruled out by for example measuring FSH levels. Urine pregnancy test will be performed for females of childbearing potential at any time during the trial if a menstrual period is missed or required by local law. If a subject during a phone contact reports missing menstrual period, an unscheduled visit should be scheduled as soon as possible to have a urine pregnancy test performed. Urine pregnancy kits will be supplied by the central laboratory. The test will be performed at site.

For Austria: A monthly urine pregnancy test is mandatory for female subjects of childbearing potential.

For Ireland: A urine pregnancy test at each visit is mandatory for female subjects of childbearing potential.

2.1.5 Section 11.1 Breaking of blinded codes

The IV/WRS will notify Novo Nordisk (monitor and the Global Safety department) immediately after the code is broken.

The Investigators are responsible for all trial related medical decisions. The code for a particular subject may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. Whenever a code is broken the person breaking the code must print the Code Break Confirmation Notification generated by the IV/WRS, record the reason, and sign and date the document. When the code is broken, the treatment allocation will be accessible to the investigator and the Novo Nordisk Global Safety department. If IV/WRS is not accessible at the time of code break the IV/WRS helpdesk should be contacted. Contact details are listed in Attachment I. If the code has been broken the subject must be withdrawn from the trial and a withdrawal session must be completed in IV/WRS.

2.2 Changes to the protocol due to corrections of minor inconsistencies and clarifications to the protocol and the subject information

2.2.1 Section 1 Summary

The clinical diagnosis of T1DM is defined by the following two paragraphs:

1. One or more of the following:
- HbA1c ≥ 6.5% or
- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or
- a 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test with a glucose load of 75 grams anhydrous glucose in water or
- classical symptoms of hyperglycaemia and a random plasma glucose ≥ 11.1 mmol/l (200 mg/dl)[1]

2. In order to:
    - ensure that the aetiology is autoimmune, the clinical diagnosis needs to be confirmed by the presence of islet-specific auto-antibodies *at screening*
    - exclude T2DM and LADA the subjects should be without severe insulin resistance (i.e. total daily insulin dose larger than 1 U/kg per day at screening).

Key exclusion criteria

9. Known impairment of the immune system, except for T1DM*, coeliac disease, alopecia and vitiligo*

2.2.2 Section 2 Flowchart

Visit 1 to 37 procedures

Extra X has been added to "immunology" visit 4, 5 and 6.

Visit type: C: Clinic, P: Phone contact	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	D-10	0	1D	3D	W1	W2	W2 + 1D	3	4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30
Visit window (days)		± 4				± 1	± 1		± 1	± 1		± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3
Diagnosis of diabetes	x																												
Diabetes treatment history	x																												
Pregnancy test[2]	x																												
Smoking habits	x																												
Family history of diabetes	x																												
Diabetes complications	x																												
Blood sample for genotyping (optional)			x																										
EFFICACY																													
Glucose metabolism	x		x										x				x				x				x				x
Meal test[3]		x															x								x				
Self-measured plasma glucose:																													
7-point profile prior to visit			x	x	x	x		x			x		x		x		x				x				x				x
4-point profile prior to visit[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires			x																						x				
Biomarkers:																													
Differential methylated *INS* DNA			x										x				x								x				
Antibodies (autoantibodies)	x		x										x				x								x				
Immunology		x	x	*x*	*x*	*x*							x				x								x				

Visit 38 to 90 procedures

~~**Collection of BG meter**~~																												~~x~~	~~x~~

2.2.3 Section 5.3.3 Insulin treatment

Subject will continue on their current insulin treatment after they have been randomised. *It is preferred that subjects continue on the same type of insulin treatment throughout the trial.* Subjects will be trained in diabetes self-care including carbohydrate counting before and at randomisation and whenever needed during the course of the study in order to achieve the most optimal diabetes control.

2.2.4 Section 6.2 Inclusion criteria

2. Type 1 diabetes mellitus (as diagnosed clinically*) ≤ 12 weeks prior to randomisation *(see Section 8.2.6)*

2.2.5 Section 6.3 Exclusion criteria

14. Evidence of ~~or~~ cytomegalovirus infection (CMV) resolved less than 2 months prior to screening (V1)

39. Known impairment of the immune system, except for T1DM*, coeliac disease, alopecia and vitiligo*

2.2.6 Section 6.8 Rationale for trial population

The clinical diagnosis of T1DM is defined by the following two paragraphs:

3. One or more of the following:
- HbA1c ≥ 6.5% or
- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or
- a 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test with a glucose load of 75 grams anhydrous glucose in water or
- classical symptoms of hyperglycaemia and a random plasma glucose ≥ 11.1 mmol/l (200 mg/dl)[1]

4. In order to:
    - ensure that the aetiology is autoimmune, the clinical diagnosis needs to be confirmed by the presence of islet-specific auto-antibodies *at screening*
    - exclude T2DM and LADA the subjects should be without severe insulin resistance (i.e. total daily insulin dose larger than 1 U/kg per day at screening).

2.2.7 Section 8.1 Visit procedures

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from the IV/WRS. *The investigator should keep a pre-screening log.*

2.2.8 Section 8.2.6 Diagnosis of diabetes

The following information has to be recorded:

- Date of diagnosis of T1DM

The date of diagnosis of T1DM is the day a doctor has confirmed the diagnosis of T1DM upon review of relevant laboratory results (see section 6.8.)

2.2.9 Section 8.3.1 Mixed meal tolerance test

~~All plasma glucose values to be measured at site must be measured with at validated BG instrument. The BG meter handed out to the subjects should not be used for this purpose.~~

2.2.10 Section 8.4.2.7 Hypoglycaemic episodes

The Investigator must review the e-diary data for correct reporting of SMPGs and hypoglycaemic episodes at each contact. If the investigator experiences missing data in the diary, the subject must

be questioned whether there have been any severe hypoglycaemic episodes since the last visit i.e. any hypoglycaemic episodes where the subject was not able to self-treat. Any severe hypoglycaemic episodes must be reported on a hypoglycaemic episode form *in the e-diary by the subject*.

If the hypoglycaemic episode fulfils the criteria for an SAE ~~and/or a medical event of special interest (MESI)~~ then an AE form and a safety information form must also be filled in, see section 12.1

2.2.11 Section 8.5.1.3 Biomarkers

The following will be analysed:

T-cell profiling including islet-specific auto reactive CD8+ T-cells*, except at Visit 4, 5 and 6*
IL-21, except~~ed~~ at Visit 2

The blood sampling for assessment of T-cell profiling including islet-specific auto reactive CD8+ T-cells should preferably be performed at about the same time of day for a given subject.

Blood sampling for the assessment of Il-21 should be ~~taken~~ pre-dose *if* ~~of the~~ NNC0114-0006 is given at the sampling visits~~administration~~. IL-21 will be analysed at a specialised laboratory only if a functioning assay is available in due time to ensure analyses and results are ready for data base lock. The investigator will receive the results of the immunology assessments at the end of the trial. If no functional assay is available the samples will be destroyed.

2.2.12 Section 9.3 Storage

Trial product	Storage conditions (not-in-use)	In-use conditions*	In-use time**
NNC0114-0006 C 100 mg/ml	Store in a refrigerator (2°C to 8°C) Protect from light Do not freeze	Below 30°C ~~Protect from light~~ Do not freeze	For 6 hours
NNC0114-0006 C 0 mg/ml			

Trial product	Storage	In-use conditions	In-use time***

	conditions (not-in-use)		
Liraglutide 6.0 mg/ml, 3 ml pre-filled pen	Store in a refrigerator (2°C to 8°C)	Store below 30°C US: 15-30° or in a refrigerator (2°C-8°C) CA: At room temperature not above 30°C or in a refrigerator (2°-8°C)	1 month US: For 30 days CA: For 30 days
Liraglutide placebo 3 ml pre-filled pen			
	Protect from light Do not freeze	Protect from light Do not freeze	

**During in-use the trial product should not be exposed to direct sun light*

***In-use time starts after removal from the refrigerator at site. The dosing should be performed within 6 hours after the trial product is removed from the refrigerator.

**** In-use time starts when first dose is taken

2.3 Master SI/IC

2.3.1 Section For how long time will your data be stored

All data from this trial will be archived for at least ~~25~~ *15* years at the site*, but the sponsor may store the data up to 20 years after the trial product has become commercially available*.

2.3.2 Section Schematic overview of the trial

Extra X has been added to "bring insulin to the site" week 65 and 69.

Time of visit in weeks (or days [D])	-4 to -2	-10D	0	1D	3D	1	2	4	6	9	12	16	18	22	24	28	30	34	36	40	42	46	48	48 + 1D	48 + 3D	49	50	52	54	60	65	69	80
Attend visit fasting		x	x						x		x		x		x		x		x		x		x						x	x	x	x	x
Bring liraglutide to the site									x		x		x		x		x		x		x		x						x				
Bring insulin to the site		x	x						x		x		x		x		x		x		x		x						x	x	*x*	*x*	x

Protocol Amendment

no 2
to Protocol, final version 3.0
dated 01 July 2015

Trial ID: NN9828-4150

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

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

ClinOps 1, Insulin, GH & Devices

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment was prepared based on feedback from participating countries resulting in scientific re-evaluation of the need for all analyses. The feedback underlines subjects' reluctance to participate in the trial due to the heavy time commitment. Further, the timing of inclusion criterion 2 has proven to be a logistical challenge.

As a result of this we have reduced the number of subjects included in the full PK analysis to the first 80 randomised subjects. The remaining subjects will attend 9 site visits less during the trial period of 90 weeks. It is estimated that planning for taking a full PK profile from 20 subjects per treatment group (80 in total) will give approximately 13 subjects per treatment group with a full PK profile if withdrawals are taken into consideration. This is the level of PK assessment in single dose and multiple dose trials found to be sufficient. This change is captured by introducing a separate flow chart for subjects included after 80 randomised subjects. In addition the visit schedule will be reduced by changing 5 site visits (V58, V59, V61, V69 and V78) into phone visits and deleting 4 site visits (V4, V5, V56 and V57), but otherwise remain the same.

It has proven challenging to identify and randomise the subjects within the diagnosis window of 12 weeks up to randomisation. There is no scientific data in adults, which shows that changing the diagnosis duration from 12 weeks to 24 weeks (including run-in period) will affect the primary endpoint of $AUC_{0\text{-}4h}$ for a mixed meal tolerance test which is a measure for the subject's beta cell mass. It is hence decided to make this change to facilitate identification of subjects within the period given by inclusion criterion 2. Changing the cut-off day to the day of screening instead of randomisation will mitigate the logistical challenges in having all eligibility parameters ready for randomisation and reduce the risk of screen failing an eligible subject due to violation of the visit window. The enrolment window of 12 weeks (inclusion criterion 2) is therefore changed from diagnosis of Type 1 diabetes mellitus ≤ 12 weeks prior to randomisation to diagnosis of Type 1 diabetes mellitus ≤ 20 weeks prior to screening.

Several subjects have failed to fulfil inclusion criterion 4 due to not fulfilling the requirement of being non-fasting, which may result in a lowering of the subjects C-peptide result. To mitigate this, the measurement of non-fasting C-peptide will be moved to Visit 2 at which the first MMTT is performed. By having the stimulated C-peptide level at Visit 2 during the MMTT above or equal to 0.2 nmol/l the eligible subjects will have the desired beta cell function, and excluding possibly eligible patients, who were fasting at Visit 1, will be avoided.

Termination of bolus insulin use is a good measure of the quality of life of the participating subjects. In order to measure this, an additional secondary endpoint has been introduced in section 4.2.2.1 assessing the number of subjects no longer using bolus insulin. Further, section 5.3.3 has been updated based on this additional endpoint. This end-point should ideally have been

implemented from start trial. Data from >200 subjects, will however provide important data from a clinical important parameter.

The INS DNA assay was hypothesized to identify waves of beta-cell death by measuring the ratio of methylated to un-methylated insulin DNA, thus providing a method of assessing beta-cell loss. No functioning assay for analysing differential INS DNA has been developed and it is hence decided to exclude this assessment from the protocol in section 4.2.2.3 and 8.5.1.3.

Treatment with liraglutide and insulin has been clarified in section 5.3.2 and section 5.3.3 with regards to escalation and missed doses.

Maximum number of subjects to be randomised has been deleted in section 1 and section 6.1 to avoid screened failing subjects due to maximum randomisation number met. The period between screening and randomisation is up to 4 weeks and screening in IV/WRS will be monitored very closely when the planned number of randomised subjects is approaching. The current screen failure rate will be considered when the decision of closing screening is taken.

Exclusion criteria 16, 21 and 39 have been updated in section 6.3 for clarification based on questions from participating sites. These changes have no medical or scientific impact on the criteria.

In section 8.1.4 it has been clarified that all screening lab samples can be re-taken if a result is inconclusive.

Section 8.2.2 Concomitant medication was updated to reflect that the insulin dose which the subject enters the trial on has to be captured on the concomitant medication form in EDC.

There is a need to further clarify the description of the exact date of diagnosis of T1DM and section 8.2.6 has hence been updated to clarify.

If the subject experiences a hypoglycaemic episode prior to the MMTT visit it should be assessed by the investigator whether the MMTT needs to be postponed or if it can be carried out as a treatment of the hypoglycaemic episode. Section 8.3.1 has been updated to reflect this.

Section 8.4.2 has been updated based on the SHARP (Simplified Handling of Adverse Events Reporting) forms to simplify/uniform safety data collection on specific event categories.

Additional editorial corrections have been made to the protocol for clarification and simplification.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Section 1 Summary

Secondary objectives
Objectives related to treatment period (from baseline *(week 0)* to week 54):

Trial Design
~~The r~~*R*andomisation will be stratified according to the non-fasting *peak* C-peptide value at ~~screening~~ *Visit 2*.

Trial population
304 adult subjects with newly diagnosed T1DM are required according to the sample size calculation. ~~A maximum number of 314 subjects will be randomised.~~

Key inclusion criteria
2. T1DM (as diagnosed clinically*) ≤ ~~12~~*20* weeks prior to ~~randomisation~~ *screening*

4. Non-fasting *peak* C-peptide ≥0.2 nmol/l *during MMTT at Visit 2*

Key exclusion criteria

9. Known impairment of the immune system, except for T1DM, coeliac disease, alopecia, *autoimmune antibodies not considered clinical important (e.g. thyroid antibodies without any clinically important thyroid disease),* and vitiligo

2.2 Section 2 Flow chart

Visit 1 to 37 procedures *for the first 80 randomised subjects only*

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	1D	3D	W1	W2	W2 + 1D	*W3*	*W4*	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4				± 1	± 1	± *1*	± 1	± 1	± *1*	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
SAFETY																																
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Hyperglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Technical complaints		~~x~~	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Body measurements[5]	x	x	x			x	x			x			x		x		x		x		x		x		x		x		x		
EFFICACY																																
Glucose metabolism	x		x										x				x				x				x				x		
Meal test[3]		x															x								x						
Self-measured plasma glucose:																																
7-point profile prior to visit			x	x	x	x		x			x		x		x		x				x				x				x		
4-point profile prior to visit[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
PRO questionnaires			x																						x							
Biomarkers:																																
~~Differential methylated *INS* DNA~~			~~x~~										~~x~~				~~x~~								~~x~~						
Anti-IAA and –GAD isotypes			*x*																						*x*						

Visit 38 to 90 procedures *for the first 80 randomised subjects only*

Trial period	Treatment																					Follow-up								
Visit type: C: Clinic, P: Phone contact	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]			
Timing of visit (weeks (~~w~~*W*), or days (D) if specified)	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80				
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± *1*	± *1*	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7			
EFFICACY																															
Glucose metabolism				x				x				x							x		x		x		x		x				
Meal test[4]				x															x				x				x				
Self-measured plasma glucose:																															
7-point profile prior to visit				x				x				x							x		x		x		x		x				
4-point profile prior to visit[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
PRO questionnaires																			x								x				
Biomarkers:																															
~~Differential methylated *INS* DNA~~				~~x~~															~~x~~				~~x~~				~~x~~				
Anti-IAA and –GAD isotypes				*x*																							*x*				

1. Only for NNC0~~0~~*1*14-0006

2. ~~For woman of childbearing potential only.~~ Blood sample at V1. For all subsequent visits a urine stick must only be measured for females of childbearing potential if a menstrual period is missed or as required by law.

3. The MMTT may be re-scheduled twice within 10 days. *At Visit 2 the MMTT must be performed before Visit 3 and leaving sufficient time for randomisation lab results*.

Visit 1 to 37 procedures after 80 subjects have been randomised

Trial periods	*S*		*R*	*Treatment*																								
Visit type: C: Clinic, P: Phone contact	*C*	*C*	*C*	*C*	*C*	*P*	*P*	*C*	*P*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
Visit number	*1*	*2*	*3*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14,15*	*16*	*17,18*	*19*	*20-22*	*23*	*24*	*25*	*26-28*	*29*	*30*	*31*	*32-34*	*35*	*36*	*37*		
Timing of visit (weeks (W), or days (D) if specified)	*-D28 to –D14*	*-D10*	*0*	*W1*	*W2*	*W2 + 1D*	*W3*	*W4*	*W4 + 1D*	*W5*	*W6*	*W7,8*	*W9*	*W10,11*	*W12*	*W13-15*	*W16*	*W17*	*W18*	*W19-21*	*W22*	*W23*	*W24*	*W25-27*	*W28*	*W29*	*W30*		
Visit window (days)		*± 4*		*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*		
SUBJECT RELATED INFO/ASSESSMENTS																													
Informed consent	*x*																												
Genotyping consent, optional	*x*																												
Long term retention consent, optional	*x*																												
In/exclusion criteria	*x*	*x*	*x*																										
Randomisation			*x*																										
Randomisation criteria			*x*																										
Withdrawal criteria			*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Dosing day exclusion criteria[1]			*x*								*x*				*x*				*x*				*x*				*x*		
Abuse of alcohol	*x*																												
Abuse of drugs	*x*																												
Medical history	*x*																												
Concomitant illness	*x*																												
Concomitant medication	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Demography	*x*																												
Diagnosis of diabetes	*x*																												
Diabetes treatment history	*x*																												

Trial periods	*S*		*R*	*Treatment*																									
Visit type: C: Clinic, P: Phone contact	*C*	*C*	*C*	*C*	*C*	*P*	*P*	*C*	*P*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
Visit number	*1*	*2*	*3*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14,15*	*16*	*17,18*	*19*	*20-22*	*23*	*24*	*25*	*26-28*	*29*	*30*	*31*	*32-34*	*35*	*36*	*37*		
Timing of visit (weeks (W), or days (D) if specified)	*-D28 to -D14*	*-D10*	*0*	*W1*	*W2*	*W2 + 1D*	*W3*	*W4*	*W4 + 1D*	*W5*	*W6*	*W7,8*	*W9*	*W10,11*	*W12*	*W13-15*	*W16*	*W17*	*W18*	*W19-21*	*W22*	*W23*	*W24*	*W25-27*	*W28*	*W29*	*W30*		
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3		
Pregnancy test[2]	x																												
Smoking habits	x																												
Family history of diabetes	x																												
Diabetes complications	x																												
Blood sample for genotyping (optional)			x																										
EFFICACY																													
Glucose metabolism	x		x								x				x				x				x				x		
Meal test[3]		x													x								x						
Self-measured plasma glucose:																													
7-point profile prior to visit			x	x		x			x		x		x		x				x				x				x		
4-point profile prior to visit[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PRO questionnaires			x																				x						
Biomarkers:																													
Antibodies (autoantibodies)	x		x								x				x								x						
Immunology		x	x	x							x				x								x						
Vitamin D (1,25 dehydroxy-calciferol			x								x				x								x						
Dose of insulin administrations		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Carbohydrate intake		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
SAFETY																													
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Trial periods	*S*		*R*	*Treatment*																										
Visit type: C: Clinic, P: Phone contact	*C*	*C*	*C*	*C*	*C*	*P*	*P*	*C*	*P*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
Visit number	*1*	*2*	*3*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14,15*	*16*	*17,18*	*19*	*20-22*	*23*	*24*	*25*	*26-28*	*29*	*30*	*31*	*32-34*	*35*	*36*	*37*			
Timing of visit (weeks (W), or days (D) if specified)	*-D28 to -D14*	*-D10*	*0*	*W1*	*W2*	*W2 + 1D*	*W3*	*W4*	*W4 + 1D*	*W5*	*W6*	*W7,8*	*W9*	*W10,11*	*W12*	*W13-15*	*W16*	*W17*	*W18*	*W19-21*	*W22*	*W23*	*W24*	*W25-27*	*W28*	*W29*	*W30*			
Visit window (days)		*± 4*		*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*			
Hyperglycaemic episodes		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*			
Hypoglycaemic episodes		*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*			
Technical complaints			*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*			
Body measurements[5]	*x*	*x*	*x*	*x*	*x*			*x*			*x*		*x*		*x*		*x*		*x*		*x*		*x*		*x*		*x*			
ECG	*x[6]*		*x*	*x*							*x*				*x*								*x*							
Eye examination			*x[7]*																											
Physical examination	*x*		*x*	*x*							*x*				*x*								*x*							
Vital signs	*x*		*x*	*x*	*x*			*x*			*x*		*x*		*x*				*x*				*x*				*x*			
Antibodies:																														
Anti-NNC0114-0006 antibodies			*x*												*x*								*x*							
Anti-liraglutide antibodies			*x*												*x*								*x*							
IgE			*x*	*x*							*x*				*x*								*x*							
Biochemistry	*x*		*x*	*x*							*x*				*x*								*x*							
Coagulation parameters	*x*		*x*	*x*							*x*				*x*								*x*							
Haematology	*x*		*x*	*x*							*x*				*x*								*x*							
Cytokines			*x*								*x*				*x*								*x*							
Urine dipsticks	*x*		*x*	*x*							*x*				*x*								*x*							
Hepatitis B	*x*							*x*					*x*				*x*				*x*				*x*					
Hepatitis C	*x*																													
Tuberculosis screening test	*x*																													

Trial periods	*S*		*R*	*Treatment*																										
Visit type: C: Clinic, P: Phone contact	*C*	*C*	*C*	*C*	*C*	*P*	*P*	*C*	*P*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
Visit number	*1*	*2*	*3*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14,15*	*16*	*17,18*	*19*	*20-22*	*23*	*24*	*25*	*26-28*	*29*	*30*	*31*	*32-34*	*35*	*36*	*37*
Timing of visit (weeks (W), or days (D) if specified)	*-D28 to -D14*	*-D10*	*0*	*W1*	*W2*	*W2 + 1D*	*W3*	*W4*	*W4 + 1D*	*W5*	*W6*	*W7,8*	*W9*	*W10,11*	*W12*	*W13-15*	*W16*	*W17*	*W18*	*W19-21*	*W22*	*W23*	*W24*	*W25-27*	*W28*	*W29*	*W30*
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3
(QuantiFERON)																											
Epstein–Barr virus	*x*							*x*					*x*				*x*				*x*				*x*		
CMV[8]	*x*							*x*					*x*				*x*				*x*				*x*		
HIV	*x*																										
Hormones	*x*														*x*								*x*				
Lipids			*x*												*x*								*x*				
OTHER ASSESSMENTS																											
PK sampling NNC0114-0006			*x*[9]	*x*	*x*			*x*			*x*		*x*		*x*				*x*				*x*				*x*
PK sampling Liraglutide[10]			*x*	*x*	*x*			*x*			*x*		*x*		*x*				*x*				*x*				*x*
TRIAL MATERIAL																											
IV/IWRS	*x*		*x*								*x*				*x*				*x*				*x*				*x*
Administration and dispensing of trial product NNC0114-0006/placebo			*x*								*x*				*x*				*x*				*x*				*x*
Dispensing of liraglutide/placebo[11]			*x*								*x*				*x*				*x*				*x*				*x*
Drug accountability for IMP[12]			*x*								*x*				*x*				*x*				*x*				*x*
REMINDERS																											
Handout ID cards	*x*																										
Handout direction for use[13]			*x*																								
Handout and instruct in e-diary		*x*																									

Trial periods	*S*		*R*	*Treatment*																										
Visit type: C: Clinic, P: Phone contact	*C*	*C*	*C*	*C*	*C*	*P*	*P*	*C*	*P*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
Visit number	*1*	*2*	*3*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14,15*	*16*	*17,18*	*19*	*20-22*	*23*	*24*	*25*	*26-28*	*29*	*30*	*31*	*32-34*	*35*	*36*	*37*				
Timing of visit (weeks (W), or days (D) if specified)	*-D28 to -D14*	*-D10*	*0*	*W1*	*W2*	*W2 + 1D*	*W3*	*W4*	*W4 + 1D*	*W5*	*W6*	*W7,8*	*W9*	*W10,11*	*W12*	*W13-15*	*W16*	*W17*	*W18*	*W19-21*	*W22*	*W23*	*W24*	*W25-27*	*W28*	*W29*	*W30*				
Visit window (days)		*± 4*		*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*				
Investigator review of e-diary			*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				
Handout and instruct in BG meter use		*x*																													
Attend fasting visit		*x*	*x*								*x*				*x*				*x*				*x*				*x*				
Blood sample for long term retention (optional)			*x*																				*x*								

1. Only for NNC0114-0006

2. Blood sample at V1. For all subsequent visits a urine stick must only be measured for females of childbearing potential if a menstrual period is missed or as required by law. ***Austria:*** *Urine-stick pregnancy test will be performed monthly.* ***Ireland:*** *Urine-stick pregnancy test will be performed at all visits to the clinic.*

3. The MMTT may be re-scheduled twice within 10 days. At Visit 2 the MMTT must be performed before Visit 3 and leaving sufficient time for randomisation lab results.

4. 4-point profile will be used for T-T-T

5. At V1 height and weight will be measured and BMI will be calculated via the eCRF. At the following visits only weight must be measured

6. A baseline ECG performed for any reason unrelated to the trial within 30 days prior to V1 is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime

7. A baseline fundoscopy/ fundus photography performed for any reason unrelated to the trial within 90 days prior to V3 is acceptable

8. Cytomegalovirus

9. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)

10. PK sample at any time during the visit

11. Liraglutide/liraglutide placebo will be administered once daily

12. Investigational medicinal product

13. Injection of liraglutide will be trained at V3 and at following visits as needed.

Visit 38 to 90 procedures <u>after 80 subjects have been randomised</u>

Trial period	*Treatment*																	*Follow-up*								
Visit type: C: Clinic, P: Phone contact	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*P*	*P*	*P*	*C*	*P*	*P*	*P*	*C*	*P*	*P*	*P*	*C*	*C*
Visit number	*38-40*	*41*	*42*	*43*	*44-46*	*47*	*48*	*49*	*50-52*	*53*	*54*	*55*	*58,59*	*60*	*61*	*62*	*63*	*64-68*	*69*	*70-73*	*74*	*75-77*	*78*	*79-88*	*89*	*90*[1]
Timing of visit (weeks (W), or days (D) if specified)	*W31-33*	*W34*	*W35*	*W36*	*W37-39*	*W40*	*W41*	*W42*	*W43-45*	*W46*	*W47*	*W48*	*W49, 50*	*W51*	*W52*	*W53*	*W54*	*W55-59*	*W60*	*W61-64*	*W65*	*W66-68*	*W69*	*W70-79*	*W80*	
Visit window (days)	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 3*	*± 7*
SUBJECT RELATED INFO/ASSESSMENTS																										
Withdrawal criteria	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Dosing day exclusion criteria[2]				*x*				*x*				*x*														
Concomitant medication	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Pregnancy test[3]																	*x*									
Diabetes complications																	*x*								*x*	
EFFICACY																										
Glucose metabolism				*x*				*x*				*x*					*x*				*x*				*x*	
Meal test[4]				*x*													*x*				*x*				*x*	
Self-measured plasma glucose:																										
7-point profile prior to visit				*x*				*x*				*x*					*x*		*x*		*x*		*x*		*x*	
4-point profile prior to visit[5]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	
PRO questionnaires																	*x*								*x*	
Biomarkers:																										
Antibodies (autoantibodies)				*x*													*x*				*x*				*x*	
Anti-IAA and –GAD isotypes				*x*																					*x*	
Immunology				*x*													*x*				*x*				*x*	
Vitamin D (1,25 dehydroxy-calciferol)				*x*													*x*				*x*				*x*	
Dose of insulin administrations	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Trial period	*Treatment*																	*Follow-up*								
Visit type: C: Clinic, P: Phone contact	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*P*	*P*	*P*	*C*	*P*	*P*	*P*	*C*	*P*	*P*	*P*	*C*	*C*
Visit number	*38-40*	*41*	*42*	*43*	*44-46*	*47*	*48*	*49*	*50-52*	*53*	*54*	*55*	*58,59*	*60*	*61*	*62*	*63*	*64-68*	*69*	*70-73*	*74*	*75-77*	*78*	*79-88*	*89*	*90*[1]
Timing of visit (weeks (W), or days (D) if specified)	*W31-33*	*W34*	*W35*	*W36*	*W37-39*	*W40*	*W41*	*W42*	*W43-45*	*W46*	*W47*	*W48*	*W49, 50*	*W51*	*W52*	*W53*	*W54*	*W55-59*	*W60*	*W61-64*	*W65*	*W66-68*	*W69*	*W70-79*	*W80*	
Visit window (days)	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 3*	*± 7*
Carbohydrate intake	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SAFETY																										
Adverse events	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Hyperglycaemic episodes	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Hypoglycaemic episodes	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Technical complaints	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*									
Body measurements		*x*		*x*		*x*		*x*		*x*		*x*					*x*				*x*				*x*	*x*
ECG				*x*								*x*					*x*				*x*				*x*	*x*
Eye examination[6]																	*x*								*x*	
Physical examination				*x*								*x*					*x*				*x*				*x*	*x*
Vital signs				*x*				*x*				*x*					*x*				*x*				*x*	*x*
Antibodies:																										
Anti-NNC0114-0006 antibodies				*x*													*x*								*x*	*x*
Anti-liraglutide antibodies				*x*													*x*								*x*	*x*
IgE				*x*								*x*					*x*				*x*				*x*	*x*
Biochemistry				*x*								*x*					*x*				*x*				*x*	*x*
Coagulation parameters				*x*								*x*					*x*				*x*				*x*	*x*
Haematology				*x*								*x*					*x*				*x*				*x*	*x*
Cytokines				*x*								*x*					*x*				*x*				*x*	*x*
Urine dipsticks				*x*								*x*					*x*				*x*				*x*	*x*
Hepatitis B		*x*				*x*				*x*							*x*									
EBV		*x*				*x*				*x*							*x*									

Trial period	*Treatment*																	*Follow-up*								
Visit type: C: Clinic, P: Phone contact	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*P*	*P*	*P*	*C*	*P*	*P*	*P*	*C*	*P*	*P*	*P*	*C*	*C*
Visit number	*38-40*	*41*	*42*	*43*	*44-46*	*47*	*48*	*49*	*50-52*	*53*	*54*	*55*	*58,59*	*60*	*61*	*62*	*63*	*64-68*	*69*	*70-73*	*74*	*75-77*	*78*	*79-88*	*89*	*90*[1]
Timing of visit (weeks (W), or days (D) if specified)	*W31-33*	*W34*	*W35*	*W36*	*W37-39*	*W40*	*W41*	*W42*	*W43-45*	*W46*	*W47*	*W48*	*W49, 50*	*W51*	*W52*	*W53*	*W54*	*W55-59*	*W60*	*W61-64*	*W65*	*W66-68*	*W69*	*W70-79*	*W80*	
Visit window (days)	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 3*	*± 1*	*± 1*	*± 1*	*± 3*	*± 7*
CMV		*x*				*x*				*x*							*x*									
Hormones				*x*								*x*					*x*				*x*				*x*	*x*
Lipids				*x*								*x*					*x*				*x*				*x*	*x*
OTHER ASSESSMENTS																										
PK sampling NNC0114-0006				*x*				*x*				*x*[7]					*x*				*x*				*x*	*x*
PK sampling Liraglutide				*x*				*x*				*x*					*x*									
TRIAL MATERIAL																										
IV/IWRS				*x*				*x*				*x*					*x*								*x*	
Administration and dispensing of trial product NNC0114-0006/placebo				*x*				*x*				*x*														
Dispensing of liraglutide/placebo				*x*				*x*				*x*														
Drug accountability for IMP				*x*				*x*				*x*					*x*									
REMINDERS																										
Investigator review of e-diary	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Attend fasting visit				*x*				*x*				*x*					*x*				*x*				*x*	*x*
Blood sampling for long term retention (optional)																	*x*								*x*	
End of dosing												*x*[8]					*x*[9]									
Collection of e-diary																									*x*	*x*
End of trial																									*x*	*x*
Sign off Casebook																									*x*	*x*

1. Safety follow-up visit. To be conducted for subjects who have been withdrawn less than 14 weeks after last dose of NNC0114-0006/placebo. The visit should be conducted 15 weeks ± 1 week after last dose of NNC0114-0006/placebo

2. Only for NNC0114-0006

3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. ***Austria:*** *Urine-stick pregnancy test will be performed monthly.* ***Ireland:*** *Urine-stick pregnancy test will be performed at all visits to the clinic.*
4. The MMTT may be re-scheduled twice within 10 days
5. 4-point profile will be used for T-T-T
6. A fundoscopy/ fundus photography may be performed up to 2 weeks before or after V63 and up to 2 weeks before V89
7. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
8. Last dosing of NNC0114-0006/placebo
9. Last dosing of liraglutide/liraglutide placebo is the day prior to V63

2.3 Section 4.1 Secondary objectives

Objectives related to treatment period (from baseline *(week 0)* to week 54):

2.4 Section 4.2.2.1 Supportive secondary efficacy endpoints

- *Change in t*~~T~~Total daily insulin dose in units per kg (three day average) ~~at~~ *from baseline to* week 54 and week 80*
- *Change in n*~~N~~umber of insulin injections per day (three day average) ~~at~~ *from baseline to* week 54 and week 80
- *Number of weeks off bolus insulin from baseline to week 54 and week 80*

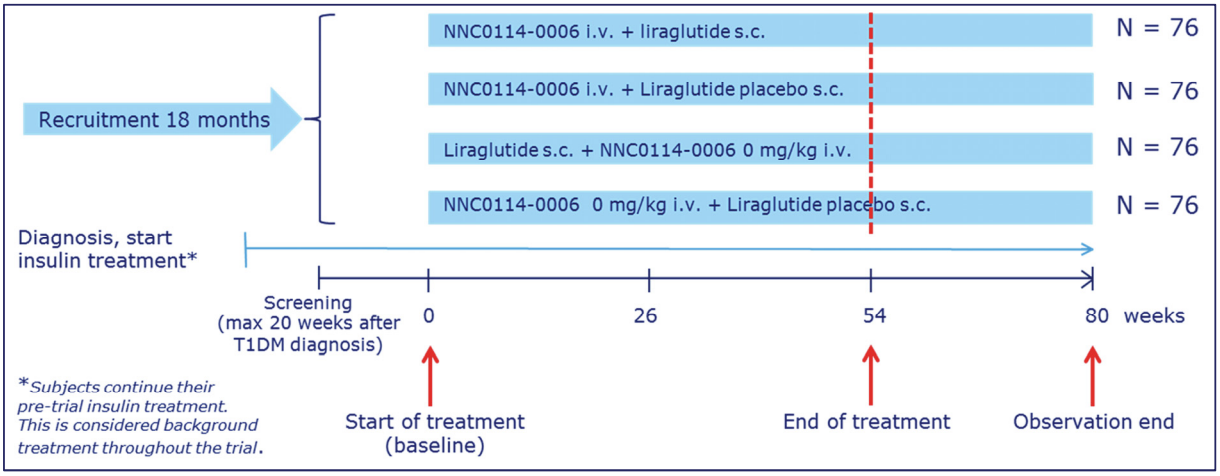
2.5 Section 4.2.2.3 Supportive secondary biomarker endpoints

- ~~Change in differential methylated INS DNA in plasma from baseline to week 54 and week 80~~
- Change in serum vitamin D (1,25 dehydroxy-calciferol) from baseline to week 54 and week 80

~~Differential methylated INS DNA and IL-21 will be analysed only if a functioning assay will be available in due time allowing to incorporate the analyses results in the database prior to database lock.~~

2.6 Figure 2–1 Trial design

New Figure 5-1



2.7 Section 5.3.1 NNC0114-0006

Dosing day exclusion criteria

The infusion of NNC0114-0006/*NNC0114-0006 placebo* must be postponed if there are symptoms or signs of infection, which in the opinion of the investigator are clinically significant (e.g. fever, pneumonia or tonsillitis or unspecific viral infection).

If NNC0114-0006/*NNC0114-0006 placebo* cannot be given within 2 weeks after the scheduled visit this should be recorded as a missed dosing in the electronic *C*~~e~~ase *R*~~r~~eport *F*~~f~~orm (eCRF). The next NNC0114-0006/*NNC0114-0006 placebo* dose will be given as planned.

2.8 Section 5.3.2 Liraglutide

Initiation and escalation of liraglutide/liraglutide placebo
In case of intolerable liraglutide side effects related to the dose escalation it is acceptable to *maintain current liraglutide dose and postpone escalation by* ~~reduce the dose to the previous dose level for up to an additional~~ 2 weeks.

Missed doses of liraglutide/liraglutide placebo before target dose is reached

If any dose is missed by the subject ≤ 3 consecutive days before reaching the target dose of 1.8 mg *liraglutide* or 0.3 ml *liraglutide* placebo (1.2 mg *liraglutide* or 0.2 ml *liraglutide* placebo, if higher dose is not tolerated), it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. After having missed liraglutide/ *liraglutide placebo* doses for ≤ 3 days the subject must be re-initiated on the dose the subject was taking prior to the missed doses. The dose escalation should be performed as originally planned.

If any dose is missed by the subject > 3 consecutive days at any time point it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. The subject must be re-initiated on 0.6 mg liraglutide/ *liraglutide* placebo and dose escalation should be every 2 weeks.

Missed doses of liraglutide/liraglutide placebo after target dose is reached

After reaching the target dose of 1.8 mg *liraglutide* or 0.3 ml *liraglutide* placebo (1.2 mg *liraglutide* or 0.2 ml *liraglutide* placebo, if higher dose is not tolerated), dose and dose frequency should not be changed at any time during the treatment period.

If any dose is missed by the subject ≤ 3 consecutive days ~~it must be documented in the medical record and~~ the investigator should discuss the importance of treatment compliance with the subject. After having missed liraglutide doses ≤ 3 days the subject ~~must~~ should be re-initiated on the target dose.

If any dose is missed by the subject > 3 consecutive days at any time point it must be documented in the medical record and the investigator should discuss the importance of treatment compliance with the subject. The subject ~~must~~ *should* be re-initiated on 0.6 mg liraglutide/placebo and dose

escalation should be every 2 weeks~~.~~ *or continue on current dose of liraglutide/placebo at the discretion of the investigator.*

2.9 Section 5.3.3 Insulin treatment

During the trial subjects will receive insulin treatment in order to achieve metabolic control according to the insulin titration guideline (Appendix A). This insulin treatment will be handled by the local trial sites in collaboration with Novo Nordisk's Insulin Titration Group. *Bolus and/or basal insulin can be stopped or paused at all times during the trial at the discretion of the investigator. The subject's need for bolus insulin will be documented in the eCRF.* ~~It is acceptable to pause or stop insulin treatment if the investigator assesses that the subject is in remission.~~

Insulin reduction on the day of liraglutide/ liraglutide placebo initiation and escalation
~~As it is a blinded trial, w~~*When* liraglutide/ liraglutide placebo is initiated, the total daily pre-randomisation insulin dose should be reduced by 25 % for a minimum of 24 hours after the initiation of liraglutide/ liraglutide placebo.

Thereafter the insulin dose should be adjusted according to the glucose target in Table 5-2. *As it is a blinded trial this insulin reduction applies to all treatment arms.*

2.10 Section 6.1 Number of subjects

~~Maximum number of subjects to be randomised: 314~~

2.11 Section 6.2 Inclusion criteria

2. Type 1 diabetes mellitus (as diagnosed clinically*) ≤ *20*~~12~~ weeks prior to ~~randomisation~~ *screening* (see Section 8.2.6).

4. Non-fasting *peak*** C-peptide ≥0.2 nmol/l *during MMTT at Visit 2*

*See Section 6.8 for the clinical diagnosis.
***The highest C-peptide value of the 11 samples performed during the MMTT.*

2.12 Section 6.3 Exclusion criteria

16. A positive QuantiFERON®-TB Gold test (test may be repeated if result is inconclusive) ~~throughout the trial~~.

21. Positive test results for hepatitis C virus (HCV) as documented by ~~any of the following:~~ ~~A~~*a*nti-HCV antibody positivity (as assessed by an enzyme immunoassay) *or* ~~P~~*p*resence of HCV ribonucleic acid (RNA) in serum.

31. One or more screening (V1) laboratory values as stated:

- Haemoglobin <6.2 mmol/l (10.0 g/dl / *100.0 g/l*)

39: Known impairment of the immune system, except for T1DM, coeliac disease, alopecia*, autoimmune antibodies not considered clinically important (e.g. thyroid antibodies without any clinical important thyroid disease),* and vitiligo.

2.13 Section 6.4 Randomisation criteria

If one or more randomisation criteria are answered "no", the subject should be offered to have the randomisation visit re-scheduled ~~not later than 12 weeks after the diagnosis of T1DM~~.

2.14 Section 6.8 Rationale for trial population

In order to ensure that patients with a residual beta-cell mass potentially can achieve a clinically meaningful improvement in glucose control, the peak or mean non-fasting C-peptide level needs to be above *or equal to* 0.2 nmol/l[26] *at Visit 2. Further, onset of T1DM must be* within ~~12~~ *20* weeks ~~after onset of T1DM~~ *before screening (Visit 1)* and ~~that the~~ subjects ~~are~~ metabolic*ally* stable (defined as no severe DKA~~,~~ (confirmed pH below 7.2) within the last 2 weeks prior to ~~screening~~ *randomisation (Visit 3)*).

2.15 Section 8.1.4 Re-screening/ re-sampling

However, if ~~the **tuberculosis screening test**~~ *a lab test* at Visit 1 or *Visit 2* is inconclusive *a* re-test~~s~~ can be performed. The repeat test results must be available for evaluating the subject's eligibility before Visit 3.

2.16 Section 8.1.6 Missed visits and unscheduled visits

If a visit is missed every effort should be made to ensure information is collected at a telephone contact. Subjects will be invited for the next scheduled visit according to the visit schedule.

An unscheduled visit can be scheduled at any time at the discretion of the investigator, e.g. in case additional blood samples must be performed for safety reasons. ~~If the investigator asks to subject to have a test described in the protocol re- done (e.g extra blood sample if some of the blood sample values are out of range) t~~*T*his should be ~~recorded~~*reported* ~~as~~ *on the* ~~an unscheduled visit and an~~ unscheduled visit form *in the eCRF* ~~must be completed~~*stating the reason for the visit*.

If the subject attends the clinic *due to re-sampling of visit-related assessments, including MMTT and dosing of NNC0114-0006/placebo, this is not considered an unscheduled visit. The date of the assessments for a specific visit must be updated in the eCRF accordingly. Likewise, coming to the site for additional trial products or ancillary supplies is not considered as an unscheduled visit. In the case of additional trial products, a dispensing session should be made in the IV/WRS selecting additional medication and the subject notes should be updated accordingly.*~~and some of the tests have to be re-scheduled (e.g. in a non-fasting state at a fasting visit) the re-scheduled tests should~~

~~NOT be recorded as an unscheduled visit. In this case blood samples will have a different date of collection than the rest of the assessments. Likewise re-scheduling of the MMTT and dosing of NNC0114-0006/placebo should not be recorded as an unscheduled visit.~~

2.17 Section 8.1.7 Withdrawn subjects

The case book must be signed *by the investigator* after all queries have been closed.

If a subject is withdrawn the e-diary must be returned to site.

If subjects fail~~s~~ to return for these visits or is unable to do so, every effort should be made by the investigator to contact him/her by phone or by sending appropriate correspondence (i.e. certified letter). *It must be documented in* ~~that will become part of~~ the investigators' file ~~to record~~ that efforts were made to reach the subject.

2.18 Section 8.1.8 Fasting visits

The subject should attend selected visits *in a* fasting *state* (see Section 2.2).

If the subject is not fasting, as required on days where fasting blood sampling should be drawn, all blood samples ~~(both fasting and non-fasting)~~ must be re-scheduled within the visit window. ~~and~~ *T*~~t~~he date for the ~~fasting~~ blood samples must be recorded in the eCRF. All other assessments can be performed even though the subject is not fasting. Re-scheduling of ~~fasting~~ blood samples is not considered as an unscheduled visit.

2.19 Section 8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than the NNC0114-0006 *and* liraglutide ~~and insulin~~, which is taken during the trial, including the screening and follow-up periods. Information on *the subject's* insulin treatment *at screening (Visit 1)* is recorded ~~in diabetes treatment history see Section 2.20 a~~*on the concomitant medication form in the eCRF a*nd *any changes to the insulin doses after Visit 2 are recorded* in the e-diary *(*see Section 8.6.3*)***Error! Reference source not found.**. *If the brand of insulin changes during the trial the new information must be entered on the concomitant medication form*.

2.20 Section 8.2.3 Smoking status

Details of smoking status must be recorded at ~~the first visit~~ *Visit 1*. Smoking is defined as smoking at least one cigarette, cigar or pipe daily.

2.21 Section 8.2.6 Diagnosis of diabetes

The date of diagnosis of T1DM is the ~~day~~ date a doctor has confirmed the diagnosis of T1DM *in the subject's medical record* upon review of relevant laboratory results (see section 6.8). *In case the*

diagnosis has not been noted in the medical record the date of diagnosis of T1DM is the date a doctor has reviewed, signed and dated the relevant laboratory results.

2.22 Section 8.2.7 Diabetes treatment history

The following information has to be recorded:

- ~~Start date of current diabetes treatment~~
- Number of severe hypoglycaemic episodes since diagnosis

2.23 Section 8.3.1 Mixed meal tolerance test

- Not to take their basal insulin ~~after 22.00 the evening~~ *within 9 hours* before the MMTT visit
  - Subjects who normally take basal insulin in the morning should bring their basal insulin to the MMTT *visit*
- Remember to bring their bolus insulin to the MMTT visits (to be given after *the* MMTT)
- Take liraglutide/liraglutide placebo at the same time as usual ~~both~~ *on* the day before the MMTT visit ~~and~~ *as well as* on the day of the MMTT
- Remember the importance of having BG ~~on~~ *at* target

Preparation and conduct of the MMTT
The MMTT will be initiated ~~in the morning~~ after fasting for at least 6 hours. The NNC0114-0006/placebo may be given during the MMTT.
~~Subjects will be instructed not to take basal insulin after 22.00 the evening before the MMTT. Receipt of insulin boluses is allowed until 2 hours prior to the MMTT.~~

The MMTT may also be re-scheduled within 1-10 days. ~~Re-scheduling of the MMTT is not considered as an unscheduled visit. Two rescheduling's are allowed per~~ *The* MMTT visit *can be rescheduled twice at a maximum*. If ~~this is~~ *still* not possible the MMTT must be reported as not done. All other assessments at the visit should be conducted as planned including dosing of NNC0114-0006/placebo.

If *the* plasma glucose value measured at the site before the MMTT is ≤3.9 mmol/l (70 mg/dl), the *hypoglycaemic episode must be reported in the subject's e-diary. The investigator should consider if the* MMTT *is appropriate treatment. If the subject needs further treatment the MMTT must* ~~will~~ be rescheduled within 1-10 days~~Re-scheduling of the MMTT is not considered as an unscheduled visit. Two rescheduling's are allowed per MMTT visit. If this is not possible the MMTT must be reported as not done. All other assessments at the visit should be conducted as planned including dosing of NNC0114-0006/placebo.~~

During the MMTT plasma glucose will be monitored ~~on a validated plasma glucose instrument~~ *using a BG meter*. If the glucose level exceeds 16.7 mmol/l (300 mg/dl) plasma ketones (betahydroxybutyrate) should be measured ~~on a BG meter~~.

Precautions during the MMTT
In case of hypoglycaemia during the MMTT (plasma glucose value ≤ ~~<~~3.9 mmol/l (70 mg/dl)), the MMTT can be stopped at the discretion of the investigator and rescue treatment according to local practice can be initiated.

After the MMTT
It ~~is up to the~~*is at the* discretion of the investigator to decide if subjects who normally take~~s~~ basal insulin in the morning should take their basal insulin after the MMTT.

2.24 Section 8.3.4 7-point profile

Subjects will be instructed to perform SMPG measurements before and 90 minutes after the start of breakfast, lunch*, and* dinner and at bedtime. Measurements will be performed *prior to a site or phone visit, preferably on the day before the visit* according to the flowchart in Section 2.
The ~~7~~*4*-point plasma glucose profile ~~includes one before breakfast~~ measurement*s will be replaced by the 7-point profile measurements on the specific day that the 7-point profile is performed.*~~, one before lunch, one before dinner and one at bedtime measurement. These measurements are the same needed for the 4-point profile.~~

2.25 Section 8.3.5 Insulin doses

Subjects will be instructed ~~in~~ how to record ~~the~~ insulin doses in the e-diaries.

If a subject~~s~~ reports an actual bolus insulin dose that deviates from the ~~prescribed~~ *recommended in the e-diary* bolus insulin dose the subject will be asked to report a reason for this deviation in the e-diary. *Likewise, if the investigator deviates from the titration algorithm the reason for deviation should be documented in Study Works.*

2.26 Section 8.3.6 Carbohydrate intake per meal

Subjects who will be titrated according to the principle of flexible insulin therapy (see Appendix A) will be instructed ~~in~~ how to record ~~the~~ carbohydrate intake in the e-diary.

2.27 Section 8.4.2.1 Pancreatitis

- Complications to the event
- *Treatment for the event*
- Relevant risk factors for pancreatic disease including:
    - History of gall-stones

- History of pancreatitis
- Family history of pancreatitis
- Trauma
- *Hyper-triglyceridemia*
- *Tumour*
- *Alcohol assumptions*
- *Hypercalcaemia*

2.28 Section 8.4.2.3 Neoplasm

- Type of neoplasm
- *Anatomic location of the neoplasm*
- Symptoms leading to identification of event
- Diagnostic imaging
- *Relevant laboratory test*

2.29 Section 8.4.2.5 Injection/Infusion site reactions

- ~~Type of reaction – local or generalised~~
- Symptoms associated to the event
- Treatment for the event
- Association with the trial product(s) *and/ or needles used*

2.30 Section 8.4.2.7 Hypoglycaemic episodes

Any severe hypoglycaemic episodes must be reported on a hypoglycaemic episode form in the e-diary by the subject. *If the severe hypoglycaemic episode is older than 7 days the investigator must report this through a Data Change Request (DCR) in Study Works.*

2.31 Section 8.4.3 Technical complaints

Technical complaints must be recorded in accordance with the procedures outlined in Section 12.4. The following information has to be recorded:

- Product
- ~~Code no~~
- DUN*, if applicable*

2.32 Section 8.4.4.3 BMI

BMI will be calculated at ~~the first visit~~*Visit* 1 ~~by~~ *in* the eCRF *by* using the equation:

2.33 Section 8.4.8 Vital signs

- Body temperature~~, ear~~
- Respiratory rate (breath*s*/minute~~s~~)

2.34 Section 8.5 Laboratory assessments

The timing of the blood samples are outlined in the flow chart (see Section 2.2). ~~Laboratory assessments can be done at another day than on the day of the actual visit as long as it is within the visit window.~~

2.35 Section 8.5.1.3 Biomarkers

~~**Differentially methylated INS DNA**~~
~~Minimally invasive methods to determine episodes of beta-cell death could be a valuable tool for patient stratification in clinical trials, assessing clinical response to therapy, and directing patient care. When beta-cells die, they release insulin (INS) DNA that can be measured in serum. Though the INS gene can be detected in cells other than beta-cells, the methylation status of this gene is tissue-dependent, e.g., beta-cell-derived INS is hypomethylated. The differentially methylated INS DNA assay is hypothesized to identify waves of beta-cell death by measuring the ratio of methylated to unmethylated insulin DNA, thus providing a method of assessing beta-cell loss. Samples will be drawn according to Section 2.2. This hypothesis-testing assay will be used by a specialised lab if a functioning assay is available in due time to ensure analysis and results ready for data base lock. If no functional assay is available the samples will be destroyed.~~

Antibodies (autoantibodies) & isotypes
Additionally, isotypes for anti-IAA and –GAD will be evaluated *according to Section 2*~~excepted at Visit 1~~.

2.36 Section 8.5.2.2 Anti-drug antibodies

Anti-drug antibodies are stable for many years when stored frozen (*i.e.*~~e.g.~~ -20 degrees Celsius), and further characterisation is therefore possible.

Anti-NNC0114-0006 antibodies
The screening analysis of serum samples for antibodies against NNC0114-0006 will be done in the two arms dosed with NNC011~~1~~4-0006 at Visit 3, 19, 31, 43, 63, 89 and 90.

2.37 Section 8.6.2 Liraglutide/liraglutide placebo

Subjects will be instructed to report the dose (0.6, 1.2 or 1.8 mg) ~~as indicated on the pen~~ in their e-diary on a daily basis. Each record should also include date, time and injection site.

2.38 Section 8.7 Subject compliance

Treatment compliance:
Throughout the trial the treatment compliance will be assessed by monitoring of drug accountability as specified in Section 9.4. The unused/used liraglutide*/liraglutide placebo* pens *DUN* ~~code numbers~~ will be ~~assessed~~ *checked* against the dispensed *DUNs* ~~code numbers~~ and in case of discrepancies the subject must be asked.
~~The target dose of liraglutide or placebo is 1.8 mg. If 1.8 mg per day is not tolerated, the subject can stay on 1.2 mg per day.~~
Subjects are asked to report the actual daily *liraglutide* dose in the e-dairy. Prior to or during each visit/phone contact the investigator or delegated staff should review the subject's compliance with regards to liraglutide/*liraglutide* placebo treatment.

2.39 Section 13.3 E-diaries

The e-diary device will be returned by the subjects at the EOT visit *or if the subject is screen failed between Visit 2 and Visit 3*.

2.40 Section 17.4.1.1 Efficacy endpoints

Number of insulin injections
The number of insulin injections will be derived as the average of the reported number on the three days prior to the visit. The endpoints will be summarised using descriptive statistics.

Number of weeks off bolus insulin
The number of weeks the subject is off bolus insulin will be summarised using descriptive statistics.

2.41 Section 26 Indemnity statement

For Austria: Arzneimittelgesetz (BGBL Nr. 185/1983) last amended with BGBl. I Nr. ~~48/2013~~ *105/2015*.

Protocol Amendment

no 3
to Protocol, final version 4.0
dated 14 March 2016

Trial ID: NN9828-4150

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

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

GLP-1 diabetes, NADs & Complications TrialOps 1

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment was prepared to accommodate the recent results from two Novo Nordisk biomarker studies. Based on the outcome of these two studies, the profiling of the immune biomarkers described in the NN9828-4150 protocol will be changed as well as the sample frequency.

In addition, to increase the recruitment pace two more countries have been added to this NN9828-4150 trial (Poland and Belgium). Since Belgium has been added as country, appropriate sections have been updated to reflect specific Belgian requirements.

Novo Nordisk has conducted two exploratory studies where the longitudinal variation of several immune biomarkers over 1 to 1.5 years was evaluated in pre-diabetic and type 1 diabetic subjects. The result from these studies demonstrated that the frequency of islet-specific auto-reactive CD8+ T-cells was too low and the variation was too high to provide meaningful information. Therefore, it has been decided not to include this analysis (QDOT) in the trial. Immune profiling using flow cytometry will still be performed and the final flow panels will be decided prior to the analysis of the first trial sample. This change will not change the sampling or the isolation of the immune cells from peripheral blood mononuclear subpopulations (PBMCs).

Furthermore, in the biomarker studies it was observed that the variation of the profiling of non-antigen-specific T-cells and other immune populations was low. This will allow for the sampling frequency to be decreased from every 3rd months with 2 baseline samples to every ½ year with 1 baseline samples.

Also as part of these two biomarker studies, anti-GAD65 and anti-insulin antibody (GAD and IAA, respectively) isotyping was performed and evaluated. The results demonstrated that such analyses was not informative, particularly in subjects who are on exogenous insulin treatment as this impacts the IAA formation and level. Therefore, isotyping of GAD and IAA will also been removed from the protocol.

Including the immune phenotyping of PBMC as biomarkers will allow us to evaluate effects related to anti-IL-21 treatment. Several publications have demonstrated IL-21 effects these immune populations. The removal of the evaluation of the specific detection of auto-reactive CD8+ T-cells and isotyping of IAA and GAD is not expected to have implications on the scientific content or interpretation

These changes will significantly lower the amount of blood samples from the subjects. The immunology profiling sample will be taken at the following visits; 3, 31, 63, 89.

In addition, editorial changes are introduced in this amendment.

In section 2 distinction between 'the first 80 subjects' and 'once 80 subjects have been randomised' flowcharts have been clarified and made clearer.

In section 4.2.2.3 the supportive secondary biomarker endpoints has been changed/updated to account for the changes made to the immune biomarkers.

In section 5.3.1 the importance of accessing infection parameters prior of NNC0114-0006/NNC0114-0006 placebo infusion has been emphasised.

Section 8.5.1 has been updated to reflect the changes made to the biomarker assessment. The isotypes have been deleted and the future PBMC analyses have been specified in details.

In addition, changes to section 6.3 are introduced to reflect specific requirements for Belgium and United Kingdom and in section 26 to reflect specific Belgian requirements in this amendment.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Section 2 Flow chart

The full PK profile consisting of 25 samples is only applicable for the first minimum 80 subjects. The remaining subjects will follow a reduced visit scheduled outlined in the flowchart (reference section 2.2) "Visit procedures once 80 subjects have been randomised"

2.1 Flowchart for the first 80 randomised subjects only

Visit 1 to 37 procedures <u>for the first 80 randomised subjects only</u>

Trial periods	S		R	Treatment																											
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	1D	3D	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4				± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
SUBJECT RELATED INFO/ASSESSMENTS																															
Informed consent	x																														
Genotyping consent, optional	x																														
Long term retention consent, optional	x																														
In/exclusion criteria	x	x	x																												
Randomisation			x																												
Randomisation criteria			x																												

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	-D10	0	1D	3D	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Dosing day exclusion criteria[1]			x										x				x				x				x				x			
Abuse of alcohol	x																															
Abuse of drugs	x																															
Medical history	x																															
Concomitant illness	x																															
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Demography	x																															
Diagnosis of diabetes	x																															
Diabetes treatment history	x																															
Pregnancy test[2]	x																															
Smoking habits	x																															
Family history of diabetes	x																															
Diabetes complications	x																															
Blood sample for genotyping (optional)			x																													
EFFICACY																																
Glucose metabolism	x		x										x				x				x				x				x			
Meal test[3]		x															x								x							
Self-measured plasma glucose:																																

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	-D10	0	1D	3D	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
7-point profile prior to visit			x	x	x	x		x			x		x		x		x				x				x				x			
4-point profile prior to visit[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
PRO questionnaires			x																						x							
Biomarkers:																																	
Antibodies (autoantibodies)	x		x										x				x								x							
~~Anti-IAA and - GAD isotypes~~			~~x~~																						~~x~~							
Immune phenotyping			*x*																						*x*							
~~Immunology~~ *Total IL-21*		~~x~~	x	x	x	x							x				~~x~~								x							
Vitamin D (1,25 dehydroxy-calciferol			x										x				x								x							
Dose of insulin administrations		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Carbohydrate intake		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
SAFETY																																	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Hyperglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Body measurements[5]	x	x	x			x	x			x			x		x		x		x		x		x		x		x		x			
ECG	x[6]		x		x								x				x								x							

Trial periods	S		R	Treatment																											
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37		
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	-D10	0	1D	3D	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30		
Visit window (days)		± 4				± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3		
Eye examination			x[7]																												
Physical examination	x		x		x	x							x				x								x						
Vital signs	x		x		x	x	x			x			x		x		x				x				x				x		x
Antibodies:																															
Anti-NNC0114-0006 antibodies			x														x								x						
Anti-liraglutide antibodies			x														x								x						
IgE			x			x							x				x								x						
Biochemistry	x		x			x							x				x								x						
Coagulation parameters	x		x			x							x				x								x						
Haematology	x		x			x							x				x								x						
Cytokines			x										x				x								x						
Urine dipsticks	x		x			x							x				x								x						
Hepatitis B	x									x					x				x				x				x				
Hepatitis C	x																														
Tuberculosis screening test (QuantiFERON)	x																														
Epstein–Barr virus	x									x					x				x				x				x				
CMV[8]	x									x					x				x				x				x				
HIV	x																														
Hormones	x																x								x						

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	-D10	0	1D	3D	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
Lipids			x														x								x							
OTHER ASSESSMENTS																																
PK sampling NNC0114-0006			x[9]	x	x	x	x			x			x		x		x				x				x				x			
PK sampling Liraglutide[10]			x	x	x	x	x			x			x		x		x				x				x				x			
TRIAL MATERIAL																																
IV/IWRS	x		x										x				x				x				x				x			
Administration and dispensing of trial product NNC0114-0006/placebo			x										x				x				x				x				x			
Dispensing of liraglutide/placebo[11]			x										x				x				x				x				x			
Drug accountability for IMP[12]			x										x				x				x				x				x			
REMINDERS																																
Handout ID cards	x																															
Handout direction for use[13]			x																													
Handout and instruct in e-diary		x																														
Investigator review of e-diary			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Handout and instruct in BG meter use		x																														
Attend fasting visit		x	x										x				x				x				x				x			
Blood sample for long term			x																						x							

Trial periods	S		R	Treatment																												
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to -D14	-D10	0	1D	3D	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4				± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3				
retention (optional)																																

1. Only for NNC0114-0006
2. Blood sample at V1. For all subsequent visits a urine stick must only be measured for females of childbearing potential if a menstrual period is missed or as required by law. **Austria:** Urine-stick pregnancy test will be performed monthly. **Ireland:** Urine-stick pregnancy test will be performed at all visits to the clinic.
3. The MMTT may be re-scheduled twice within 10 days. At Visit 2 the MMTT must be performed before Visit 3 and leaving sufficient time for randomisation lab results.
4. 4-point profile will be used for T-T-T
5. At V1 height and weight will be measured and BMI will be calculated via the eCRF. At the following visits only weight must be measured
6. A baseline ECG performed for any reason unrelated to the trial within 30 days prior to V1 is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime
7. A baseline fundoscopy/ fundus photography performed for any reason unrelated to the trial within 90 days prior to V3 is acceptable. *Fundoscopy/ fundus photography can be performed at V2.*
8. Cytomegalovirus
9. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
10. PK sample at any time during the visit
11. Liraglutide/liraglutide placebo will be administered once daily
12. Investigational medicinal product
13. Injection of liraglutide will be trained at V3 and at following visits as needed.

Visit 38 to 90 procedures <u>for the first 80 randomised subjects only</u>

Trial period	Treatment																				Follow-up								
Visit type: C: Clinic, P: Phone contact	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]	
Timing of visit (weeks (W), or days (D) if specified)	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80		
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7	
SUBJECT RELATED INFO/ASSESSMENTS																													
Withdrawal criteria	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Dosing day exclusion criteria[2]				x				x				x																	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[3]																			x										
Diabetes complications																			x								x		
EFFICACY																													
Glucose metabolism				x				x				x							x		x		x		x		x		
Meal test[4]				x															x				x				x		
Self-measured plasma glucose:																													
7-point profile prior to visit				x				x				x							x		x		x		x		x		
4-point profile prior to visit[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PRO questionnaires																			x								x		
Biomarkers:																													
Antibodies (autoantibodies)				x															x				x				x		
~~Anti-IAA and GAD isotypes~~				~~x~~																							~~x~~		

Trial period	Treatment																				Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]	
Timing of visit **(weeks (W), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80		
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7	
Immune phenotyping																			*x*								*x*		
~~Immunology~~ *Total IL-21*				~~x~~															x				~~x~~				x		
Vitamin D (1,25 dehydroxy-calciferol)				x															x				X				x		
Dose of insulin administrations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Carbohydrate intake	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY																													
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hyperglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x										
Body measurements		x		x		x		x		x		x			x		x		x		x		x		x		x	x	x
ECG				x								x							x				x				x	x	
Eye examination[6]																			x								x		
Physical examination				x								x							x				x				x	x	
Vital signs				x				x				x							x		x		x		x		x	x	
Antibodies:																													
Anti-NNC0114-0006 antibodies				x															x								x	x	
Anti-liraglutide antibodies				x															x		x						x	x	
IgE				x								x							x		x		x				x	x	
Biochemistry				x								x							x				x				x	x	
Coagulation parameters				x								x							x				x				x	x	

Trial period	Treatment																				Follow-up									
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]			
Timing of visit **(weeks (W), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80				
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7			
Haematology				x								x							x				x				x	x			
Cytokines				x								x							x				x				x	x			
Urine dipsticks				x								x							x				x				x	x			
Hepatitis B		x				x				x									x												
EBV		x				x				x									x												
CMV		x				x				x									x												
Hormones				x								x							x				x				x	x			
Lipids				x								x							x				x				x	x			
OTHER ASSESSMENTS																															
PK sampling NNC0114-0006				x				x				x[7]	x	x	x		x		x		x		x		x		x	x			
PK sampling Liraglutide				x				x				x	x	x	x		x		x												
TRIAL MATERIAL																															
IV/IWRS				x				x				x							x								x				
Administration and dispensing of trial product NNC0114-0006/placebo				x				x				x																			
Dispensing of liraglutide/placebo				x				x				x																			
Drug accountability for IMP				x				x				x							x												
REMINDERS																															
Investigator review of e-diary	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Attend fasting visit				x				x				x							x		x		x		x		x	x			
Blood sampling for long term retention (optional)																			x								x				

Trial period	Treatment																Follow-up									
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit **(weeks (W), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7
End of dosing												x [8]							x [9]									
Collection of e-diary																											x	x
End of trial																											x	x
Sign off Casebook																											x	x

1. Safety follow-up visit. To be conducted for subjects who have been withdrawn less than 14 weeks after last dose of NNC0114-0006/placebo. The visit should be conducted 15 weeks ± 1 week after last dose of NNC0114-0006/placebo
2. Only for NNC0114-0006
3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. **Austria:** Urine-stick pregnancy test will be performed monthly. **Ireland:** Urine-stick pregnancy test will be performed at all visits to the clinic.
4. The MMTT may be re-scheduled twice within 10 days
5. 4-point profile will be used for T-T-T
6. A fundoscopy/ fundus photography may be performed up to 2 weeks before or after V63 and up to 2 weeks before V89
7. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
8. Last dosing of NNC0114-0006/placebo
9. Last dosing of liraglutide/liraglutide placebo is the day prior to V63

2.2 Flowchart for once 80 subjects have been randomised

Visit 1 to 37 procedures <u>once 80 subjects have been randomised</u>

Trial periods	S		R	Treatment																								
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37		
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30		
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3		
SUBJECT RELATED INFO/ASSESSMENTS																													
Informed consent	x																												
Genotyping consent, optional	x																												
Long term retention consent, optional	x																												
In/exclusion criteria	x	x	x																										
Randomisation			x																										
Randomisation criteria			x																										
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dosing day exclusion criteria[1]			x								x				x				x				x						x
Abuse of alcohol	x																												
Abuse of drugs	x																												
Medical history	x																												
Concomitant illness	x																												
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																												
Diagnosis of diabetes	x																												
Diabetes treatment history	x																												
Pregnancy test[2]	x																												
Smoking habits	x																												

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	P	P	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Family history of diabetes	x																													
Diabetes complications	x																													
Blood sample for genotyping (optional)			x																											
EFFICACY																														
Glucose metabolism	x		x								x				x				x				x				x			x
Meal test[3]		x													x								x							
Self-measured plasma glucose:																														
7-point profile prior to visit			x	x		x			x		x		x		x				x				x				x			x
4-point profile prior to visit[4]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
PRO questionnaires			x																				x							
Biomarkers:																														
Antibodies (autoantibodies)	x		x								x				x								x							
~~Anti IAA and GAD Isotypes~~			~~x~~																				~~x~~							
Immune phenotyping			*x*																				*x*							
~~Immunology~~ *Total IL-21*			~~x~~ x	x							x				~~x~~								x							
Vitamin D (1,25 dehydroxy-calciferol			x								x				x								x							
Dose of insulin administrations		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Carbohydrate intake		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
SAFETY																														

Trial periods	S		R	Treatment																									
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Hyperglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Body measurements[5]	x	x	x	x	x			x			x		x		x		x		x		x		x		x		x			
ECG	x[6]		x	x							x				x								x							
Eye examination			x[7]																											
Physical examination	x		x	x							x				x								x							
Vital signs	x		x	x	x			x			x		x		x				x				x				x			
Antibodies:																														
Anti-NNC0114-0006 antibodies			x												x								x							
Anti-liraglutide antibodies			x												x								x							
IgE			x	x							x				x								x							
Biochemistry	x		x	x							x				x								x							
Coagulation parameters	x		x	x							x				x								x							
Haematology	x		x	x							x				x								x							
Cytokines			x								x				x								x							
Urine dipsticks	x		x	x							x				x								x							
Hepatitis B	x							x					x				x				x				x					

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	P	P	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Hepatitis C	x																													
Tuberculosis screening test (QuantiFERON)	x																													
Epstein–Barr virus	x							x					x				x				x				x					
CMV[8]	x							x					x				x				x				x					
HIV	x																													
Hormones	x														x								x						
Lipids			x												x								x						
OTHER ASSESSMENTS																														
PK sampling NNC0114-0006			x[9]	x	x			x			x		x		x				x				x			x				x
PK sampling Liraglutide[10]			x	x	x			x			x		x		x				x				x			x				x
TRIAL MATERIAL																														
IV/IWRS	x		x								x				x				x				x			x				x
Administration and dispensing of trial product NNC0114-0006/placebo			x								x				x				x				x			x				x
Dispensing of liraglutide/placebo[11]			x								x				x				x				x			x				x
Drug accountability for IMP[12]			x								x				x				x				x			x				x
REMINDERS																														
Handout ID cards	x																													

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37				
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30				
Visit window (days)		± 4		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3		
Handout direction for use[13]			x																											
Handout and instruct in e-diary		x																												
Investigator review of e-diary			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Handout and instruct in BG meter use		x																												
Attend fasting visit		x	x								x				x				x				x				x			
Blood sample for long term retention (optional)			x																				x							

1. Only for NNC0114-0006
2. Blood sample at V1. For all subsequent visits a urine stick must only be measured for females of childbearing potential if a menstrual period is missed or as required by law. **Austria:** Urine-stick pregnancy test will be performed monthly. ***For Belgium:*** *A monthly urine pregnancy test is mandatory for female subjects of childbearing potential.* **Ireland:** Urine-stick pregnancy test will be performed at all visits to the clinic.
3. The MMTT may be re-scheduled twice within 10 days. At Visit 2 the MMTT must be performed before Visit 3 and leaving sufficient time for randomisation lab results.
4. 4-point profile will be used for T-T-T
5. At V1 height and weight will be measured and BMI will be calculated via the eCRF. At the following visits only weight must be measured
6. A baseline ECG performed for any reason unrelated to the trial within 30 days prior to V1 is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime
7. A baseline fundoscopy/ fundus photography performed for any reason unrelated to the trial within 90 days prior to V3 is acceptable. *Fundoscopy/ fundus photography can be performed at V2.*
8. Cytomegalovirus

9. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
10. PK sample at any time during the visit
11. Liraglutide/liraglutide placebo will be administered once daily
12. Investigational medicinal product
13. Injection of liraglutide will be trained at V3 and at following visits as needed.

Visit 38 to 90 procedures *once* ~~after~~ 80 subjects have been randomised

Trial period	Treatment																	Follow-up								
Visit type: C: Clinic, P: Phone contact	P	C	P	C	P	C	P	C	P	C	P	C	P	P	P	P	C	P	P	P	C	P	P	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit (weeks (W), or days (D) if specified)	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 7
SUBJECT RELATED INFO/ASSESSMENTS																										
Withdrawal criteria	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dosing day exclusion criteria[2]				x				x				x														
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[3]																	x									
Diabetes complications																	x							x		
EFFICACY																										
Glucose metabolism				x				x				x					x				x			x		
Meal test[4]				x													x				x			x		
Self-measured plasma glucose:																										
7-point profile prior to visit				x				x				x					x		x		x		x		x	
4-point profile prior to visit[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Trial period	Treatment																	Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	P	P	P	P	C	P	P	P	C	P	P	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit **(weeks (W), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 7
PRO questionnaires																	x								x	
Biomarkers:																										
Antibodies (autoantibodies)				x													x				x				x	
~~Anti-IAA and GAD isotypes~~				~~x~~																					~~x~~	
Immune phenotyping																	x								x	
~~Immunology~~ *Total IL-21*				~~x~~													x				~~x~~				x	
Vitamin D (1,25 dehydroxy-calciferol)				x													x				x				x	
Dose of insulin administrations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Carbohydrate intake	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY																										
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hyperglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x									
Body measurements		x		x		x		x		x		x					x				x				x	x
ECG				x								x					x				x				x	x
Eye examination[6]																	x								x	
Physical examination				x								x					x				x				x	x
Vital signs				x				x				x					x				x				x	x
Antibodies:																										
Anti-NNC0114-0006 antibodies				x													x								x	x
Anti-liraglutide antibodies				x													x								x	x

Trial period	Treatment																	Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	P	P	P	P	C	P	P	P	C	P	P	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit **(weeks (W), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 7
IgE				x								x					x				x				x	x
Biochemistry				x								x					x				x				x	x
Coagulation parameters				x								x					x				x				x	x
Haematology				x								x					x				x				x	x
Cytokines				x								x					x				x				x	x
Urine dipsticks				x								x					x				x				x	x
Hepatitis B		x				x				x							x									
EBV		x				x				x							x									
CMV		x				x				x							x									
Hormones				x								x					x				x				x	x
Lipids				x								x					x				x				x	x
OTHER ASSESSMENTS																										
PK sampling NNC0114-0006				x				x				x[7]					x				x				x	x
PK sampling Liraglutide				x				x				x					x									
TRIAL MATERIAL																										
IV/IWRS				x				x				x					x								x	
Administration and dispensing of trial product NNC0114-0006/placebo				x				x				x														
Dispensing of liraglutide/placebo				x				x				x														
Drug accountability for IMP				x				x				x					x									
REMINDERS																										
Investigator review of e-diary	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x
Attend fasting visit				x				x				x					x				x				x	x

Trial period	Treatment																	Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	P	P	P	P	C	P	P	P	C	P	P	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit **(weeks (W), or days (D) if specified)**	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 7
Blood sampling for long term retention (optional)																	x								x	
End of dosing												x[8]					x[9]									
Collection of e-diary																									x	x
End of trial																									x	x
Sign off Casebook																									x	x

1. Safety follow-up visit. To be conducted for subjects who have been withdrawn less than 14 weeks after last dose of NNC0114-0006/placebo. The visit should be conducted 15 weeks ± 1 week after last dose of NNC0114-0006/placebo
2. Only for NNC0114-0006
3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. **Austria:** Urine-stick pregnancy test will be performed monthly. ***For Belgium:*** *A monthly urine pregnancy test is mandatory for female subjects of childbearing potential*. **Ireland:** Urine-stick pregnancy test will be performed at all visits to the clinic.
4. The MMTT may be re-scheduled twice within 10 days
5. 4-point profile will be used for T-T-T
6. A fundoscopy/ fundus photography may be performed up to 2 weeks before or after V63 and up to 2 weeks before V89
7. PK sample for NNC0114-0006 (pre-dose and 1 hour sample after start of infusion)
8. Last dosing of NNC0114-0006/placebo
9. Last dosing of liraglutide/liraglutide placebo is the day prior to V63

2.2 Section 4.2.2.3 Supportive secondary biomarker endpoints

- Change in biomarker parameters from baseline to week 54 and week 80
  - ~~T-cell profiling including islet-specific auto-reactive CD8+ T-cells~~
  - *Immune phenotyping of peripheral blood mononuclear cells (PBMC) (the analyses will include, but are not restricted to, the following populations):*
    - *NK subpopulations*
    - *Monocyte subpopulations*
    - *CD8+ & CD4+ subpopulations (e.g., anergy/exhaustion vs. activation; memory, effector, regulatory cells; follicular helper (Tfh) & regulatory Tfh)*
  - *Total* IL-21
  - ~~Islet a~~*A*utoantibodies against glutamic acid decarboxylase *65* (GAD), zinc-transporter 8 (ZnT8), islet antigen-2 (IA2), insulin autoantibody (IAA)~~, isotypes of IAA and GAD~~
- Change in serum vitamin D (1,25 dehydroxy-calciferol) from baseline to week 54 and week 80

2.3 Section 5.3.1 NNC0114-0006

NNC0114-0006 C 100 mg/ml and NNC0114-0006 C 0 mg/ml will be administered as an i.v. infusion every 6 weeks (first administration Week 0 and last administration Week 48) at the trial sites. The i.v. infusion of NNC0114-0006 C 100 mg/ml or NNC0114-0006 C 0 mg/ml will be administered according to instructions as detailed in the Trial Materials Manual (TMM). Subjects will remain at the clinical trial site for at least 2 hours after completion of NNC0114-0006 C 100 mg/ml or NNC0114-0006 C 0 mg/ml administration to be observed for AEs. On days with MMTT the administration of NNC0114-0006/placebo, may be done during the MMTT.

It must be confirmed by the investigator that infection parameters for Epstein-Barr, cytomegalovirus and hepatitis B (i.e. IgM EBV antibodies, IgG EBV nuclear antigen, CMV IgM, CMV IgG, HBcAB, HBsAb, HBsAg) have been accessed prior each infusion.

2.4 Section 6.3 Exclusion criteria

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential not using highly effective contraceptive methods for the duration of the trial (highly effective contraceptive measures, as required by local regulations or practice, i.e. a measure that results in less than 1% per year failure rate when used consistently and correctly)

For Belgium: *Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used*

consistently and correctly; such as implants, injectables, combined oral contraceptives, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) or vasectomised partner.

4. Male of reproductive age who or whose partner(s) is not using highly effective contraceptive methods for the duration of the trial (highly effective contraceptive measures, as required by local regulation or practice, i.e. a measure that results in less than 1% per year failure rate when **used consistently and correctly**).

For United Kingdom: *Male patients who are sexually active and have partners must use a barrier method of contraception (e.g. condom) for the duration of the study*

2.5 Section 8.5.1.3 Biomarkers

Auto-Antibodies ~~& isotypes~~

The autoantibodies are used to confirm the clinical diagnosis of T~~D~~1*D*M at screening and the assessments during the trial will give information of disease development. ~~Further during the trial, isotypes of anti-insulin (IAA) and of anti-GAD autoantibodies will also be determined. Isotypes will change over time as the diabetes-associated immune response progresses or is modified by therapy. Therefore, autoantibody isotypes will provide information regarding the immune and disease status of an individual.~~

Blood samples for ~~a~~*A*utoantibodies will be drawn according to Section 2. ~~The following autoantibodies will beanalysed:~~

- Anti-GAD
- Anti-ZnT8
- Anti-IA2
- Anti-IAA, excepted at Visit 1

~~Additionally, isotypes for anti-IAA and –GAD will be evaluated according to Section 2..~~

~~Anti-IAA and –GAD isotypes will be analysed at a specialised laboratory and only if the sample is positive for anti-IAA or anti-GAD antibodies. These results will be reported to the investigator at the end of the trial.~~

Immunology

T1DM is mediated by immune destruction of the islets, characterised by T-cell infiltrate and detectable autoantibodies in the periphery. ~~Additionally, IL-21 is an important immune-modifying~~

~~cytokine that has been demonstrated to impact B- and T-cell compartments.~~ The assays proposed will assess the disease- and treatment-associated effects on the immune response mediating T1D*M*.

Samples will be drawn according to Section 2. ~~The investigator must record the date and the exact time for sampling the blood.~~

The following will be analysed *for exploratory reasons:*

- ~~T-cell profiling including islet-specific auto reactive CD8+ T-cells, except at Visit 4, 5 and 6~~
- ~~IL-21, except at Visit 2~~

- *Immune phenotyping of PBMC populations (the analyses will include, but are not restricted to, the following populations):*

    - *NK subpopulations*

    - *Monocyte subpopulations*

    - *CD8+ & CD4+ subpopulations (e.g., anergy/exhaustion vs. activation; memory, effector, regulatory cells; follicular helper (Tfh) & regulatory Tfh)*

- The blood sampling for assessment of ~~T cell profiling including islet specific auto reactive CD8+ T cells~~ *PBMC populations* should ~~preferably~~, if possible, be performed at about the same time of day *each time* for a given subject.

- *The PBMCs will be stored for up to 15 years for potential future assessments if the subject has consented to it (see Section 24.2).*

- *Total IL-21*~~, except at Visit 2~~

The IL-21 analysis will be of exploratory reasons and analysed at a specialised laboratory. The assay measure IL-21 bound to NNC0114-0006. Samples taken at predose will be equal to free IL-21 ~~should be pre-dose if the NNC0114-0006 is given at the sampling visits~~. *All other sampling will measure total IL-21*

~~The blood sampling for assessment of T-cell profiling including islet-specific auto reactive CD8+ T-cells should preferably be performed at about the same time of day for a given subject.~~

Blood sampling for the assessment of Il-21 should be pre-dose if the NNC0114-0006 is given at the sampling visits. IL-21 will be analysed at a specialised laboratory only if a functioning assay is available in due time to ensure analyses and results are ready for data base lock. The investigator will receive the results of the immunology assessments at the end of the trial. If no functional assay is available the samples will be destroyed.

~~The periphery blood mononuclear cells (PBMCs) used for the analyses of the T-cell profiling including islet-specific auto reactive CD8+ T-cells will be stored for up to 15 years for potential future assessments if the subject has consented to it (see Section **Error! Reference source not found.**).~~

2.6 Section 8.5.2.1 Pregnancy test

For Belgium: *A monthly urine pregnancy test is mandatory for female subjects of childbearing potential.*

2.7 Section 9.1 Trial products

- The following non-IMPs are used in this trial:

  - Insulin:

  During the trial subjects will receive insulin treatment in order to achieve a metabolic control according to the insulin titration guideline. Subjects will continue their pre-trial insulin treatment. Thus treatment will be considered background treatment. Preferably the type and/or brand of basal and bolus insulin should not be changed throughout the trial.
  Insulin will not be provided by Novo Nordisk.

  - Glucagon

  Glucagon ~~will~~ *can* be used as rescue medication for the treatment of severe hypoglycaemia.
  Glucagon will not be provided by Novo Nordisk.

2.8 Section 18.2 Informed consent

Furthermore if the subject agrees to have a blood sample taken for long term storage of human samples (see Section 8.5.3.2) and/or to have some of the blood stored from the ~~T-cell profiling islet-specific auto reactive CD8+ T-cells~~ *PBMC* samples (see Section 8.5.1.3) a separate signed informed consent form will be obtained from the subject.

2.9 Section 26 Indemnity statement

For Belgium*: Law concerning experiments on the human person of 07 May 2004 - Article 29: §1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain and which shows either a direct or an indirect connection with the trial.*

Protocol Amendment

no 4
to Protocol, final version 4.0
dated 14 March 2016

Trial ID: NN9828-4150

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

Trial phase: 2

Applicable to Poland

Amendment originator:

[redacted]

Clinical, Medical & Regulatory, Poland

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment has been prepared following a request for additional information from the Polish Health Authority - The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Department for Clinical Trials of Medicinal Products – to implement in the protocol the following:

- for women of childbearing potential to use highly effective methods of contraception with their partners during the clinical trial;
- to perform a pregnancy test every month in patients enrolled in the trail.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

Text to be inserted; relates to protocol version 4.0:

2.1 Section 6.3 Exclusion criteria (page 51)

For Poland: Highly effective contraceptive measures are: oral (except low-dose gestagen (lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives, intrauterine device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

2.2 8.5.2.1 Pregnancy test (page 82)

Poland: Urine-stick pregnancy test will be performed monthly.

2.3 Section 2, table text below the table, point 2 (page 20, 25, 30, and 34)

Poland: Urine-stick pregnancy test will be performed monthly.

Protocol Amendment

no 5
to Protocol, final version 6.0
dated 08 November 2016

Trial ID: NN9828-4150

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

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted]

GLP-1 diabetes, NADs & Complications TrialOps 1

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment was prepared to update Protocol NN9828-4150 version 6.0 dated 08 November 2016 with the following changes:

- To allow for the use of Continuous Glucose Monitoring (CGM) and Flash Glucose Monitoring devices for patients having access to these. Allowing the use of these devices will ease the burden for the patients during their trial participation. All end point related data are still to be measured using the BG meter provided by Novo Nordisk and it is hence assessed that neither patient safety nor data integrity is affected by introducing the two device options.

- Visit 4 (V4), in the flowchart for section 2.2 Visit 1 to 37 procedures once 80 subjects have been randomised, was removed in Global Protocol Amendment No. 2 due to removal of PK sampling at this visit. As this visit also serves the purpose of monitoring the patient after initiation of liraglutide/ liraglutide placebo, V4 is re-instated as a phone contact and with safety monitoring only.

- In section 2, the flowchart has been updated to reflect the re-introduction of V4 once 80 patients have been randomised. Furthermore, the tick mark for IV/IWRS call for visit 89 and the drug accountability for visit 3 are removed as these are not applicable. In addition, monthly mandatory urine pregnancy test for female Polish subjects has been incorporated due to a local requirement.

- In section 5.3.4, the period for which systemically corticosteroids, monoamine oxidase (MAO) inhibitors, systemic non-selective beta-blockers and growth hormone as well as treatment with any medication for the indication of diabetes or obesity other than insulin and trial medication is prohibited has been extended to include the follow-up period (week 54 to week 80). Patients may not initiate these medications at any time during the trial period as secondary efficacy parameters may be influenced.

- In section 6.3, contraceptive requirements for Poland have been added. In addition, clarifying editorial changes has been made to the UK requirement for males of reproductive age.

- In section 6.6, it has been clarified that vaccines taken during the follow-up period will not lead to exclusion from the trial as no trial medication is administered. Vaccines are, however, still prohibited medication during the entire trial period.

- In section 8.3.2, the option of using CGM and Flash Glucose Monitoring devices has been introduced.

- In section 8.5.1.1, measurement of non-fasting C-peptide at visit 1 (V1) is removed to reflect the updates in Global Amendment No. 2.

- In section 8.7, it has been emphasised that patients should be re-trained if they fail to comply with the data entry in the eDiary.

- In addition, minor editorial changes are introduced in this amendment.

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 List of abbreviations

CGM Continuous Glucose Monitoring

2.2 Section 2.1 Flowchart for the first 80 randomised subjects only

Visit 1 to 37 procedures <u>for the first 80 randomised subjects only</u>

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	P	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	4	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37		
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	1D	W1	W2	W2+ 1D	W3	W4	W4+ 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30		
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3		
TRIAL MATERIAL																														
Drug accountability for IMP[12]			*									x				x				x				x				x		

2. Blood sample at V1. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. Austria *& Poland*: Urine-stick pregnancy test will be performed monthly. For Belgium: A monthly urine pregnancy test is mandatory for female subjects of childbearing potential. Ireland: Urine-stick pregnancy test will be performed at all visits to the clinic.

Visit 38 to 90 procedures <u>for the first 80 randomised subjects only</u>

Trial period	Treatment																			Follow-up								
Visit type: **C: Clinic, P: Phone contact**	P	C	P	C	P	C	P	C	P	C	P	C	C	C	C	P	C	P	C	P	C	P	C	P	C	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	56	57	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]

Timing of visit (weeks (W), or days (D) if specified)	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W48 + 1D	W48 + 3D	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 7
IV/IWRS				x				x				x							x								~~x~~	

3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. Austria *& Poland*: Urine-stick pregnancy test will be performed monthly. For Belgium: A monthly urine pregnancy test is mandatory for female subjects of childbearing potential. Ireland: Urine-stick pregnancy test will be performed at all visits to the clinic.

2.3 Section 2.2 Flowchart for once 80 subjects have been randomised

Visit 1 to 37 procedures <u>once 80 subjects have been randomised</u>

Trial periods	S		R	Treatment																										
Visit type: C: Clinic, P: Phone contact	C	C	C	*P*	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	*4*	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37		
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	*1D*	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
SUBJECT RELATED INFO/ASSESSMENTS																														
Informed consent	x																													
Genotyping consent, optional	x																													
Long term retention consent, optional	x																													
In/exclusion criteria	x	x	x																											

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	*P*	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	*4*	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	*1D*	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Randomisation			x																											
Randomisation criteria			x																											
Withdrawal criteria			x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Dosing day exclusion criteria[1]			x									x				x				x				x				x		
Abuse of alcohol	x																													
Abuse of drugs	x																													
Medical history	x																													
Concomitant illness	x																													
Concomitant medication	x	x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Demography	x																													
Diagnosis of diabetes	x																													
Diabetes treatment history	x																													
Pregnancy test[2]	x																													
Smoking habits	x																													
Family history of diabetes	x																													

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	*P*	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	*4*	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	*1D*	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Diabetes complications	x																													
Blood sample for genotyping (optional)			x																											
EFFICACY																														
Glucose metabolism	x		x									x				x				x				x				x		
Meal test[3]		x														x								x						
Self-measured plasma glucose:																														
7-point profile prior to visit			x		x		x			x		x		x		x				x				x				x		
4-point profile prior to visit[4]			x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires			x																					x						
Biomarkers:																														
Antibodies (autoantibodies)	x		x									x				x								x						
Immune phenotyping			x																					x						

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	*P*	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	*4*	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	*1D*	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Total IL-21			x		x							x												x							
Vitamin D (1,25 dehydroxy-calciferol)			x									x				x								x						
Dose of insulin administrations		x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Carbohydrate intake		x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY																														
Adverse events	x	x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hyperglycaemic episodes		x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes		x	x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints			x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Body measurements[5]	x	x	x		x	x			x			x		x		x		x		x		x		x		x		x		x
ECG	x[6]		x		x							x				x								x						
Eye examination			x[7]																											
Physical examination	x		x		x							x				x								x						
Vital signs	x		x		x	x			x			x		x		x				x				x						x
Antibodies:																														
Anti-NNC0114-0006 antibodies			x													x								x						
Anti-liraglutide antibodies			x													x								x						
IgE			x		x							x				x								x						
Biochemistry	x		x		x							x				x								x						

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	*P*	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	*4*	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	*1D*	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
Coagulation parameters	x		x		x							x				x								x						
Haematology	x		x		x							x				x								x						
Cytokines			x									x				x								x						
Urine dipsticks	x		x		x							x				x								x						
Hepatitis B	x								x					x				x				x				x				
Hepatitis C	x																													
Tuberculosis screening test (QuantiFERON)	x																													
Epstein–Barr virus	x								x					x				x				x				x				
CMV[8]	x								x					x				x				x				x				
HIV	x																													
Hormones	x															x								x						
Lipids			x													x								x						
OTHER ASSESSMENTS																														
PK sampling NNC0114-0006			x[9]		x	x			x			x		x		x				x				x				x		
PK sampling Liraglutide[10]			x		x	x			x			x		x		x				x				x				x		
TRIAL MATERIAL																														
IV/IWRS	x		x									x				x				x				x				x		
Administration and dispensing of trial			x									x				x				x				x				x		

Trial periods	S		R	Treatment																										
Visit type: **C: Clinic, P: Phone contact**	C	C	C	*P*	C	C	P	P	C	P	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
Visit number	1	2	3	*4*	6	7	8	9	10	11	12	13	14,15	16	17,18	19	20-22	23	24	25	26-28	29	30	31	32-34	35	36	37			
Timing of visit (weeks (W), or days (D) if specified)	-D28 to –D14	-D10	0	*1D*	W1	W2	W2 + 1D	W3	W4	W4 + 1D	W5	W6	W7,8	W9	W10,11	W12	W13-15	W16	W17	W18	W19-21	W22	W23	W24	W25-27	W28	W29	W30			
Visit window (days)		± 4			± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3	± 1	± 3			
product NNC0114-0006/placebo																															
Dispensing of liraglutide/placebo[11]			x									x				x				x				x				x			
Drug accountability for IMP[12]			~~x~~									x				x				x				x				x			
REMINDERS																															
Handout ID cards	x																														
Handout direction for use[13]			x																												
Handout and instruct in e-diary		x																													
Investigator review of e-diary			x	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Handout and instruct in BG meter use		x																													
Attend fasting visit		x	x									x				x				x				x				x			
Blood sample for long term retention (optional)			x																					x							

2. Blood sample at V1. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. Austria *& Poland*: Urine-stick pregnancy test will be performed monthly. For Belgium: A monthly urine pregnancy test is mandatory for female subjects of childbearing potential. Ireland: Urine-stick pregnancy test will be performed at all visits to the clinic.

Visit 38 to 90 procedures <u>once 80 subjects have been randomised</u>

Trial period	Treatment																	Follow-up								
Visit type: C: Clinic, P: Phone contact	P	C	P	C	P	C	P	C	P	C	P	C	P	P	P	P	C	P	P	P	C	P	P	P	C	C
Visit number	38-40	41	42	43	44-46	47	48	49	50-52	53	54	55	58,59	60	61	62	63	64-68	69	70-73	74	75-77	78	79-88	89	90[1]
Timing of visit (weeks (W), or days (D) if specified)	W31-33	W34	W35	W36	W37-39	W40	W41	W42	W43-45	W46	W47	W48	W49, 50	W51	W52	W53	W54	W55-59	W60	W61-64	W65	W66-68	W69	W70-79	W80	
Visit window (days)	±1	±3	±1	±3	±1	±3	±1	±3	±1	±3	±1	±3	±1	±1	±1	±1	±3	±1	±1	±1	±3	±1	±1	±1	±3	±7
IV/IWRS				x				x				x					x								*	

3. Blood sample at V63. A urine stick pregnancy test must be performed throughout the trial for females of childbearing potential if a menstrual period is missed or as required by local law. Austria *& Poland*: Urine-stick pregnancy test will be performed monthly. For Belgium: A monthly urine pregnancy test is mandatory for female subjects of childbearing potential. Ireland: Urine-stick pregnancy test will be performed at all visits to the clinic.

2.4 Section 5.3.4 Prohibited medication

The following medications must not be used during the treatment period (week 0-54):

~~1. Systemically corticosteroids, monoamine oxidase (MAO) inhibitors, systemic non-selective beta-blockers and growth hormone~~

1. ~~2.~~ Medications or herbal products that can influence the glucose homeostasis (except for insulin) and/or the immune system. It is up to the investigator to judge which herbal products influence on the glucose homeostasis

~~1. Treatment with any medication for the indication of diabetes or obesity other than insulin and trial medication.~~

The following medications must not be used during the trial period (week 0-80):

1. ~~Live v~~*V*accines *with the exception of influenza vaccination according to local diabetes treatment requirements. The influenza vaccine can be given 3 weeks after a dose of NNC0114-0006 and 2 weeks before next dose of NNC0114-0006.*

2. *Systemically corticosteroids, monoamine oxidase (MAO) inhibitors, systemic non-selective beta-blockers and growth hormone unless only prescribed for a short period of time and if determined by investigator not to have an significant extended half-life*

3. *Treatment with any medication for the indication of diabetes or obesity other than insulin and trial medication.*

2.5 Section 6.3 Exclusion criteria

3. *For Poland: Highly effective contraceptive measures are: oral (except low-dose gestagen (lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives, intrauterine device, intrauterine system (for example, progestin-releasing coil), vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate).*

4. For United Kingdom: Male patients who are sexually active ~~*and have partners*~~ must use a barrier method of contraception (e.g. condom) for the duration of the study.

2.6 Section 6.6 Withdrawal criteria

8. Initiation of any prohibited medication (see Section 5.3.4). *Use of vaccines in the follow-up period (week 54 to week 80) is prohibited but will not lead to subject withdrawal.*

2.7 Section 8.3.2 Self-measured blood glucose

Subjects will be instructed in how to record the results of the self-measured blood glucose (SMBGs) in the e-diaries. The record of each SMPG will include date, time point (e.g. before breakfast, before lunch, etc.) and value. BG should always be measured when a hypo- or hyperglycaemic episode is suspected. Hypoglycaemic and hyperglycaemic episodes will be recorded by the subject in the e-diary (see Section 8.6.3). The investigator may ask the subject to perform additional SMPG measurements if needed for any safety reason.

If subjects have their own CGM or Flash Glucose Monitoring devices they may use these for measuring the 4-point profiles only (i.e. before breakfast, before lunch, before dinner and bedtime) as per section 8.3.3 The use of these devices must be recorded in EDC.

The instruction of use of the CGM and Flash Glucose Monitoring devices is at the discretion of the investigator. These devices will not be supplied nor compensated by Novo Nordisk.

All subjects must receive and be instructed in the use of the blood glucose meter provided by Novo Nordisk. This Novo Nordisk supplied blood glucose meter must be used to:

- *confirm any glucose values measured in connection with a hypoglycaemic episode*
  - *≤ 3.9 mmol/l (70 mg/dl) or*
  - *> 3.9 mmol /l (70 mg/dl) occurring in conjunction with hypoglycaemic symptoms*
- *confirm any glucose values measured in connection with a hyperglycaemic episode*
  - *> 16.7 mmol/l (300 mg/dl)*
- *measure all 7-point profiles (all 7 SMPGs from the same device)*

2.8 Section 8.5.1.1 Glucose metabolism

~~• C-peptide (non-fasting) will be measured at Visit 1~~

2.9 Section 8.5.3.3 Serum concentration of NNC0114-0006 for pharmacokinetics

PK samples will be taken according to Section 2. At Visit 3 and 55, samples will be taken pre-dose (up to 60 min before *V55*) and 1 hour after start of the infusion. At NNC0114-0006 dosing visits, the sample should be taken pre-dose. The investigator must record the date and the exact time for sampling the blood.

2.10 Section 8.7 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed. Substantial failure to comply with the prescribed dose regimen can lead to withdrawal at the discretion of the investigator.

In case of subject non-compliance with data entry in the eDiary, re-training should be performed and documented.

Protocol Amendment

no 6

to Protocol, version 7 dated 02 May 2017

Trial ID: NN9828-4150

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

Trial phase: 2

Applicable to Ireland

Amendment originator:

[redacted]

CMR, Ireland

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment was prepared to update protocol NN9828-4150 version 7.0 dated 02 May 2017 with the following change:

- To update contraceptive requirements for subjects in Ireland as per request from the Irish regulatory authority, the Health Products Regulatory Authority on 12 Oct 2017

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

6.3 Exclusion Criteria

3. ~~For Ireland: Highly effective contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, IUD or intrauterine system or true sexual abstinence.~~

For United Kingdom *and Ireland*: Only highly effective methods of birth control for the duration of the trial are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly). Highly effective contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence*(when in line with preferred and usual lifestyle).
*Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

4. For United Kingdom *and Ireland*: Male patients who are sexually active must use a barrier method of contraception (e.g. condom) for the duration of the study.

Protocol Amendment

no 7

to Protocol, version 7.0 dated 02-May-2017

Trial ID: NN9828-4150

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

Trial phase: 2
Applicable to all countries

Amendment originator:
[redacted]
GLP-1 diabetes, NADs & Complications, TrialOps 1

Table of Contents

1 Introduction including rationale for the protocol amendment

This amendment was prepared to update Protocol NN9828-4150 version 7.0, dated 02 May 2017 with the following changes:

- NN9828-4150 is a 1 year proof of principle trial with 6 months follow-up period. As originally planned, the primary endpoint is at week 54 (visit 63, being last patient last treatment (LPLT)). In addition to the data analysis after last patient last visit (LPLV), Novo Nordisk will introduce an additional database lock (DBL) after visit 63 in order to perform an internal main phase analysis. The DBL will be performed, when all patients have completed the main phase of the trial (treatment period), i.e. after LPLT at visit 63. After the additional DBL, Novo Nordisk will become unblinded, while the trial investigators and patients will remain blinded throughout the entire trial. The objective of the main phase analysis is to inform on future clinical trials. Conduct and design of the ongoing trial will remain unchanged. Following the end of trial, results from the entire trial period (main and extension phase) will be reported.

- To include local Irish Protocol Amendment no 6, dated 17 October 2017, to Protocol version 7.0, dated 02 May 2017. This Amendment contains updates to contraceptive requirements for subjects in Ireland as per request from the Irish regulatory authority, the Health Products Regulatory Authority on 12 October 2017.

- In addition, minor editorial changes are introduced in this amendment.

In this protocol amendment:
- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

2.1 List of abbreviations

DBL	*Database lock*
LPLT	*Last patient last treatment*
~~SMBG~~	~~self-measured blood glucose~~

2.2 Section 6.3 Exclusion criteria

3. ~~For Ireland: Highly effective contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, IUD or intrauterine system or true sexual abstinence.~~

For United Kingdom *& Ireland*: Only highly effective methods of birth control for the duration of the trial are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly). Highly effective contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence*(when in line with preferred and usual lifestyle).

*Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

4. Male of reproductive age who or whose partner(s) is not using highly effective contraceptive methods for the duration of the trial (highly effective contraceptive measures, as required by local regulation or practice, i.e. a measure that results in less than 1% per year failure rate when used consistently and correctly).

For United Kingdom *& Ireland*: Male patients who are sexually active must use a barrier method of contraception (e.g. condom) for the duration of the study.

2.3 Section 17.5 Interim analysis

No formal interim analysis has been planned.-*However, an internal Novo Nordisk analysis is to be conducted after global last patient last treatment (LPLT) (visit 63) to inform on future clinical trials. An additional database lock (DBL) will be performed, when all patients have completed the main phase of the trial, i.e. after LPLT at visit 63. After the additional DBL, Novo Nordisk will become unblinded, while the trial investigators and patients will remain blinded throughout the entire trial.*

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff