# Cover Page for Protocol

| | |
|---|---|
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# Protocol version 7.0

# Trial ID:NN2211-3659:

**Updated protocol including:**
**-Original protocol, version 1.0, dated 20 January 2012**
**-Local Substantial protocol amendment no. 1, version 1.0, dated 23 February 2012 (Israel)**
**-Local Substantial protocol amendment no. 2, version 1.0, dated 30 May 2012 (United States of America)**
**-Global Substantial protocol amendment no. 3, version 1.0, dated 26 July 2012 (All countries)**
**-Global Substantial protocol amendment no. 4, version 1.0, dated 11 October 2012 (All countries)**
**Local Substantial protocol amendment no. 5, version 1.0, dated 29 October 2012 (Sweden)**
**Global Substantial protocol amendment no. 7, version 1.0 dated 23 May 2013 (All countries)**
**Global protocol amendment no. 10, version 1.0 dated 09 Feb 2015 (All countries)**
**Local amendment no 11 version 1.0 dated 22 April 2014 (Sweden)**
**Global protocol amendment no. 13, version 2.0 dated 28 March 2017 (All countries)**

# Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes

A 26-week double-blind, randomised, parallel group, placebo controlled multi-centre trial followed by a 26-week open-label extension

**Trial phase: 3a**

*Redacted protocol*
*Includes redaction of personal identifiable information only.*

**Protocol originator:**
Name: [redacted], [redacted]
Department or business area: Clinical Operations, Victoza



.

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# List of abbreviations

| | |
|---|---|
| AB | Antibody |
| ADA | American Diabetes Association |
| AE | adverse event |
| ALAT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| ASAT | aspartate aminotransferase |
| Anti-GAD | anti-glutamic acid decarboxylase antibodies |
| AUC | area under the curve |
| BG | blood glucose |
| BMI | body mass index |
| BP | blood pressure |
| CCDS | company core data sheet |
| CEA | carcinoembryonic antigen |
| CFR | code of federal regulation |
| CLAE | clinical laboratory adverse event |
| CNS | central nervous system |
| CRF | case report form |
| CRO | contract research organisation |
| CTA | clinical trial application |
| CTX | C-telopeptide |
| CTR | clinical trial report |
| DCF | data clarification form |

| | |
|---|---|
| DHEAS | dehydroepiandrosterone sulfate |
| DL | detection limit |
| DMC | data monitoring committee |
| DUN | dispensing unit number |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EMA | European Medicines Agency |
| EU | European Union |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FPFV | first patient first visit |
| FPG | fasting plasma glucose |
| FSH | follicle stimulating hormone |
| FU | follow-up visit |
| GCP | good clinical practice |
| GLP-1 | glucagon-like peptide-1 |
| $HbA_{1C}$ | glycosylated haemoglobin $A_{1c}$ |
| HDL | high density lipoprotein |
| HIV | human immunodeficiency virus |
| HOMA | homeostasis model assessment |
| IA-2 | insulinoma associated-protein 2 |
| IB | investigator's brochure |
| ICH | International Conference on Harmonisation |

| | |
|---|---|
| ICMJE | International Committee of Medical Journal Editors |
| ID | identification |
| IEC | independent ethics committee |
| IGF-1 | insulin-growth factor-1 |
| IGF BP-3 | insulin-growth factor-binding protein-3 |
| IMP | investigational medicinal product |
| IND | investigational new drug application |
| IRB | institutional review board |
| i.v. | intravenous |
| IV/WRS | interactive voice/web response system |
| LAR | legally acceptable representative |
| LDL | low density lipoprotein |
| LH | luteinizing hormone |
| LLOQ | lower limit of quantification |
| LOCF | last observation carried forward |
| LPLV | last patient last visit |
| LSMean | least square Mean |
| MAR | missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEN | multiple endocrine neoplasia |
| MESI | medical event of special interest |
| MIDF | monitor initiated discrepancy form |
| MODY | maturity onset of the young |
| MRHD | maximum recommended human dose |

| | |
|---|---|
| MTC | medullary thyroid carcinoma |
| MTD | maximum tolerated dose |
| N | number of subjects |
| NIMP | non-investigational medicinal product |
| NTX | N-telopeptide |
| OAD | oral antidiabetic drug |
| P1NP | serum type 1 procollagen |
| PD | pharmacodynamics |
| PDCO | European Paediatric Committee |
| PG | plasma glucose |
| PP | per protocol |
| PPG | postprandial glucose |
| PK | pharmacokinetics |
| REML | restricted maximum likelihood |
| RMA | repeated measurement analysis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| s.c. | Subcutaneous |
| SD | standard deviation |
| SDS | standard deviation score |
| SDV | source data verification |
| SIF | safety information form |
| SmPC | summary of product characteristics |
| SMPG | self-measured plasma glucose |

| | |
|---|---|
| SOP | standard operational procedure |
| SUSAR | suspected unexpected serious adverse reaction |
| $T_{½}$ | half life |
| TC | telephone contact |
| TMM | trial materials manual |
| TSH | thyroid stimulating hormone |
| UNR | upper normal range |
| US | United States |
| UTN | universal trial number |
| VDLV | very low density lipoprotein |
| WHO | World Health Organisation |

# 1 Summary

**Objectives and endpoints**

**Primary objective**

To confirm the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg) versus placebo when added to metformin with or without basal insulin treatment in controlling glycaemia in children and adolescents (ages 10–17 years) with type 2 diabetes.

**Primary endpoint**

- Change in $HbA_{1c}$ from baseline to week 26

**Key secondary objectives**

To assess and compare the effect of liraglutide versus placebo in combination with metformin with or without basal insulin treatment on:

- Parameters of glycaemic control
- Safety and tolerability

**Key secondary endpoints**

At 26 and 52 weeks of treatment:

- $HbA_{1c}$ <7.0% (yes/no)
- $HbA_{1c}$ ≤6.5% (yes/no)
- $HbA_{1c}$ <7.0% without severe or minor hypoglycaemic episodes (yes/no)

Change from baseline at 26 and 52 weeks of treatment in:

- Fasting plasma glucose (FPG)
- 7-point self-measured plasma glucose
- Body weight
- BMI standard deviation score (SDS)

Safety

- Adverse events (AEs) and serious adverse events (SAEs)
- Safety follow-up after 1 and 2 years**:** AEs and SAEs, growth velocity and pubertal progression

Primary endpoint and key secondary endpoints will be used for clinical trial registers as www.clinicaltrials.gov.

**Trial design**

This is a multi-centre, 26-week randomised double-blind, parallel-group, placebo-controlled clinical trial followed by a 26-week open-label extension in subject's ages 10–17 years with type 2 diabetes. After being titrated to 2000 mg of metformin or maximum tolerated dose (MTD) (metformin dose must be ≥1000 mg and ≤2000 mg) subjects will be randomised 1:1 to receive liraglutide (1.8 mg or MTD) or liraglutide placebo. Subjects treated with basal insulin will continue treatment with basal insulin.

Subjects already treated with 2000 mg or more of metformin and with a stable dose for at least 56 days prior to Visit 1 may advance directly to randomisation (Visit 7) when eligibility according to the inclusion and exclusion criteria has been confirmed. Subjects who are treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days in order to advance directly to Visit 7.

After 26 weeks of blinded treatment, the treatment allocation will be unblinded. Subjects treated with liraglutide will continue their trial medication until end of treatment. Subjects treated with liraglutide placebo will discontinue their liraglutide placebo treatment. Rescue treatment will be allowed for subjects in both treatment groups experiencing confirmed hyperglycaemia. Subjects on rescue medication will stay in the trial.

Subjects treated with liraglutide for more than 3 months will complete 1 and 2 year follow-up visits.

**Trial population**

It is planned to randomise 94 subjects in this trial.

**Key inclusion criteria**

- Children and adolescents between the ages of 10–16 years. Subjects cannot turn 17 and 11 months before the end of treatment (52 weeks)
- Diagnosis of type 2 diabetes mellitus and treated for at least 30 days with:
    - diet and exercise alone
    - diet and exercise in combination with metformin monotherapy
    - diet and exercise in combination with metformin and a stable* dose of basal insulin.
    - diet and exercise in combination with a stable* dose of basal insulin.

*Stable is defined as basal insulin adjustments up to 15%

- HbA1c
    - ≥7.0% and ≤11% if diet and exercise treated
    - ≥6.5% and ≤11% if treated with metformin as monotherapy, basal insulin as monotherapy or metformin and basal insulin in combination

- Body mass index (BMI) >85% percentile of the general age and gender matched population

**Key exclusion criteria**

- Type 1 diabetes
- Maturity onset diabetes of the young (MODY)
- Use of any antidiabetic agent other than metformin and/or basal insulin within 90 days prior to screening.
- Recurrent severe hypoglycaemia or hypoglycaemic unawareness as judged by the investigator
- History of chronic pancreatitis or idiopathic acute pancreatitis
- Any clinically significant disorder, except for conditions associated with type 2 diabetes history which in the investigator's opinion could interfere with results of the trial
- Uncontrolled hypertension, treated or untreated >99th percentile for age and gender in children
- Known or suspected abuse of alcohol or drugs/narcotics

**Key assessments**

Efficacy:

- Glucose metabolism
- Body measurements
- Blood pressure
- Lipids

Safety:

- AEs and SAEs
- Hypoglycaemic episodes
- Biochemistry
- Haematology
- Growth parameters
- Pubertal assessment (Tanner staging)
- Hormones
- Biochemical parameters of bone metabolism
- Formation of anti-liraglutide antibodies

**Trial products**

Novo Nordisk will supply the following trial products:

- Liraglutide, 6.0 mg/mL, 3 mL pen-injector for s.c. injection
- Liraglutide placebo, 3 mL pen-injector for s.c. injection
- Metformin, 500 mg tablets (non-investigational medicinal product)

# 2 Flow chart

| **Trial period** | **Screening and Run-in** | | | | | | **Blinded Treatment** | | | | | | | | | | | | **Unblinded Treatment** | | | | | | | | **FU** | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of visit** | Screen-ing | S | TC | TC | S | TC | (Rando-misation) S | S | S | TC | TC | S | TC | S | TC | S | TC | S | S | TC | S | TC | S | TC | S | S | S | S |
| **Visit number** | 1 | 2[1] | 3[1] | 4[1] | 5[1] | 6[1] | 7 | 8 | 9 | 10 | 10A, 10B[21] | 11, 12 | 11A, 11B[21] | 13 | 14 | 15 | 16 | 17[2,3] | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25[3] | 26 | 27, 28[19] |
| **Time of visit (week)** | -13 | -11 | -10 | -9 | -8 | -4 | 0 | 1 | 2 | 3 | 4, 5 | 6, 10 | 7, 8 | 14 | 17 | 20 | 23 | 26 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 52 | 53 | 104, 156 |
| **Visit window (day)** | Day -91 to day -82 | ±2 | ±2 | ±2 | ±2 | ±2 | 0 | ±2 | ±2 | ±2 | ±2 | ±3 | ±2 | ±3 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±3 | ±14 |
| Informed consent[4] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed assent[4] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| In/exclusion criteria | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomisation | | | | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Randomisation criteria | | | | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Rescue criteria | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | 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 | | | |
| Concomitant illness | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[6] | X[6] |
| Attend blood sampling fasting | X | | | | | | X | | | | | | | X | | | | X | | | | | X | | | X | X[20] | |
| Demography | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Diabetes history | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Smoking habits | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| **Trial period** | **Screening and Run-in** | | | | | | **Blinded Treatment** | | | | | | | | | | | | **Unblinded Treatment** | | | | | | | | **FU** | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of visit** | Screen-ing | S | TC | TC | S | TC | (Rando-misation) S | S | S | TC | TC | S | TC | S | TC | S | TC | S | S | TC | S | TC | S | TC | S | S | S | S |
| **Visit number** | 1 | 2[1] | 3[1] | 4[1] | 5[1] | 6[1] | 7 | 8 | 9 | 10 | 10A, 10B[21] | 11, 12 | 11A, 11B[21] | 13 | 14 | 15 | 16 | 17[2,3] | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25[3] | 26 | 27, 28[19] |
| **Time of visit (week)** | -13 | -11 | -10 | -9 | -8 | -4 | 0 | 1 | 2 | 3 | 4, 5 | 6, 10 | 7, 8 | 14 | 17 | 20 | 23 | 26 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 52 | 53 | 104, 156 |
| **Visit window (day)** | Day -91 to day -82 | ±2 | ±2 | ±2 | ±2 | ±2 | 0 | ±2 | ±2 | ±2 | ±2 | ±3 | ±2 | ±3 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±3 | ±14 |
| Alcohol screen | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine drug screen | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **EFFICACY** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Body weight | X | | | | | | X | | | | | X | | X | | X | | X | X | | X | | X | | X | X | | X |
| Height | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | X |
| BMI | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Waist circumference | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Vital signs | X | | | | X | | X | X | X | | | X | | X | | X | | X | X | | X | | X | | X | X | X | |
| Glucose metabolism[7] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • $HbA_{1c}$ | X | | | | | | X | | | | | X[12] | | X | | | | X | | | | | | | | X | | |
| • Fasting plasma glucose | X | | | | | | X | | | | | | | X | | | | X | | | | | X | | | X | | |
| • Fasting insulin | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| • Fasting pro-insulin | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |

| **Trial period** | **Screening and Run-in** | | | | | | **Blinded Treatment** | | | | | | | | | | | | **Unblinded Treatment** | | | | | | | | | **FU** | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of visit** | Screen-ing | S | TC | TC | S | TC | (Rando-misation) S | S | S | TC | TC | S | TC | S | TC | S | TC | S | S | TC | S | TC | S | TC | S | S | S | S |
| **Visit number** | 1 | 2[1] | 3[1] | 4[1] | 5[1] | 6[1] | 7 | 8 | 9 | 10 | 10A, 10B[21] | 11, 12 | 11A, 11B[21] | 13 | 14 | 15 | 16 | 17[2,3] | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25[3] | 26 | 27, 28[19] |
| **Time of visit (week)** | -13 | -11 | -10 | -9 | -8 | -4 | 0 | 1 | 2 | 3 | 4, 5 | 6, 10 | 7, 8 | 14 | 17 | 20 | 23 | 26 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 52 | 53 | 104, 156 |
| **Visit window (day)** | Day -91 to day -82 | ±2 | ±2 | ±2 | ±2 | ±2 | 0 | ±2 | ±2 | ±2 | ±2 | ±3 | ±2 | ±3 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±3 | ±14 |
| • Fasting C-peptide | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| • Fasting glucagon | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Lipids[7] | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| 7-point SMPG profile | | | | | | | 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 |
| 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 | |
| SMPG measurements[14] | | | | | | | X | X | X | X | X | X[14] | X | | | | | | | | | | | | | | | | |
| ECG[9] | X | | | | | | | | | | | | | | | | | X | | | | | | | | X | | |
| Eye examination [9] | X | | | | | | | | | | | | | | | | | X | | | | | | | | X | | |
| Physical examination | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Tanner staging[17] | | | | | | | X[17] | | | | | | | X[17] | | | | X[17] | | | | | | | | X[17] | | X[17] |
| Bone Age | | | | | | | X | | | | | | | | | | | | | | | | | | | X[18] | | X[18] |
| Haematology[7] | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Biochemistry[7] | X | | | | | | X | | | | | | | X | | | | X | | | | X | | | | X | | |
| Hormones[7] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • Calcitonin | X | | | | | | X | | | | | | | X | | | | X | | | | X | | | | X | | |

| **Trial period** | **Screening and Run-in** | | | | | | **Blinded Treatment** | | | | | | | | | | | | **Unblinded Treatment** | | | | | | | | **FU** | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of visit** | Screen-ing | S | TC | TC | S | TC | (Rando-misation) S | S | S | TC | TC | S | TC | S | TC | S | TC | S | S | TC | S | TC | S | TC | S | S | S | S |
| **Visit number** | 1 | 2[1] | 3[1] | 4[1] | 5[1] | 6[1] | 7 | 8 | 9 | 10 | 10A, 10B[21] | 11, 12 | 11A, 11B[21] | 13 | 14 | 15 | 16 | 17[2,3] | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25[3] | 26 | 27, 28[19] |
| **Time of visit (week)** | -13 | -11 | -10 | -9 | -8 | -4 | 0 | 1 | 2 | 3 | 4, 5 | 6, 10 | 7, 8 | 14 | 17 | 20 | 23 | 26 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 52 | 53 | 104, 156 |
| **Visit window (day)** | Day -91 to day -82 | ±2 | ±2 | ±2 | ±2 | ±2 | 0 | ±2 | ±2 | ±2 | ±2 | ±3 | ±2 | ±3 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±3 | ±14 |
| • Other hormones | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Pregnancy test[7, 10] | X | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Bone metabolism markers[7] | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| Insulin Antibodies[7] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HIV-antibodies[7] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis B and hepatitis C[7] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Liraglutide antibodies[7] | | | | | | | X | | | | | | | | | | | X | | | | | | | | X | | |
| Urinalysis[7] | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| **OTHER ASSESSMENTS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Compliance | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Diet and exercise counselling | | X | | | X | | X | X | X | | | X | | X | | X | | X | X | | X | | X | | X | X | | |
| First day of most recent menstrual period[13] | | | | | | | X | | | | | | | X | | | | X | | | | | | | | X | | |
| PK Sampling[7] | | | | | | | | X | X | | | X[11] | | X | | | | X | | | | | | | | | | |
| **TRIAL MATERIAL** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dispensing visit | | X | | | X | | X | | | | | X | | X | | X | | X[2] | X | | X | | X | | X | | | |

| **Trial period** | **Screening and Run-in** | | | | | | **Blinded Treatment** | | | | | | | | | | | | **Unblinded Treatment** | | | | | | | | **FU** | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of visit** | Screen-ing | S | TC | TC | S | TC | (Rando-misation) S | S | S | TC | TC | S | TC | S | TC | S | TC | S | S | TC | S | TC | S | TC | S | S | S | S |
| **Visit number** | 1 | 2[1] | 3[1] | 4[1] | 5[1] | 6[1] | 7 | 8 | 9 | 10 | 10A, 10B[21] | 11, 12 | 11A, 11B[21] | 13 | 14 | 15 | 16 | 17[2,3] | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25[3] | 26 | 27, 28[19] |
| **Time of visit (week)** | -13 | -11 | -10 | -9 | -8 | -4 | 0 | 1 | 2 | 3 | 4, 5 | 6, 10 | 7, 8 | 14 | 17 | 20 | 23 | 26 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 52 | 53 | 104, 156 |
| **Visit window (day)** | Day -91 to day -82 | ±2 | ±2 | ±2 | ±2 | ±2 | 0 | ±2 | ±2 | ±2 | ±2 | ±3 | ±2 | ±3 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±3 | ±14 |
| Metformin dose titration[16] | | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Liraglutide dose escalation | | | | | | | | X | X | (X) | | | | | | | | | | | | | | | | | | |
| Basal insulin dose titration | | | | | | | | | | | X | X[22] | X | | | | | | | | | | | | | | | |
| Drug accountability | | | | | X | | X | | | | | X | | X | | X | | X | X | | X | | X | | X | X | | |
| IV/WRS call | X | X | | | X | | X | | | | | X | | X | | X | | X[2] | X | | X | | X | | X | X | | |
| Confirmation of liraglutide dose | | | | | | | | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Confirmation of metformin dose | | | | | | | X | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Basal insulin dose information[23] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Dispense subject ID card | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Diary dispense and instruct | X | X | | | X | | X | X | X | | | X | | X | | X | | X | X | | X | | X | | X | | | |
| Diary collect, review, transcribe[8] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Glucose meter dispense and instruct | X[15] | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine container dispense | X[15] | | | | X | | | | | | | X[12] | | | | X | | | | | | | | | X | | | |
| **REMINDERS** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| **Trial period** | **Screening and Run-in** | | | | | | **Blinded Treatment** | | | | | | | | | | | | **Unblinded Treatment** | | | | | | | | **FU** | **FU** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Type of visit** | Screen-ing | S | TC | TC | S | TC | (Rando-misation) S | S | S | TC | TC | S | TC | S | TC | S | TC | S | S | TC | S | TC | S | TC | S | S | S | S |
| **Visit number** | 1 | 2[1] | 3[1] | 4[1] | 5[1] | 6[1] | 7 | 8 | 9 | 10 | 10A, 10B[21] | 11, 12 | 11A, 11B[21] | 13 | 14 | 15 | 16 | 17[2,3] | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25[3] | 26 | 27, 28[19] |
| **Time of visit (week)** | -13 | -11 | -10 | -9 | -8 | -4 | 0 | 1 | 2 | 3 | 4, 5 | 6, 10 | 7, 8 | 14 | 17 | 20 | 23 | 26 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 52 | 53 | 104, 156 |
| **Visit window (day)** | Day -91 to day -82 | ±2 | ±2 | ±2 | ±2 | ±2 | 0 | ±2 | ±2 | ±2 | ±2 | ±3 | ±2 | ±3 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±3 | ±14 |
| End of trial | | | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Case book sign off | | | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Affirmation statement | | | | | | | | | | | | | | | | | | | | | | | | | | | | X |

Unscheduled visits can be scheduled at any time at the discretion of the investigator.

1. Visits 2, 3, 4, 5 and 6 are not applicable for subjects already treated with 2000 mg or more of metformin, diet and exercise for at least 56 days prior to Visit 1 These subjects may advance directly to Visit 7 and be randomised.
2. All assessments at visit 17 should be performed prior to trial medication dispensing as the trial medication dispensing session in IV/WRS at Visit 17 will unblind subjects treatment.
3. In case a subject is being prematurely withdrawn from the trial prior to Visit 17 the investigator must aim to undertake procedures for Visit 17 (End of blinded treatment visit) as soon as possible, if possible. In case a subject is being prematurely withdrawn from the trial after Visit 17 the investigator must aim to undertake procedures for Visit 25 (End of treatment visit) as soon as possible, if possible. In addition Visit 26 should in both cases be completed, between 5 and 10 days after the early termination visit, if possible.
4. Subject will be expected to arrive fasting for Visit 1 blood sampling. The informed consent and assent form must be signed at least one day prior to Visit 1 blood sampling.
   **Only applicable to Israel:** Child assent by signature is not mandatory. Child assent form is not used. A minor may sign the local ICF (form 3A).
5. Type of rescue medication must be captured in the concomitant medication form in the eCRF. Doses should be captured in relevant forms in the eCRF. In addition diabetes medication prescribed at the end of treatment (Visit 25) should be captured in the concomitant medication section of the eCRF.
6. Concomitant medication will be captured only for subjects reporting AEs and SAEs at Visits 26-28.
7. Blood and urine samples will be sent to a central laboratory for analysis. PK and anti liraglutide antibody samples will be shipped from the central laboratory to special laboratories for analysis. Unblinded subjects not treated with liraglutide should not have a blood sample drawn for determination of anti-liraglutide antibodies.
8. At telephone contacts (TCs) information from the diary as reported by the subject and not the physical diary will be collected.
9. At Visit 1 the eye examination (fundoscopy) and ECG can be omitted if the assessments have been performed within 12 weeks of Visit 1. At Visits 17 and 25 the assessments may be performed in the two weeks prior to the visits.

10. At Visits 1, 7, 13, 17 and 25 a blood pregnancy test will be performed in females of childbearing potential. In addition at Visit 7, prior to randomisation, a urine-stick pregnancy test will be performed. During the rest of the trial a urine-stick pregnancy test will be performed if a menstrual period is missed.
    **Austria:** Urine-stick pregnancy test will be performed at all visits to the clinic.
11. PK sampling will be performed at Visit 11 only.
12. Blood sampling for $HbA_{1c}$ and dispensing of urine container will be performed at Visit 12 only.
13. First day of the most recent menstrual period should be captured for females of childbearing potential in the diary prior to Visits 7, 13, 17 and 25.
14. Fasting SMPG measurements should be performed and captured in the diary on 3 consecutive days prior to Visits 7, 8, 9 and 10. Subjects treated with basal insulin at screening will be asked to perform fasting SMPG measurements on the 3 consecutive days preceding Visits 10A, 10B, 11A and 11B. For all other subjects fasting SMPG measurements should be performed 3 times a week (on a weekly basis) between Visits 10 and 11.
15. Subjects already treated with metformin 2000 mg/day for at least 56 days prior to screening may have their BG meter, urine collection container for Visit 7 provided at Visit 1 and advance directly to Visit 7. Subjects who are treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days to advance directly to visit 7**.**
16. In case an extra week for titrating to 2000 mg or maximum tolerated dose of metformin is needed, the titration period can be extended with an additional week, from 3 to 4 weeks. An unscheduled visit between Visits 4 and 5 may be performed to ensure compliance and the safety of the subject before the last dose step at the discretion of the investigator. All subjects who undergo metformin titration including those who require a fourth week to reach a dose of metformin of 2000mg or a maximum tolerated dose, need to undergo the full 8 weeks maintenance period with 2000 mg or maximum tolerated dose of metformin before randomisation.
17. At Visits 7, 13, 17, 25, 27 and 28 the assessments may be performed in the two weeks prior to the visits. Once the subject reaches the Tanner stage V, the Tanner staging assessment no longer requires to be performed.
18. A repeat bone age assessment will not be performed for subjects in whom the bone age assessment at the previous assessments indicates that the epiphyses are fused.
19. Visits 27 and 28 are only applicable for subjects treated with liraglutide for more than 3 months.
20. Prior to blood sampling for liraglutide antibodies subjects must attend without food or drink intake except for water and prescribed medication for at least 2 hours.
21. Visits 10A, 10B, 11A and 11B are only applicable to subjects treated with basal insulin.
22. Basal insulin titration only applicable at Visit 11.
23. Only applicable to subjects treated with basal insulin.

**Explanations**: Rand = randomisation; S = site visit; TC= telephone contact

# 3 Background information and rationale for the trial

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 Basic information

### 3.1.1 Treatment of type 2 diabetes mellitus in the paediatric population

Despite the increased prevalence and the potential short and long term risks associated with early onset of type 2 diabetes, the most effective regimens to treat adolescents with type 2 diabetes are not known, and treatment approaches are often extrapolated from those used for adults[1].

Metformin is currently the most commonly used treatment for type 2 diabetes in children-and adolescents[2, 3]. The addition of other therapies including a glucagon-like peptide-1 (GLP-1) receptor agonist has been suggested when glycaemic control is not achieved with metformin alone in children and adolescents with type 2 diabetes[4]. However, metformin is the only non-insulin treatment with regulatory approval at this time, for use in children and adolescents with type 2 diabetes, 10 years of age and older.

### 3.1.2 Glucagon-like peptide-1

GLP-1 is an incretin hormone secreted from the L-cells in the lower gut in response to meal ingestion, which stimulates endogenous insulin secretion in a glucose-dependent manner. GLP-1 also decreases elevated blood glucagon levels, reduces gastric emptying, and reduces food intake.

The combination of these mechanisms makes GLP-1 a potent blood glucose lowering agent. This, together with the glucose dependency of action (i.e., stimulation of insulin secretion only when plasma glucose levels are above normal) makes GLP-1 hormone a potential candidate for the treatment of type 2 diabetes[5-11]. However, a major drawback with endogenous GLP-1 with regard to administration as a medical treatment is the short elimination half-life ($t_{½} < 1.5$ minutes after i.v. administration). That is due to rapid degradation by dipeptidyl peptidase (DPP-4), present for example, on the capillary endothelium[12]. From human trials it has become clear that 24-hour infusion of native GLP-1 would be necessary to achieve satisfactory glycaemic control[13]. Hence, endogenous GLP-1 treatment has limited clinical value and treatment strategies circumventing this limitation have been sought.

### 3.1.3 Liraglutide

Liraglutide (Victoza®) is a once-daily human GLP-1 analogue marketed and developed by Novo Nordisk. Compared to human GLP-1, liraglutide has a C16 fatty (palmitic) acid chain attached at

position 26 (lysine) of the peptide, and has lysine at position 34 replaced by arginine. When administered s.c., these structural modifications result in kinetic properties of the compound suitable for once daily administration[14]. In vitro receptor studies have shown that liraglutide is a selective, potent and full agonist of the cloned human GLP-1 receptor. In animal studies liraglutide has been shown to lower blood glucose, stimulate insulin secretion, decrease plasma glucagon levels, inhibit gastric emptying, inhibit food intake, decrease body weight and improve beta-cell function when administered subcutaneously.

Liraglutide has been approved for treatment of type 2 diabetes in adults in the European Union (EU), United States (US) and in a number of other countries. As of July 2011, 52 clinical trials had been completed, and the safety database includes more than 11,000 subjects, of whom more than 7500 were treated with liraglutide[15]. The 52 completed trials include 31 phase 1 trials, 9 phase 2 trials, and 12 phase 3 trials.

Data from finalised trials have shown liraglutide to have a pharmacokinetic (PK) profile suitable for once daily administration, as evidenced by a relatively slow absorption ([$t_{max}$] =8-12 hours) with a terminal elimination half-life of approximately 13 hours. The PK profile is comparable between healthy subjects and subjects with type 2 diabetes.

**Efficacy**

Mode-of-action trials in adult subjects with type 2 diabetes have demonstrated glucose lowering (fasting plasma glucose (FPG), postprandial glucose (PPG)), increased insulin secretion, restored beta-cell responsiveness to increasing glucose concentrations and delayed gastric emptying after a single s.c. dose of liraglutide. Importantly, during hypoglycaemia liraglutide did not impair glucagon action or the general counter-regulatory response, indicating a low risk of hypoglycaemia. Results from the phase 3a trials in adult subjects with type 2 diabetes showed an improvement of glycaemic control after treatment with liraglutide. A substantial and clinically relevant lowering of glycosylated haemoglobin $A_{1c}$ ($HbA_{1c}$) and FPG was observed after 26 weeks and 52 weeks of treatment with liraglutide. The various treatment regimens included in the trials were liraglutide doses of 0.6 mg, 1.2 mg or 1.8 mg per day as monotherapy or in combination with sulfonylurea, metformin or a thiazolidinedione.

Based on the $HbA_{1c}$ assessment it was concluded that treatment with liraglutide in monotherapy (1.2 or 1.8 mg) was superior to treatment with glimepiride 8 mg. Furthermore, liraglutide in combination with one or two oral anti-diabetic drugs (OADs) was superior to treatment with the same OAD(s) alone. Furthermore, the weight loss observed in earlier trials was confirmed by results from the phase 3a programme.

Treatment with the combination of basal insulin and liraglutide has been studied in adults with type 2 diabetes and has obtained regulatory approval in some countries.

There are case reports in the literature, published clinical trials and retrospective studies with exenatide (another marketed GLP-1 receptor agonist) and liraglutide added to insulin therapy. These studies indicate that addition of a GLP-1 receptor agonist to pre-existing insulin therapy can favourably affect the daily glucose variability by reducing plasma glucose excursions and provide improved glycaemic control with significant reductions in $HbA_{1c}$ in adults. These effects of the combination therapy seemed associated with a reduced need for insulin, weight loss and no substantial increase in the risk of hypoglycaemic events, in adults[16-20].

The efficacy and safety of liraglutide as add on to basal insulin analogues was studied in a controlled, double blind setting, demonstrating that treatment with insulin detemir as add-on to liraglutide 1.8 mg + metformin resulted in statistically significant reductions in $HbA_{1c}$ and FPG compared to treatment with liraglutide 1.8 mg + metformin alone[21, 22].

**Safety**

The safety profile of liraglutide exhibits the features expected for a GLP-1 analogue and is in accordance with observations from administration of both native GLP-1 and another GLP-1 receptor agonist (exenatide). More than 400,000 patients with type 2 diabetes are estimated to have been treated with Victoza® after its approval and availability in marketed use.

Gastrointestinal adverse events (AEs), including mostly transient events of nausea, diarrhoea and vomiting were the most frequently reported events during the overall clinical development programme for liraglutide. The highest reporting frequency was seen during initiation of therapy. The gastrointestinal AEs could however be mitigated by the use of a dose titration scheme. Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in patients treated with liraglutide. Subjects treated with liraglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Few cases of acute pancreatitis (inflammation of the pancreas) presenting with persistent severe abdominal pain (usually accompanied by vomiting) have been reported with liraglutide and exenatide. Post marketing safety surveillance has not altered the favourable risk-benefit ratio of liraglutide in this regard. A causal relation between treatment with liraglutide and pancreatitis has not been established. Subjects should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide and other potentially suspected medicinal products should be discontinued, see withdrawal criteria in section 6.5.

In a 2-year repeat subcutaneous dose carcinogenicity study of liraglutide injected once a day in CD-1 mice, a treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide

concentration in the clinical formulation (6 mg/mL) is 10 times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

Liraglutide causes dose dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) are excluded from this trial.

Liraglutide has been shown to be teratogenic in rats at or above 0.8 times the human systemic exposures resulting from the maximum recommended human dose (MRHD) of 1.8 mg/day based on plasma area under the time-concentration curve (AUC). Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below human exposure at the MRHD based on plasma AUC.

A five week PK/PD trial in paediatric subjects with type 2 diabetes ages 10-17 years has been completed (NN2211-1800). In this 5-week trial, no serious AEs were reported. The most common AEs in liraglutide treated subjects were of gastrointestinal origin as seen in trials including adults. All AEs seen with liraglutide were classified as mild. A total of 57% of liraglutide treated subjects and 29% of placebo treated subjects experienced gastrointestinal AEs. In the pooled data from all NN2211 trials including adult subjects with type 2 diabetes, 42% of the liraglutide-treated subjects had at least one gastrointestinal related adverse event compared with 19% of the subjects treated with placebo and 23% of the subjects treated with active comparators.

A relationship with dose escalation level was not seen, with the majority of these mild events seen at 0.3 and 0.6 mg. In placebo treated subjects, gastrointestinal AEs were mild to moderate.

Three (3) liraglutide treated subjects and 1 placebo treated subject experienced hypoglycaemic episodes. Some of the episodes of hypoglycaemia occurred after excessively long periods of fasting, as long as approximately 18 hours. The 3 liraglutide treated subjects experienced 4 episodes of “minor hypoglycaemia” (confirmed plasma glucose <3.1 mmol/L with or without symptoms). All episodes were self-treated and most occurred approximately 2-3 hours after a meal.

An external hormonal safety board of the trial, concluded that there was no evidence of hormonal disruption in this short-term trial based on evaluation of the following hormones and biomarkers measured during the trial: estradiol (female subjects), testosterone (male subjects),

carcinoembryonic antigen (CEA), insulin-growth factor-1 (IGF-I), dehydroepiandrosterone sulfate (DHEAS), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, C-peptide and fructosamine.
Mean FPG, HbA1c and fructosamine decreased during this short-term treatment period, but mean body weight did not change.

Further information can be obtained in latest version of the investigator's brochure (IB) for liraglutide or any updates hereof[15].

### 3.1.4 Rationale for the trial

The first trial to assess safety and tolerability of liraglutide in children and adolescents was the pharmacokinetic and pharmacodynamic trial (NN2211–1800), conducted in paediatric subjects with type 2 diabetes, ages 10-17 years, in the EU and US.

The liraglutide pharmacokinetics in the paediatric population was similar to that observed in adults.

The NN2211–3659 trial is being conducted to assess the efficacy and safety of liraglutide in the paediatric population in order to potentially address the unmet need for treatment of children and adolescents with type 2 diabetes and also to fulfil the regulatory requirement for paediatric trials from the European Paediatric Committee (PDCO) of the European Medicines Agency (EMA) and from the U.S. Food and Drug Administration (FDA).

### 3.1.5 Risk and benefits assessment (Only Applicable for Sweden)

The nonclinical safety programme of liraglutide reveals no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity. Nonclinical studies have shown that liraglutide lowers blood glucose and body weight in numerous animal models. Also, in some models, liraglutide has been shown to have beneficial effects on cardiovascular related parameters.

The current available data on clinical safety and efficacy of liraglutide is summarized in section 3.1.3. It is assumed that the benefits and risks associated with long-term liraglutide treatment will be the same for the paediatric population as for the adult populations with the exception of any unforeseen effects on growth and pubertal development. Pubertal and growth related hormonal levels, biochemical parameters of bone metabolism and growth and pubertal development will therefore be monitored through the clinical trial in this paediatric population.

Other relevant precautions have also been implemented in the design and planned conduct of this trial in order to minimise the risks described in section 3.1.3 and the inconveniences of trial participation. All subjects participating in the trial will be monitored closely through frequent site visits and telephone contacts. Throughout the trial, subjects will be in regular contact (by telephone

or visits) with the investigator or a designated person. Subjects will be monitored for elevated levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.
Liraglutide causes dose dependent and treatment-duration–dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice.
Based on the nonclinical findings of C-cell tumours in rodents, monitoring of serum calcitonin at regular intervals will be performed in the present trial. Subjects with a personal or family history of medullary thyroid carcinoma (MTC) and patients with Multiple Endocrine Neoplasia type 2 (MEN2) and/or subjects with a screening calcitonin value >50 ng/L are excluded from this trial.
A few cases of MTC have been reported in patients treated with the marketed product. No cases of MTC have been reported to date in subjects treated with liraglutide in completed clinical trials.

Blood sampling and contacts with the clinic are considered an inconvenience for the children participating in the trial. On the other hand, the intensified treatment may help to improve glycaemic control.

The current standard of care for this paediatric population is metformin and when needed, insulin treatment.

The most common side effect of all available insulin preparations is hypoglycaemia. The investigator will explain to the subject how to check blood sugar with the BG meter provided by Novo Nordisk and the signs and symptoms of hypoglycaemia. Furthermore, it is encouraged that subjects participating in the trial do not miss meals or have a prolonged period of fasting.

Subjects on basal insulin will have additional telephone visits. Additionally to reduce the risk of hypoglycaemia, subjects on basal insulin will have their insulin dose decreased by 20% at randomisation. It is anticipated that benefit will be gained from participating in this trial due to the closer and more frequent assessments of the subject's diabetes, focus on diet and exercise and/or intensified anti-diabetes therapy.

It has recently been demonstrated that there is a need for improvement of type 2 diabetes treatment in children and adolescents. Metformin in combination with life style changes was insufficient for maintenance of acceptable glycaemic control in a large proportion of adolescents with type 2 diabetes[23].

All subjects will, in order to ensure adequate treatment, be treated with metformin throughout the trial. Subject treatment with liraglutide or liraglutide placebo will be blinded during the first 26 weeks of randomised treatment. After that the subjects' treatment allocation will be revealed due to the anticipated need for rescue treatment for subjects treated with metformin and liraglutide placebo. In the event that a subject treated with liraglutide experiences severe intolerance or recurrent hypoglycaemia as judged by the investigator, the liraglutide dose will be lowered. If a

subject treated with 0.6 mg liraglutide experiences severe intolerance or recurrent hypoglycaemia as judged by the investigator, the subject will be withdrawn from the trial.

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of liraglutide generated from the nonclinical and clinical studies in adults has not revealed any safety issues that should prohibit administration of liraglutide to children and adolescents. The results of this trial will contribute to the development of new improved treatments for children and adolescents with type 2 diabetes in the future.

# 4 Objectives and endpoints

## 4.1 Objectives

**Primary objective**

To confirm the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg) versus placebo when added to metformin with or without basal insulin treatment in controlling glycaemia in children and adolescents (ages 10–17 years) with type 2 diabetes.

**Secondary objectives**

To assess and compare the effect of liraglutide versus placebo in combination with metformin with or without basal insulin treatment on:

- Parameters of glycaemic control
- Parameters of beta-cell function
- Parameters of body composition
- Vital signs
- Growth velocity (if subject is still growing)
- Safety and tolerability
- Growth and pubertal development at 1 and 2 year follow up after trial drug cessation at week 52

## 4.2 Endpoints

**Primary endpoint to be assessed at 26 weeks of treatment**

- Change in $HbA_{1c}$ from baseline to week 26

**Confirmatory secondary endpoints to be assessed at 26 weeks of treatment**

- Change from baseline in FPG
- $HbA_{1c}$ <7.0% (yes/no)
- Change from baseline in BMI standard deviation score (SDS)

**Secondary endpoints to be assessed at 26 and 52 weeks of treatment unless otherwise stated**

- $HbA_{1c}$ <7.0% (yes/no) at 52 weeks
- $HbA_{1c}$ ≤6.5% (yes/no)
- $HbA_{1c}$ <7.0% without severe or minor hypoglycaemic episodes (yes/no)
- $HbA_{1c}$<7.5% (yes/no)

Change from baseline at 26 and 52 weeks of treatment unless otherwise stated:

- $HbA_{1c}$ at 52 weeks
- FPG at 52 weeks
- 7-point self-measured plasma glucose (SMPG)
  - Mean 7-point SMPG
  - Post-prandial increments
- Fasting insulin, fasting pro-insulin, pro-insulin to insulin ratio, fasting glucagon, fasting C-peptide, and homeostasis model assessment (HOMA-B and HOMA-IR)
- Fasting lipid profile (cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL), triglycerides and free fatty acids
- Body weight
- Waist circumference
- Body mass index (BMI)
- BMI SDS at 52 weeks
- BMI percentile (age and gender adjusted)
- Systolic and diastolic blood pressure
- Basal insulin dose

**Safety endpoints**

Change from baseline at 26 and 52 weeks of treatment unless otherwise stated

- Clinical evaluations (physical examination including fundoscopy [fundoscopy at 26 and 52 weeks])
- Electrocardiography (ECG) with rhythm strip (at 26 and 52 weeks)
- Pulse
- Laboratory tests:
  - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes and differential count (eosinophils, neutrophils, basophils, lymphocytes and monocytes)
  - Biochemistry (creatinine, creatine kinase, urea, albumin, bilirubins (total), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, calcium, calcium (albumin corrected), amylase and lipase)
  - Hormones (calcitonin, prolactin, follicle stimulating hormone (FSH), estradiol, luteinizing hormone (LH), testosterone, dehydroepiandrosterone sulfate (DHEAS), carcinoembryonic antigen (CEA) and thyroid stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1), insulin–like growth factor binding protein 3 (IGFBP-3)
  - First morning urinalysis (micro albumin, creatinine, albumin:creatinine ratio calculated, protein, ketone, glucose, pH)
  - Biochemical parameters of bone metabolism: Alkaline Phosphatase, N-telopeptide (NTX), C-telopeptide (CTX), serum type 1 procollagen (P1NP)
  - Formation of anti liraglutide antibodies (at 26 and 53 weeks)

- Height SDS
- Bone age assessment (x-ray of left hand and wrist) at 52 weeks
- Pubertal assessment/ progression (Tanner staging)

In addition the following will be assessed at 26, and 52 weeks:

- Assessment of compliance (questioning of subjects and subjects legally acceptable representative)
- Growth velocity in cm/year and height velocity SDS (if subject is still growing). A growth velocity < 1.0 cm/year is defined as no longer growing.
- Hypoglycaemic episodes
- AEs and serious adverse events (SAEs)

**Safety follow-up at 1 and 2 years after trial drug cessation at week 52 (only applicable for subjects on active liraglutide treatment for more than 3 months)**

- AEs and SAEs
- Growth velocity in cm/year (if subject is still growing)
- Height velocity SDS (if subject is still growing)

Change in:

- Height SDS
- Pubertal assessment/progression (Tanner staging)
- Bone Age assessment (x-ray of left hand and wrist)

# 5 Type of trial

## 5.1 Type of trial

This is a multi-centre 26 week randomised double-blind, parallel-group, placebo-controlled clinical trial followed by a 26 –week open-label extension in subjects aged 10 -17 years with type 2 diabetes. Subjects will be randomised 1:1 to receive liraglutide or liraglutide placebo in combination with metformin with or without basal insulin treatment. Subjects will be stratified at randomisation by sex and according to their age at end of treatment (with two levels: 1:≤ 14, 2:> 14 years of age; ≤ 14 years of age is defined as not reaching 14 years and 11 months at the end of treatment (52 weeks)).

The trial consists of a 2 weeks screening period where all screening parameters are assessed. Screening is followed by 11 to 12-weeks run-in period starting at Visit 2 (3 to 4 weeks metformin titration and 8 weeks metformin maintenance). After the run-in period subjects will, if fulfilling the randomisation criteria, be randomised to either liraglutide or liraglutide placebo treatment for 26 weeks. Subjects already treated with a stable dose ≥ 2000 mg of metformin or more for at least 56 days at the time of screening may skip the run-in period and advance directly to randomisation. Subjects who are treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days to advance directly to Visit 7.

At the end of the 26 weeks blinded treatment period, the treatment allocation will be unblinded and subjects will continue in a 26 weeks open-labelled treatment period. All subjects will attend a follow-up visit one week after end of treatment.

Further for subjects experiencing confirmed hyperglycaemia according to rescue criterion no. 1(see section 6.5) rescue treatment will be allowed. Subjects on rescue treatment will remain in the trial.

Subjects receiving rescue treatment should continue to follow the trial schedule for the remainder of the trial.

The maximum duration of the trial including screening and one week follow-up will be up to 67 weeks.

Subjects treated with liraglutide (active treatment) for more than 3 months will be asked to return one and two years after the end of the open label phase of the trial (after trial drug cessation at week 52).

The trial design is shown schematically below in Figure 5–1.

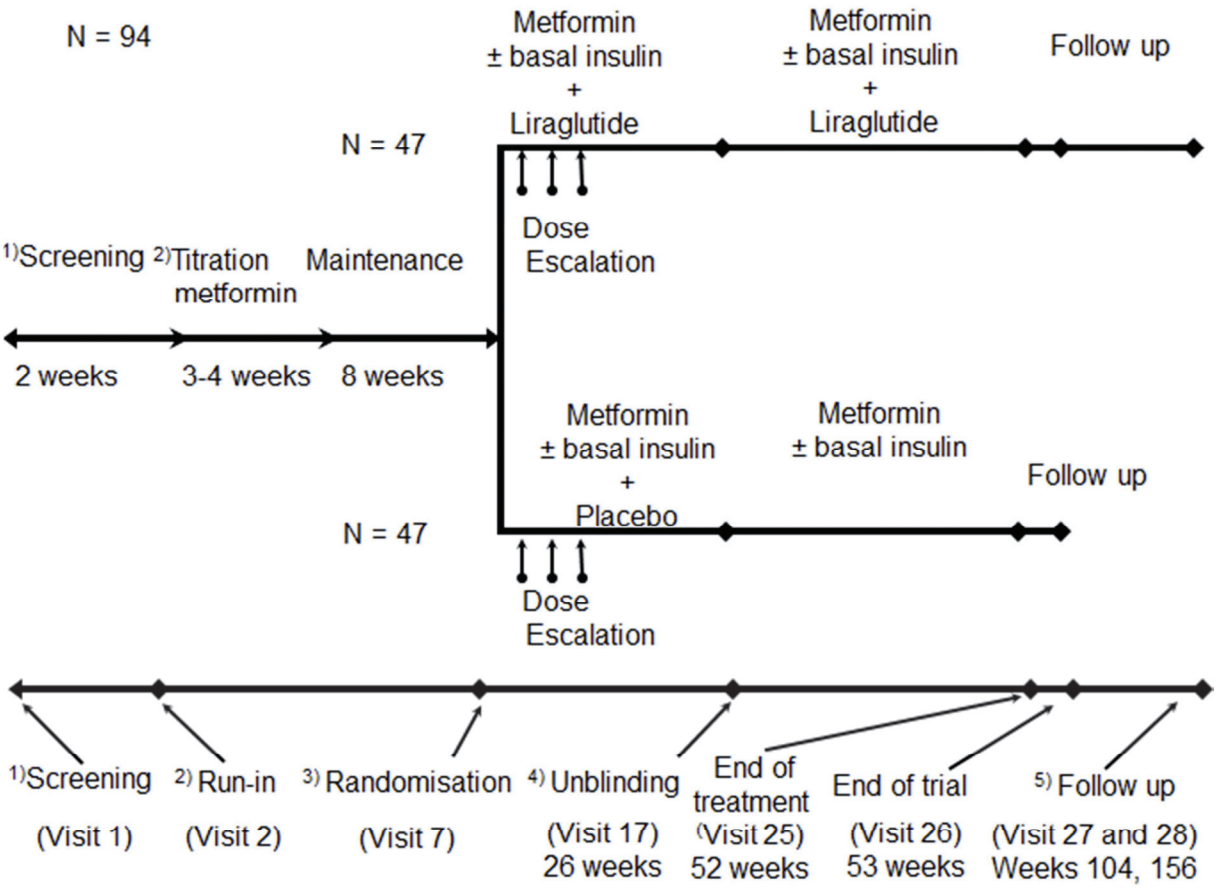


**Figure 5–1 Trial diagram**

1) Screening prior to metformin titration

2) Run-in: metformin titration to 2000 mg daily if possible or maximum tolerated dose (MTD)≥1000 mg and ≤2000 mg after verification of eligibility according to the inclusion and exclusion criteria. Subjects already treated with a stable dose≥ 2000 mg of metformin or more for at least 56 days at the time of screening may skip the run-in period and advance directly to randomisation. Subjects who are treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days to advance directly to Visit 7.

3) Randomised treatment: Escalation of liraglutide in 0.6 mg increments over 2-3 weeks to 1.8 mg if possible or MTD. Subjects on basal insulin will have their insulin dose decreased by 20% at randomisation.

4) All subjects will be unblinded at Visit 17. Subjects treated with liraglutide will continue with unchanged doses of metformin± basal insulin and their treatment with liraglutide. Subjects treated with liraglutide placebo will discontinue liraglutide placebo and will continue on metformin ± basal insulin.

5) All subjects will complete the Visit 26. Subjects treated with liraglutide for more than 3 months will complete Visits 27 and 28.

## 5.2 Rationale for trial design

A randomised double-blind design was chosen for the efficacy endpoints in order to limit the bias in the conduct and interpretation of the trial. An effect on $HbA_{1c}$ as well as durability effects should be seen by 26 weeks[23]. Stratification has been implemented in order to avoid bias arising from gender

and age at end of treatment (≤ 14 and > 14 years of age) (see section 5.1 for definition of ≤ 14 years of age).

Subjects' treatment allocation will be unblinded after 26 weeks in order to enable discontinuation of the liraglutide placebo injections which are considered a burden to the children and adolescents.

The current standard of care for this population is metformin treatment or insulin if needed. Subjects will, in order to ensure adequate treatment, be treated with metformin at a dose ≥1000 mg and ≤2000 mg, throughout the trial. This metformin dose is generally approved for children and adolescents. Subjects entering the trial on a dose of metformin >2000 mg will be allowed to remain on that dose.

The 26 weeks open label extension has been added in order to assess the safety of liraglutide treatment in the paediatric population. The 2 years follow-up for subjects treated with liraglutide for more than 3 months is added in order to assess any potential long time effect on growth, pubertal development and general safety.

A rescue criterion has been implemented in order to attempt to improve retention in order to obtain additional safety information, and to mimic what would likely occur in clinical practice.

## 5.3 Treatment of subjects

### 5.3.1 Metformin

Metformin is an oral anti-diabetic agent in the biguanide class. In this trial metformin is characterised as background treatment (non-investigational medicinal product [NIMP]).

Subjects will undergo 3-4 weeks of metformin titration to a maximum tolerated dose (MTD) of ≥1000 mg and ≤2000 mg. Titration and MTD will be at the discretion of the investigator. It must be aimed to reach a dose of 2000 mg metformin. The titration period can be extended from 3 to 4 weeks in total, if needed for tolerability. Once MTD is reached, the metformin dose must stay unchanged throughout the trial, unless subjects meet rescue criterion no. 1 (see section 6.5) The titration of metformin is followed by 8 weeks maintenance period whereafter subjects may be randomised if they fulfil the randomisation criteria (see section 6.4).

Subjects treated with metformin < 2000 mg at Visit 1, may use their current dose as the starting dose for the titration. Subjects with an established MTD of ≥1000 mg and ≤2000 mg may advance directly to Visit 5. An established MTD is where previous attempts to escalate the metformin dose were not tolerated, and that the Investigator does not consider up-titration possible in the subject because of tolerability issues**.** Subjects treated with 2000 mg or more of metformin for less than 56 days at Visit 1 may proceed directly to the 8 weeks maintenance period.

Subjects already treated with 2000 mg or more of metformin and with a stable dose for at least 56 days prior to Visit 1 may advance directly to randomisation (Visit 7) continuing their current metformin dose when eligibility according to the inclusion and exclusion criteria has been confirmed. Subjects who are treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days to advance directly to Visit 7.

Metformin should be temporarily discontinued in subjects undergoing radiologic studies involving intravascular iodinated contrast materials (see local label).

### 5.3.2 Liraglutide

Liraglutide and liraglutide placebo are administered once daily by s.c. injections, either in the abdomen, thigh or upper arm. The injection site does not have to be consistent throughout the trial. Injections can be done at any time of the day and irrespective of meals. It is recommended that the time of injection is consistent throughout the trial. Subjects will be instructed to perform an air shot before the first use of a new prefilled pen. Liraglutide vehicle will be used as placebo. In this trial liraglutide and liraglutide placebo are characterised as investigational medicinal products (IMPs).

After randomisation, liraglutide or liraglutide placebo will be escalated weekly starting at 0.6 mg and increasing with 0.6 mg increments over 2-3 weeks. Dose escalation will be based on tolerability (dose should not be increased in case severe intolerability is experienced, as judged by the investigator) and the following: the average of 3 measurements of FPG > 6.1 mmol/L (110 mg/dL) performed by the subject at home on the three consecutive days preceding the dose escalation visit (Visits 8, 9 and 10, please see Figure 5–2). After end of the liraglutide dose escalation period no further dose escalations must be performed.

Subjects treated with basal insulin experiencing hypoglycaemia should reduce the dose of basal insulin (if needed to 0 units) before the dose of liraglutide/liraglutide placebo is decreased.

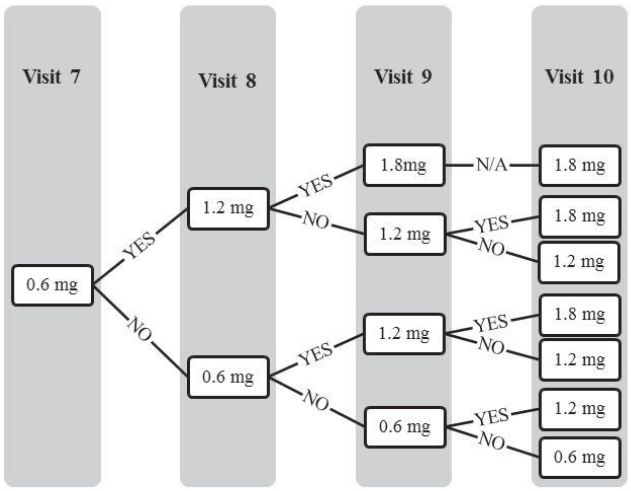


**Figure 5–2 Dose escalation of liraglutide**
During the blinded period, escalation at each YES/NO decision point should be determined by whether the subjects average FPG is > 6.1 mmol/L (110 mg/dL).

In the event that a subject experiences severe intolerance or recurrent hypoglycaemia as judged by the investigator (such as ≥ 3 unexplained minor hypoglycaemic events or 1 severe unexplained hypoglycaemic event in a week) the dose will be lowered to the next decreased level (from 1.8 mg to 1.2 mg or from 1.2 mg to 0.6 mg). The reason for down escalation of liraglutide must be documented in the subject's medical record and transferred to the eCRF.

If a subject treated with 0.6 mg experiences severe intolerance or recurrent hypoglycaemia as judged by the investigator (such as ≥ 3 unexplained minor hypoglycaemic events or 1 unexplained severe hypoglycaemic event in a week) the subject must be withdrawn from the trial.

### 5.3.3 Basal insulin

Subjects may enter the trial on a stable dose of basal insulin. A stable dose of basal insulin (intermediate acting human insulin, intermediate acting insulin analogue or long acting insulin analogue) is defined as basal insulin adjustments up to 15% at the investigator's discretion. Subjects treated with basal insulin must initiate treatment with metformin as described in section 5.3.).

The pre-trial basal insulin regimen will be considered background medication and will not be provided by Novo Nordisk.

Subjects treated with basal insulin at screening should reduce their basal insulin dose by 20% at randomisation.

Subjects on a stable dose of metformin ≥ 2000 mg as per section 5.3.1 can advance directly to maintenance period or randomisation depending on the time on stable insulin:

- Subjects with a stable dose of basal insulin for at least 30 days but less than 56 days at screening (visit 1) may proceed directly to the 8 week maintenance period (Visit 5)
- Subjects on a stable dose of basal insulin for 56 days or more at screening (Visit 1) may advance directly to randomisation (Visit 7) when eligibility according to the inclusion and exclusion criteria has been confirmed.

After the MTD dose of liraglutide/liraglutide placebo is reached, the dose of basal insulin can be up-titrated to no higher than the screening dose level. This up-titration will be based on the average of three pre-visit fasting SMPG values before visits between weeks 4 and 8 (Visits 10A -11B). Up-titration is only allowed between Visits 10A and 11B. Up-titration of basal insulin dose is to be performed at the discretion of the investigator in accordance with the algorithm described in Table 5-1.

**Table 5–1 Algorithm for up-titration of basal insulin dose**

| **Average fasting SMPG** | **Increase in basal insulin dose** |
|---|---|
| >10 mmol/L (>180 mg/dL ) | +6 units |
| 7.8 to 10 mmol/L (141–180 mg/dL) | +4 units |
| 6.7 to <7.8 mmol/L (121–140 mg/dL) | +2 units |
| 5.6 to <6.7 mmol/L (100–120 mg/dL) | +1 units |

SMPG=self-measured plasma glucose
(adapted from the Texas Diabetes Council 2013[21])

Basal insulin should be down-titrated for unexplained hypoglycaemia ≤ 3.9 mmol/L (≤70 mg/dL) at any time during the trial at the discretion of the investigator in accordance with Table 5-2

**Table 5–2 Algorithm for down-titration of basal insulin dose**

| PG | Reduction of basal insulin dose |
|---|---|
| One or more values < 3.1 mmol/L (56 mg/dL) without obvious explanation | Reduce insulin dose by 4 units (if dose >50 units, a dose reduction of 10% is suggested) |
| One or more values between 3.1−3.9 mmol/L (56−70) mg/dL) without obvious explanation | Reduce insulin dose by 2 units (if dose > 50 units, a dose reduction of 5% is suggested). |

PG=plasma glucose

The basal insulin dose can be increased again to the dose the subject was on prior to the hypoglycaemic event if safety allows and at the discretion of the investigator. Subjects should continue in the trial even if the insulin treatment is down-titrated to 0 U. Subjects will be instructed to contact the investigator in case of hypoglycaemia.

No shifts in type of insulin will be allowed during the trial and for the 30 days prior to screening.

### 5.3.4 Open Label period

After 26 weeks of treatment, treatment allocation will be unblinded. The open-label period will last for 26 weeks until the end of treatment (week 52).

Subjects treated with liraglutide will continue their trial medication under the same circumstances as listed above for the blinded period.

Subjects treated with liraglutide placebo will discontinue liraglutide placebo and continue their treatment with MTD of metformin with or without basal insulin.

The total duration of treatment with liraglutide will be 52 weeks for subjects randomised to liraglutide. The total duration of treatment with liraglutide placebo will be 26 weeks for subjects randomised to liraglutide placebo.

### 5.3.5 Rescue treatment

Subjects experiencing confirmed hyperglycaemia as per rescue criterion no. 1 (see section 6.5), will be offered rescue treatment. Subjects on rescue treatment will remain in the trial.

Rescue treatment will be as follows:

- Subjects treated with metformin and liraglutide/liraglutide placebo may have basal insulin added. The start dose and basal insulin titration will be at the discretion of the investigator. If subjects continue to experience confirmed hyperglycaemia as

per rescue criterion no. 1 a rapid acting insulin may be added and titrated at the discretion of the investigator.

- Subjects treated with metformin, basal insulin and liraglutide/liraglutide placebo may have the basal insulin dose increased; the dose and basal insulin titration will be at the discretion of the investigator. If subjects continue to experience confirmed hyperglycaemia as per rescue criterion no 1 a rapid acting insulin may be added and titrated at the discretion of the investigator.

If hyperglycaemia is persistent and meets the withdrawal criterion no. 5 despite rescue treatment having been initiated, the subject must be withdrawn from the trial (see section 6.5)

## 5.4 Rationale for treatment

Liraglutide escalation and doses used in the present trial have been chosen based on results from the NN2211-1800 trial performed in children and adolescents as described below, and on the current approved labelling for Victoza®[15].

In the NN2211-1800 trial liraglutide treatment or corresponding volume of placebo was initiated with 0.3 mg/day for the first week. The dose was escalated weekly to 0.6, 0.9, 1.2 and 1.8 mg/day of liraglutide or placebo. Dose escalation took place only if the mean fasting plasma glucose (FPG) taken on three consecutive days before the dose escalation visits was above 6.1 mmol/L (110 mg/dL). Nine (9) liraglutide subjects escalated to the maximum dose of 1.8 mg liraglutide, while 3 subjects remained on 0.6 mg liraglutide. One (1) subject, who was diet and exercise treated, remained on 0.3 mg liraglutide ($HbA_{1c}$ of [redacted]% at screening). The decision to escalate subjects to the maximum dose of 1.8 mg was based on FPG measurements, and not on lack of tolerability or AEs. All subjects randomised to placebo were escalated to a dose volume corresponding to 1.8 mg liraglutide. Two subjects (one treated with liraglutide and one with placebo) withdrew prematurely from treatment for other reasons than tolerability (blood draw issue and did not want to undergo procedures).

The American Diabetes Association (ADA) recommends the use of metformin in 2000 based on the efficacy and safety data for adults[24] Metformin is the ADA preferred first oral agent because it does not induce hypoglycaemic events. In 2002 a trial demonstrated the safety and efficacy of metformin in children and adolescent and concluded that the efficacy and safety profile was similar to the adult population[2]. Metformin doses of ≥1000 mg and ≤2000 mg have been shown to have an acceptable safety and efficacy profile in children and adolescent and these doses were therefore chosen for this trial. The use of 2500 mg of metformin has only been tested in adults where FPG was slightly reduced. Therefore doses higher than 2000 mg of metformin will only be permitted for subjects entering the trial with a dose > 2000 mg at the time, if in accordance with local standard of care.

Insulin therapy is a key component in the treatment of children and adolescents with type 2 diabetes[25]. The SEARCH incidence study identified 119 adolescents between 10-19 years of age, 31.1% of whom (GAD65 negative) were being treated with insulin[26]. Recent guidelines recommend that insulin therapy be initiated in children and adolescents who have random venous or plasma blood glucose levels > 250 mg /dL, or whose $HbA_{1c}$ >9%, and certainly in patients who exhibit ketosis or ketoacidosis[27]. An earlier recommendation was to treat patients with blood glucose >200 mg/dL, $HbA_{1c}$ more than 8.5%, or severe manifestations of insulin deficiency (e.g. ketosis/diabetic ketoacidosis) with insulin initially to achieve metabolic control rapidly. After resolution of ketosis (hydration and treatment with insulin, metformin should be started and insulin may be gradually weaned if normoglycaemia is maintained[28].

Inclusion of children and adolescents with type 2 diabetes with basal insulin in this clinical trial is consistent with clinical practice[25, 27].

# 6 Trial population

## 6.1 Number of subjects to be investigated

Number of subjects planned to be screened: 269

Number of subjects planned to be randomised and started on trial products: 94

Number of subjects expected to complete the trial (Visit 26): 63

At least 30% of randomised subjects must be 10-14 years (see section 5.1 for definition of ≤14).

At least 40% of randomised subjects must be female.

## 6.2 Inclusion criteria

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

1. Informed consent from a legally acceptable representative (LAR) and child assent from the subject must be obtained before any trial-related activities (see section 18.1 for further details). Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial (e.g. fasting prior to Visit 1 blood sampling)
   **Only applicable to Israel:** Child assent by signature is not mandatory. Child assent form is not used. A minor may sign the local ICF (form 3A).
2. Children and adolescents between the ages of 10 –16 years. Subjects cannot turn 17 years and 11 months before the end of treatment (52 weeks)
3. Diagnosis of type 2 diabetes mellitus and treated for at least 30 days with:
   - diet and exercise alone
   - diet and exercise in combination with metformin monotherapy
   - diet and exercise in combination with metformin and a stable* dose of basal insulin.
   - diet and exercise in combination with a stable* dose of basal insulin.

   *Stable is defined as basal insulin adjustments up to 15%

4. $HbA_{1c}$
   - ≥7.0% and ≤11% if diet and exercise treated
   - ≥6.5% and ≤11% if treated with metformin as monotherapy, basal insulin as monotherapy or metformin and basal insulin in combination
5. BMI >85$^{th}$ percentile of the general age and gender matched population (see Appendix A)

## 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. Any contraindications to use of metformin according to local label
3. Previous participation in this trial. Participation is defined as having been randomised. Re-screening is allowed however there must be at least 3 months between screenings
4. Female of child-bearing potential who is pregnant, breast-feeding or intend to become pregnant or who is sexually active and is not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice). **China**: Sterilisation, intrauterine device (IUD), oral contraceptives or barrier methods. **Germany**: Adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomised partner. **UK**: Contraception requirements as per the MHRA guidelines.
5. Receipt of any investigational medicinal product within 30 days before to Visit 1. Participation in another medication related research trial while taking part in this clinical trial. **Brazil**: Participation in other clinical trials within one year prior to Visit 1 unless there is a direct benefit to the research subject at the investigator´s discretion
6. Type 1 diabetes
7. Positive insulinoma associated-protein 2 (IA-2) or anti-glutamic acid decarboxylase antibodies (anti-GAD)
8. Fasting C-peptide < 0.6 ng/ml
9. Maturity onset diabetes of the young (MODY)
10. Use of any antidiabetic agent other than metformin and/or basal insulin 90 days prior to Visit 1.
11. Previous treatment with liraglutide
12. History of pancreatitis (acute or chronic)
13. Screening calcitonin value ≥50 ng/L
14. Subjects with personal or family history MTC or MEN 2
15. Impaired liver function defined as alanine aminotransferase (ALAT) ≥2.5 times upper normal range (UNR)
16. Impaired renal function defined as serum-creatinine <u>≥UNR for age in children</u> unless renal function is proven normal by further assessments at the discretion of the investigator
17. Known history of heart disease (including history of arrhythmias or conduction delays on ECG) within 6 months of Visit 1, new arrhythmias or conduction delays on ECG identified at the screening visit
18. Known proliferative retinopathy or maculopathy requiring acute treatment as judged by the investigator
19. Hepatitis B or hepatitis C positive
20. Human immunodeficiency virus (HIV) positive

21. Uncontrolled hypertension, treated or untreated ≥99th percentile for age and gender in children (see Appendix B). If "white coat hypertension" is suspected at Visit 1 a repeat blood pressure measurement either during Visit 1, or at Visit 2 prior to other trial related activities is allowed, with the last measurement being conclusive
22. Any history of or diagnosis/treatment of cancer within the last 5 years (except basal cell skin cancer or squamous cell skin cancer)
23. Any clinically significant disorder, except for conditions associated with type 2 diabetes history which in the investigator's opinion could interfere with results of the trial
24. Surgery scheduled for the trial duration period (excluding minor surgical procedures performed in local anaesthesia, as judged by the investigator)
25. Recurrent severe hypoglycaemia or hypoglycaemic unawareness as judged by the investigator
26. Use of any drug (except for metformin and/or basal insulin), which in the Investigator's opinion, could interfere with the blood glucose level (e.g. systemic corticosteroids)
27. Known or suspected abuse of alcohol or drugs/narcotics
28. Mental incapacity or language barrier precluding adequate understanding or cooperation or unwillingness to adhere to protocol requirements

Proportion of subjects above 14 years of age will be restricted to a total of 70% of randomised subjects (see section 5.1). Proportion of male subjects will be restricted to a total of 60% of randomised subjects. When the individual target is reached, subjects above 14 years of age and male subjects respectively may not be randomised into the trial.

### 6.4 Randomisation criteria

For subjects to be eligible for randomisation the randomisation criteria must be answered "yes".

1. FPG measured prior to the randomisation visit (Visit 7), must be ≥126 mg/dL (7.0 mmol/L) and ≤ 220 mg/dL (12.2 mmol/L). The measurement must be based on an average of fasting SMPG values taken on the 3 consecutive days leading up to the randomisation visit (Visit 7)
2. Subject must be on a stable dose for at least 56 days of metformin ≥1000 mg and ≤ 2000 mg per day (subjects who enter the trial on > 2000 mg may be randomised continuing with that dose)
3. Subjects treated with basal insulin must be on a stable dose for at least 56 days. Stable dose of basal insulin is defined as basal insulin adjustments up to 15%

### 6.5 Rescue criteria

If the fasting SMPG values taken on 3 consecutive days or any of the FPG samples analysed by the central laboratory exceeds the limits of >12.2 mmol/L (220 mg/dL) during the first 14 weeks after randomisation (after end of liraglutide dose escalation, i.e. the subject has reached 1.8 mg or the MTD, and after week 8 for subjects on basal insulin) or >10.3 mmol/L (185 mg/dL) after week 14

the subject should be called for an unscheduled visit as soon as possible. A confirmatory FPG should be obtained and analysed by the central laboratory. The unscheduled visit should be documented in the eCRF. If the FPG exceeds the above described values and no intercurrent cause for the hyperglycaemia has been diagnosed rescue treatment should be initiated according to section 5.3.5. If hyperglycaemia is persistent and meets the FPG limits as set above after rescue treatment having been initiated, the subject must be withdrawn from the trial (see section 6.6)

## 6.6 Withdrawal criteria

A subject must be withdrawn if the following applies:

1. The subject may withdraw at will or be withdrawn by the subject's LAR at any time
2. 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
3. The subject must be withdrawn if randomised in error
4. Pregnancy or intention to become pregnant
5. If the subject experiences persistent hyperglycaemia despite initiation of rescue treatment as described in section 6.5 the subject must be withdrawn. Persistent hyperglycamia: If fasting SMPG values taken on 3 consecutive days or any FPG samples analysed by the central laboratory exceeding the limits set below the subject must be called for an unscheduled visit as soon as possible. A confirmatory FPG must be obtained and analysed by the central laboratory. If the confirmed FPG exceeds the below described values and no intercurrent cause for the hyperglycaemia has been diagnosed the subject is experiencing persistent hyperglycaemia. The unscheduled visit must be documented in the eCRF.

   FPG limits:

   - during the first 14 weeks after randomisation (after end of liraglutide dose escalation, i.e. the subject has reached 1.8 mg or the MTD): FPG > 12.2 mmol/L (220 mg/dL)
   - after week 14: FPG >10.3 mmol/L (185 mg/dL)
6. Subjects who need to have their dose of metformin reduced due to tolerability after having reached their MTD must be withdrawn.
7. Subjects treated with 0.6 mg of liraglutide who experience severe intolerance or recurrent hypoglycaemia as judged by the investigator (such as ≥ 3 unexplained minor hypoglycaemic events or 1 unexplained severe hypoglycaemic event in a week) must be withdrawn

8. Calcitonin ≥50 ng/L. A referral to a specialist in thyroid disease is recommended (See Appendix D)
9. If the investigator suspects acute pancreatitis, all drugs suspected to relate to this condition should be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. Subjects that are diagnosed with acute pancreatitis and/or exhibit at least 2 of the following criteria must be withdrawn from the trial; 1) abdominal pain, 2) amylase and/or lipase > 3x UNR or 3) characteristic findings on ultrasound, computerised axial tomography (CT) or magnetic resonance imaging (MRI)

10. Initiation of any systemic treatment (other than anti-diabetes treatment) with products which in the investigator's opinion could interfere with glucose metabolism (e.g.: systemic corticosteroids)

### 6.7 Subject replacement

Subjects who are withdrawn will not be replaced.

### 6.8 Rationale for trial population

There is an unmet need for treatment of children and adolescents with type 2 diabetes. Metformin is the most commonly used treatment for type 2 diabetes in children and adolescents[2, 3]. However, it is also the only non-insulin treatment with regulatory approval, for use in children and adolescents. The addition of other therapies including a GLP-1 analogue has been suggested when glycaemic control is not achieved with metformin alone[4].

Children and adolescent ages 10–17 are the target population for this trial since the mean age for diagnosis of type 2 diabetes mellitus is 13.5 years[4, 29] and the incidence of type 2 diabetes in children less than 10 years old is low[26].

The inclusion of subjects on basal insulin is consistent with current clinical practice. Insulin therapy is a key component in the treatment of children and adolescents with type 2 diabetes[25].

# 7 Trial schedule

It is aimed to limit the period of competitive recruitment to a minimum and a recruitment strategy will be developed in cooperation with the participating countries.

**Planned date for first patient first visit (FPFV)** **01-Nov-2012**

**Planned date for last patient last visit (LPLV) (Visit 26)** **15-July 2018**

**Planned date for last follow-up visit (Visit 28)** **15-July 2020**

**The end of the clinical trial is defined as LPLV (Visit 26)**

**Only applicable for Mexico**: Mexico can recruit up to 20 subjects

All investigators will be notified immediately when the recruitment period ends, after which no further subjects will be screened and the interactive voice/web response system (IV/WRS) will be closed for further screening.

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, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[30], the Food and Drug Administration Amendment Act (FDAAA)[31], European Commission Regulation for EudraCT[32] and other relevant recommendations or regulations. If a patient 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 patient.

# 8 Methods and assessments

## 8.1 Visit procedures

**Introduction**
Throughout the trial the investigator should ensure working in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)[33] 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 actions to avoid recurrence of the detected discrepancies.

### 8.1.1 Informed consent and assent procedure

The investigator must obtain informed assent and consent for each subject and subject's LAR respectively prior to any protocol related procedures. For information on informed consent procedure please refer to section 18.1.

All subjects and subject's LAR will be provided with a copy of their own signed and dated informed assent and consent form.

**Note**: Subjects should arrive fasting for Visit 1 blood sampling. Fasting is considered a trial related activity and no trial related activities may be initiated prior to a signed assent and consent form.

**Only applicable to Israel:** Child assent by signature is not mandatory. Child assent form is not used. A minor may sign the local ICF (form 3A).

### 8.1.2 Investigator site logs

The investigator must keep a subject identification code list; a subject screening log 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 delegation of tasks at trial site. The investigator must sign the log of staff and delegation of tasks at trial site at the time of delegation of tasks.

### 8.1.3 Screening, screening failures and re-screening

At screening, subjects will be provided with a card stating that they are 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.

At screening subjects must be assigned a unique screening number (the lowest available number allocated to the site) which should remain the same throughout the trial. A screening session must be performed in the IV/WRS.

Subjects that are found to be eligible for the trial after assessing all in- and exclusion criteria will advance to Visit 2, Visit 5 or Visit 7 depending on their metformin treatment at trial entry.

For screening failures a screening failure session must be made in the IV/WRS and the screening failure form in the electronic Case Report Form (eCRF) must be completed with the reason for not continuing in the trial. Serious and non-serious AEs from screening failures must be transcribed by the investigator into the CRFs. Follow-up of serious AEs (SAEs) should be carried out according to section 12.

Re-screening of screening and run-in failures is allowed however there must be at least 90 days from screening failure date to re-screening. In case of re-screening, a new informed consent and assent must be obtained, a new screening number must be allocated and samples and assessments must be performed once more as according to the screening procedures.

**Only applicable to Israel:** child assent form is not applicable.

### 8.1.4 Randomisation and run-in failures

At Visit 7 subjects fulfilling the randomisation criteria (see section 6.4) will be randomised. A randomisation session must be performed in the IV/WRS.

Run-in failures are subjects withdrawn from the trial in the run-in period or not fulfilling the randomisation criteria. They are regarded as screening failures and should be treated as such in the IV/WRS and eCRF.

### 8.1.5 Visits

Procedures for the scheduled site visits and phone contacts are described in the following section and in the flow chart (please refer to section 2). In order to secure consistency in data over time it is encouraged that assessments are performed consistently (e.g. using the same type of equipment and trial site staffs with alike qualifications) during the trial.

For visit numbers, timing of site visits, phone contacts and visit windows during the trial period, please refer to the flow chart (section 2). It is the responsibility of the investigator to ensure that all site visits and phone contacts occur according to the flowchart. A phone contact may be converted to a site visit, if needed.

There will be one follow-up visit (Visit 26) for all subjects. Subjects treated with liraglutide for more than 3 months should in addition attend a 1 and 2 year follow-up visit (Visits 27 and 28). There will be no diaries attached to these visits and hence reporting of AEs and SAEs will be by the subject's and subject's LAR's memory.

***Visits attended fasting***
Subjects must attend the clinic in a fasting state for Visits 1, 7, 13, 17, 22 and 25 blood sampling. Fasting is defined as at least eight hours without food or drink intake except for water and prescribed medication other than diabetes medication.

In addition subjects must be without food or drink intake except for water and prescribed medication for at least 2 hours before Visit 26 blood sampling.

Should a subject attend a fasting blood sampling in a non-fasting state blood sampling must be re-scheduled, preferably within the visit window.

***Unscheduled and missed visits***
If a subject attends the clinic for an unscheduled visit, the unscheduled visit form must be completed unless the subject attends the clinic to obtain additional IMP, NIMP, auxiliary supplies or to perform a re-test of a blood sample. If the subject needs additional IMP and/or NIMP an additional dispensing call should be made in the IV/WRS.

Should a visit be missed, every effort should be made to re-schedule the visit within the allowed visit window. If this is not possible the visit should be re-scheduled at the earliest possible date.

### 8.1.6 Rescue treatment

If a subject fulfils rescue criterion no. 1 as described in section 6.5 the following procedures should be performed:

- Body measurements (weight and height)
- A blood sample will be drawn and analysed at the central laboratory to determine levels of $HbA_{1c}$

The following should in addition to result of above assessments be recorded in the eCRF:

- SMPG values from 3 consecutive days where this is what led to the confirmatory FPG sample
- Details of the rescue treatment

When all assessments have been performed rescue treatment as described in section 5.3.5 should be initiated.

### 8.1.7 Withdrawal

If a subject is withdrawn from the trial prior to Visit 17, the investigator must aim to undertake procedures for Visit 17 (End of blinded treatment visit) as soon as possible, if possible. If a subject is withdrawn from the trial after Visit 17 the investigator must aim to undertake procedures for Visit 25 (End of treatment visit) as soon as possible, if possible. In addition Visit 26 should in both cases be completed, between 5 and 10 days after the early termination visit, if possible. In addition if the subject has been treated with liraglutide for more than 3 months the investigator must aim to have the subject return to the clinic for the 1 and 2 year follow up visits.

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 site. In addition a withdrawal session must be performed in the IV/WRS and the case book (eCRF) must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason(s) (i.e. adverse event, non-compliance with protocol or other) for discontinuation must be specified in the eCRF.

### 8.1.8 Subject training

***Diaries***

The subject should be provided with diaries at Visits 1, 2, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 20, 22 and 24 and be instructed in filling in the diary. It is the responsibility of the investigator to review the diary for subject notes regarding possible AEs and concomitant medication (please see sections 12 and 8.3). The investigator must transcribe data from the diary into the eCRF throughout the trial. The investigator should, if necessary, convert the format of data used by the subject into the format used in the eCRF. The subject's dispensed diaries should be collected at the following clinic visit (Visits 2, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 20, 22, 24 and 25).

The diaries will contain the below information:

- Date, actual clock time and value of all 7-point profile (SMPG) measurements
- Date and time of first liraglutide injection
- Date and dose of metformin and insulin on the day just prior to each visit
- Date and dose of liraglutide on the day just prior to each visit (not applicable after Visit 17 for subjects treated with liraglutide placebo)
- Information on fasting SMPG measurements
- Details on hypoglycaemic episodes
- Date, time and dose of liraglutide injections on two days just prior to Visits 8, 9, 11, 13 and 17

- Date of first day of most recent menstrual period prior to Visits 7, 13, 17 and 25 (only for females of childbearing potential)
- Adverse events
- Concomitant medication

If clarification of entries or discrepancies in the diary is needed, the subject should be questioned and a conclusion made in the medical record. Entries in the diary should only be made by the subject or the subject's LAR. Care should be taken not to bias the subject.

***Trial product***
Investigator should instruct the subject in the use of the pen-injector and the direction for use should be handed out at each dispensing visit. Instructions in use should be repeated as necessary. The investigator must document that direction for use is given to each subject orally and/or in writing at each dispensing visit.

***Blood glucose meter***
Subjects should also be instructed in the use of the BG meter provided. Subjects should be explained that the BG meter is to be used exclusively by them.

### 8.1.9 Investigator evaluations and review

Review of diary, laboratory reports, ECGs and eye examination (fundoscopy) must be documented with investigator's dated signature.

For ECGs and eye examinations the evaluations must follow the categories:
- Normal
- Abnormal, not clinically significant (abnormal NCS)
- Abnormal, clinically significant (abnormal CS)

For laboratory report values outside the reference range, the investigator must specify whether this is clinically significant.

In case of abnormal clinically significant findings (laboratory reports, ECGs and eye examination) the investigator must state a comment in the subject's medical record and record this on the concomitant illness form in the eCRF at Visit 1. At subsequent visits any clinically significant changes or new clinically significant findings must be reported as an AE according to section 12.

## 8.2 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit). All concomitant illnesses should be reported however information on diabetes will be reported separately.

If a level of calcitonin ≥20 ng/L is found at Visit 1 this should be reported as concomitant illness.

**Medical history** is an account of medical events that the subject has experienced in the past. Any relevant and significant medical history as judged by the investigator must be reported in the medical record and eCRFs. The investigator should consider any medical history that is required to properly document that the subject does not fulfil any of the exclusion see section 6.3.

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

## 8.3 Concomitant medication

A **concomitant medication** is any medication, other than metforminand liraglutide which is taken during the trial. Diabetes treatment prescribed at the end of trial should be registered in concomitant medication form in the eCRF. Medication given for a concomitant illness must be recorded in the eCRF. Insulin treatment incl. rescue medication should be registered in concomitant medication form in the eCRF. In addition there are specific forms to capture information on insulin dose in the eCRF.

Details of any concomitant medication must be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication must be recorded at each visit as they occur.
The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date and stop date or continuation.
If a change is due to an AE, then this must be recorded and reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

## 8.4 Laboratory assessments

A central laboratory will be responsible for providing laboratory supplies for the analysis of blood and urine samples taken during the trial. All samples obtained during the trial will be analysed at a central laboratory or a special laboratory (PK and antibody samples). The urine pregnancy test will be performed locally during subject visits. Descriptions of assay methods, laboratory supplies and procedures for obtaining samples, handling and storage of samples and information on who will

perform the assessments, are described in a trial-specific laboratory manual provided by the central laboratory.

Laboratory samples can be drawn at another day than on the day of the actual visit as long as it is within the visit window stated in the flow chart (section 2). It should be ensured that where fasting is required for the sensitivity of the analysis (Visits 1, 7, 13, 17 and 25) that subjects will attend the visit in a fasting state for blood draw.

Note: Subjects should arrive fasting for Visit 1 blood sampling. Fasting is considered a trial related activity and no trial related activities may be initiated prior to a signed assent and consent form.

Samples will be coded in order to keep subject identity anonymous.

Information on central laboratory results will be available to the investigator on an ongoing basis. All laboratory printouts must be dated and signed by the investigator on the day of evaluation. If a result is outside the normal range, the investigator must judge whether the abnormality is clinically significant and document this. If considered clinically significant the result must be reported as a concomitant illness at Visit 1 and as an AE according to section 12 at all other visits.

All samples will be analysed and destroyed on an ongoing basis or at the latest at the completion of the clinical trial report (CTR), unless otherwise stated.

The central laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the trial database, but may be reported to the investigator according to specifications in the laboratory standard operating procedures and requirements. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

## 8.5 Subject related information and assessments

### 8.5.1 Demography

Demography consists of:

- Date of birth (according to local regulations)
- Sex
- Race (according to local regulations)
- Ethnicity (according to local regulations)

### 8.5.2 Diabetes history

The following information on subject's diabetes history should be recorded:

- Date of diagnosis

- Complications
  - Diabetic retinopathy (incl. date of diagnosis)
  - Diabetic neuropathy (incl. date of diagnosis)
  - Diabetic nephropathy (incl. date of diagnosis)
  - Macroangiopathy including peripheral vascular disease (incl. date of diagnosis)

- Diabetes treatment
  - Current diabetes treatment
  - Dose of current diabetes treatment
  - Start date of current diabetes treatment

### 8.5.3 Smoking habits

It should be recorded at Visit 1 if the subject:

- Never smoked
- Is a previous smoker
- Is a current smoker

### 8.5.4 Alcohol and drug screen

A urine drug screen will be performed to test for the presence of therapeutic and drugs of abuse at Visit 1. Subjects testing positive for commonly abused substances or alcohol must not be enrolled in this trial.

## 8.6 Assessments for efficacy

### 8.6.1 Body measurements

Body measurements consist of the following parameters:

- Body weight (Visits 1, 7, 11, 12, 13, 15, 17, 18, 20, 22, 24, 25, 27 and 28)
- Height (safety endpoint) (Visits 1, 7, 13, 17, 25, 27and 28)
- BMI (calculated at Visit 1)
- Waist circumference (Visits 1, 7, 13, 17 and 25)

***Body weight***

Body weight should be measured (kilogram or pound [kg or lb], one decimal) without shoes and only wearing light clothing. Preferably the same set of scales should be used throughout the trial.

***Height***

Height should be measured (centimetres or inches, one decimal) without shoes as two individual measurements performed by a single observer using identical technique with a Harpenden or other wall mounted stadiometer. The subject should be repositioned between the two measurements.

***Waist circumference***

The waist circumference is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest.

Three consecutive measurements of waist circumference should be taken and recorded in the eCRF. The waist circumferences will be measured to the nearest 0.5 cm (0.2 inches) using a non-stretchable measuring tape.

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin, but not compress soft tissue and twist in tape should be avoided. The subjects should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

***BMI***

The BMI will be calculated by the eCRF based on the height and weight as described above. At the screening visit the investigator must verify subject's eligibility for the trial according to the BMI inclusion criteria see section 6.2 and Appendix A.

### 8.6.2 Vital signs

Vital signs will be measured at Visits 1, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 20, 22, 24, 25 and 26. Vital signs consist of the following parameters:

- Pulse (safety endpoint)
- Systolic blood pressure, sitting
- Diastolic blood pressure, sitting

***Pulse***

Pulse (beats per minute) should be recorded at site visits after resting for 5 minutes in a sitting position.

***Systolic and diastolic blood pressure***

For measurement of systolic and diastolic blood pressure the following method should be used. Avoid caffeine, smoking and exercise at least 30 minutes prior to blood pressure measurement. The measurement should be taken in a sitting position, with legs uncrossed, the back and arm supported. Subjects should be sitting for at least 5 minutes before the first measurement is taken. The subject

should not talk during the measurement. The site should measure blood pressure using their usual method, the method should be consistent throughout the trial using the same devices. For blood pressure at screening visit (Visit 1) three measurements need to be performed and all three values should be entered into the eCRF. The mean value will be calculated by the eCRF system and must be in accordance with exclusion criterion 21 (see section 6.3 and Appendix B). It is recommended to use the same arm used at Visit 1 for measurements of pulse and blood pressure at subsequent visits.

If investigator suspects white coat hypertension at the screening visit one re-assessment of the systolic and diastolic blood pressure (using the same procedure as described above) is allowed as described in exclusion criterion 21.

In case of an "abnormal, clinically significant" finding, the investigator must comment in the medical records and, if it occurs at Visit 1, record this on the concomitant illness form. Any clinically significant worsening from baseline during the trial must be reported as an AE.

### 8.6.3 Blood samples

Blood samples will be drawn at site at the specified time-points (section 2) and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

- Glucose metabolism
  - $HbA_{1c}$
  - FPG
  - Fasting C-peptide
  - Fasting insulin
  - Fasting pro-insulin
  - Fasting glucagon

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

### 8.6.4 Self-measured plasma glucose

At Visit 2, subjects should be supplied with a glucose meter and oral and written instruction on use of the device including regular calibration according to the manufacturer's instructions. Sites should as necessary, repeat the instruction of use at visits to the clinic. Subjects already treated with metformin 2000 mg/day at a stable dose for at least 56 days prior to screening may have their BG meter for Visit 7 provided at Visit 1.

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

Subjects should be instructed in how to record the results of the SMPG values (including date) in the provided diaries and should only record the SMPG values based on glucose meter measurements.

***Self-measured plasma glucose***

Subjects will be asked to perform fasting SMPG measurements on the 3 consecutive days preceding Visit 7. The average of these 3 measurements will be used to evaluate subject's eligibility according to randomisation criterion no. 1 (see section 6.4).

After randomisation, subjects will be asked to perform fasting SMPG measurements on the 3 consecutive days preceding Visits 8, 9 and 10. Subjects treated with basal insulin will be asked to perform fasting SMPG measurements on the 3 consecutive days preceding Visits 10A, 10B, 11A and 11B for adjustment of insulin dose. For all other subjects fasting SMPG measurements should be performed 3 times a week (on a weekly basis) between Visits 10 and 11. The measurements should be captured in the subjects' diary. These measurements are used to evaluate the safety of the subject during their first weeks of treatment with liraglutide. In addition the first two to three weeks'measurements are used for dose escalation of liraglutide.

In addition all subjects are encouraged to measure their FPG on a regular basis as agreed with the investigator. Also subjects should measure their plasma glucose at least every time the subject has symptoms of hypoglycaemia or hyperglycaemia. Hypoglycaemic episodes should be recorded in the diary (see section 8.1). The investigator may ask the subject to perform additional SMPGs if needed for any safety reason.

The subject should be instructed to contact the Investigator if:

- self-measured FPG falls below 3.9 mmol/L (70 mg/dL),

or if:

- During the first 14 weeks after randomisation: FPG increases above 12.2 mmol/L (220 mg/dL) on three consecutive days, or if:

- After Week 14 (Visit 13): FPG increases above 10.3 mmol/L (185 mg/dL) on three consecutive days

The outcome of the contact will be recorded on an Unscheduled Visit Form.

***7-point self-measured plasma glucose profile***

Subjects will be instructed to perform a 7-point SMPG profile preferably within one week prior to Visits 7, 13, 17 and 25 on days where the subject do not anticipate unusual strenuous exercise.

The plasma glucose levels should be measured and recorded in the diary (including date, actual, clock time and plasma glucose value) at the following time points, always starting with measurement just before breakfast.

Time-points for 7-point profile:

- Before breakfast
- 90 min after the start of breakfast
- Before lunch
- 90 min after the start of lunch
- Before dinner
- 90 min after the start of dinner
- At bedtime

## 8.7 Assessments for safety

### 8.7.1 Adverse events

At all visits following screening investigator should ask subjects for any AEs. For more information on AEs refer to section 12.

### 8.7.2 Hypoglycaemic episodes

To avoid hypoglycaemic episodes subjects should be advised to avoid prolonged excessive fasting. Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.
All plasma glucose values:

- equal or below 3.9 mmol/L (70 mg/dL)

or

- higher than 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subjects in the diaries.

These must be transcribed into the CRF throughout the trial from Visit 2 to Visit 26.

The record should include the following information:

- The plasma glucose level before treating the episode (if available)
- Date of hypoglycaemic episode
- Time of hypoglycaemic episode
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Time of antidiabetic treatment administration prior to episode
- Type of antidiabetic treatments taken within 24 hours prior to episode
- Time of last main meal prior to episode
- Whether the episode occurred in relation to exercise

The answer to the question: "Was subject able to treat him/herself?" should be answered "No" if oral carbohydrates, glucagon or IV glucose had to be administered to the subject by another person because of severe central nervous system (CNS) dysfunction associated with the hypoglycaemic episode. Oral carbohydrates should not be given if the subject is unconscious.

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

#### 8.7.2.1 ADA classification of hypoglycaemia

According to the ADA the definition of a hypoglycaemic episode (Figure 8–1) is categorised as:

**Severe hypoglycaemia:** An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

**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).

**Relative hypoglycaemia:** An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL).

**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]).

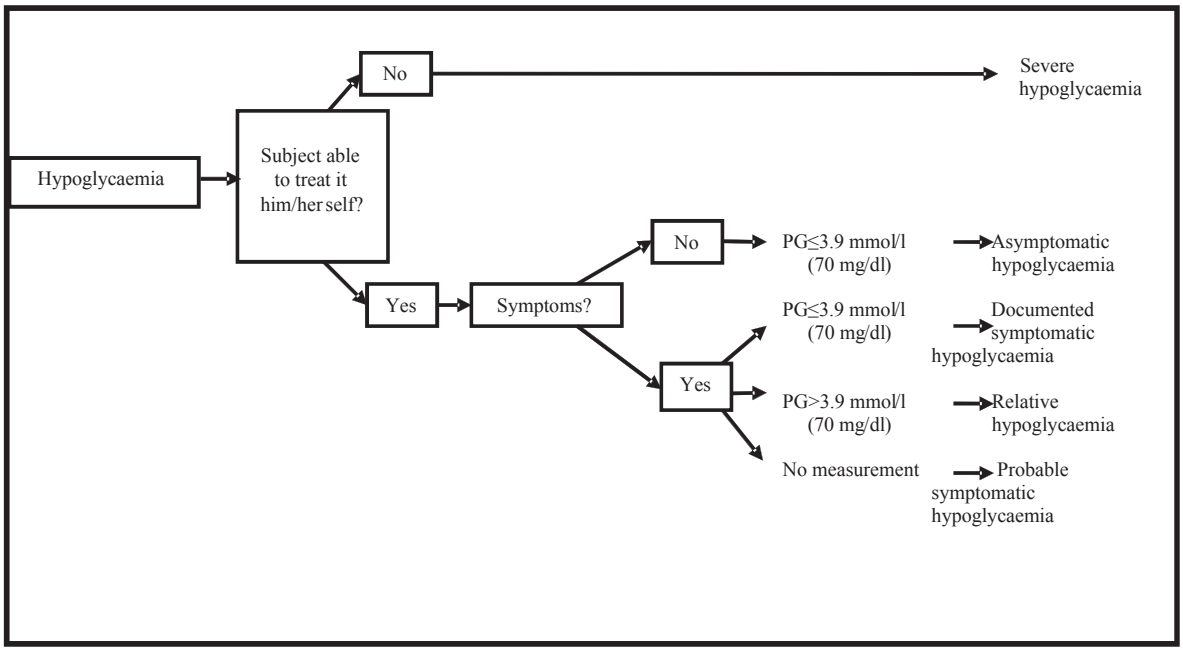


**Figure 8–1 ADA classification of hypoglycaemia**

### 8.7.2.2 Additional definitions of hypoglycaemia

A hypoglycaemic episode will be defined as treatment emergent if the onset of the episode occurs after the first administration of IMP, and no later than one day after the last day on trial product (both inclusive).

Hypoglycaemic episodes will be defined as nocturnal if the time of onset is between 00:01 and 05.59 inclusive.

In normal physiology, symptoms of hypoglycaemia occur below a blood glucose level of approximately 2.8 mmol/L (50 mg/dL) or plasma glucose level 3.1 mmol/L (56 mg/dL). Therefore, Novo Nordisk has used this cut-off point to define confirmed hypoglycaemia.

A confirmed hypoglycaemicepisode (referred to as minor hypoglycaemia) is defined as either:

- An episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose < 2.8 mmol/L (50 mg/dL) or plasma glucose < 3.1 mmol/L (56 mg/dL), and which is handled by the subject him/herself,

or

- Any asymptomatic blood glucose value < 2.8 mmol/L (50 mg/dL) or plasma glucose value < 3.1 mmol/L (56 mg/dL).

### 8.7.3 Electrocardiogram – 12 lead

A 12-lead ECG must be performed at Visits 1, 17 and 25 and interpreted locally by the investigator in relation to the trial. Investigators evaluation must be documented, signed and dated on the ECG print out.
An ECG performed for any reason unrelated to this trial within 12 weeks prior to Visit 1 is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime. The investigator must still interpret, sign and date the ECG. If an ECG was performed before the informed consent and assent have been signed, it must be documented in the subject's medical record that the reason for performance was not related to this trial.

**Only applicable to Israel:** Child assent form is not applicable.

An ECG performed 2 weeks before Visits 17 and 25 is acceptable as Visits 17 and 25 data respectively.

### 8.7.4 Eye examination

A fundoscopy must be performed at Visits 1, 17 and 25 by the investigator or a local ophthalmologist according to local practice. Investigators evaluation must be documented in the subject's medical records.
If a fundoscopy has been performed within 12 weeks prior to Visit 1 and if the results are available, the procedure does not need to be repeated. The investigator must still interpret, sign and date the fundoscopy results. If a fundoscopy was performed before the informed consent and assent have been signed, it must be documented in the subject's medical record that the reason for performance was not related to this trial.

**Only applicable to Israel:** child assent form is not applicable.

A fundoscopy performed 2 weeks before Visits 17 and 25 is acceptable as Visits 17 and 25 data respectively.

### 8.7.5 Physical examination

At Visits 1, 7, 13, 17 and 25 a physical examination must be performed

Physical examination should include:
- Head, ears, eyes, nose, throat, neck
- Respiratory system

- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- General appearance
- Lymph node palpation
- Thyroid gland

Any abnormalities found at Visit 1 should be recorded as a concomitant illness. Any clinically significant worsening from Visit 1 as well as any new clinically significant findings during the trial must be reported as an AE (see section 12).

### 8.7.6 Tanner staging

Pubertal status will be recorded in the CRF at Visits 7, 13, 17, 25, 27 and 28 for children-and adolescents. Pubertal development will be assessed by the Tanner staging in accordance with stages I-V[34]. Assessment of testicular volume (by orchidometer) stages for boys will be included. The assessments must be conducted by personnel trained in pubertal assessments.

A Tanner staging assessment performed 2 weeks before Visits 7, 13, 17, 25, 27 and 28 is acceptable as Visits 7, 13, 17, 25, 27 and 28 data assessment respectively.

The Tanner staging assessment is no longer required to be performed, once the subject reaches the Tanner stage V, as judged by the investigator.

Evidence of accelerated pubertal development as judged by the investigator at Visit 1 should be recorded as concomitant illness. Acceleration of pubertal development after Visit 1 as judged by the investigator should be recorded as an AE

### 8.7.7 Bone age assessment

An x-ray of left hand and wrist will be performed at Visits 7 and 25 for all subjects for evaluation of bone age. In addition subjects treated with liraglutide for more than three months will have an x-ray performed at Visits 27 and 28. A repeat bone age assessment will not be performed at subsequent visits (25, 27 or 28) for subjects for whom the bone age assessment at Visit 7, or at a later visit, indicates that the epiphyses are fused. The x-rays will be analysed by a central reader for determination of bone age. Further requirements and details will be described in the x-ray site manual.

An x-ray performed within 2 weeks prior to Visit 7, 25, 27 and 28 is acceptable.

### 8.7.8 Blood samples

Blood samples will be drawn at site at the specified time-points (section 2) and analysed at the central laboratory to determine levels of the following safety parameters:

- Haematology
  - Haemoglobin
  - Haematocrit
  - Thrombocytes
  - Erythrocytes
  - Leucocytes
  - *Differential count:*
    - Eosinophils
    - Neutrophils
    - Basophils
    - Lymphocytes
    - Monocytes

- Biochemistry
  - creatinine
  - creatine kinase
  - urea
  - albumin
  - bilirubins (total)
  - ALAT
  - ASAT
  - Alkaline phosphatase
  - Sodium
  - Potassium
  - Calcium, total
  - Calcium, albumin corrected
  - Amylase
  - Lipase

- Hormones
  - Calcitonin (please refer to Appendix D for actions to be taken if calcitonin is > UNR)
  - Prolactin
  - FSH
  - Estradiol
  - LH
  - Testosterone

- DHEAS
- CEA
- TSH
- IGF-1
- IGFBP-3

- Pregnancy test
  Females of childbearing potential will have a serum pregnancy test (beta-human chorionic gonadotropin) performed at Visits 1, 7, 13, 17 and 25. In addition they will have a urine pregnancy test performed at Visit 7 prior to randomisation. During the rest of the trial a urine-stick pregnancy test will be performed at the site if a menstrual period is missed. The investigator should comply with local laws with regard to pregnancy testing in minors during clinical trials.
  **Austria**: A urine-stick pregnancy test will be performed at all visits to the clinic.

  If a girl becomes of childbearing potential (has first menstrual period) during the trial a serum pregnancy test must be performed for that subject as soon as possible or at the latest at the next clinic visit.

- Bone metabolism markers
  - Alkaline phosphatase
  - P1NP
  - NTX
  - CTX

- Insulin antibodies:
  - IA-2
  - anti-GAD

- HIV
- Hepatitis B and C

**Liraglutide antibody samples**
Blood samples for determination of anti-liraglutide antibodies will be drawn at Visits 7, 17 and 26. Unblinded subjects who are not treated with liraglutide should not have a blood sample drawn for determination of anti-liraglutide antibodies.

Samples will be analysed for anti-liraglutide antibody formation including cross reactivity to endogenous GLP-1. Samples from Visit 26 that are found to be positive for anti-liraglutide antibodies will be assessed for neutralising effect.

The blood samples collected for determination of anti-liraglutide antibodies will be stored until marketing authorisation for paediatric patient is given for liraglutide or as long as the local authorities permit the storage of blood samples, whichever comes first.

The antibody samples will be analysed at a special laboratory (please refer to Attachment I for details). The results of the antibody samples will only be reported to the investigator upon request at the end of trial.

### 8.7.9 Urine samples

Urinalysis will be performed at Visits 7, 13, 17 and 25. For these visits the subjects should collect a morning urine sample on the day of the visit and bring the sample to the site. For information on collection, storage and transport to site, please refer to the laboratory manual. Urine samples will be analysed at the central laboratory to determine the levels of the following safety laboratory parameters:

Urinalysis
- Micro albumin
- Creatinine
- Albumin:creatinine ratio (calculated)
- Protein
- Ketone
- Glucose
- pH

## 8.8 Other assessments

In addition to the assessments mentioned in sections 8.1- 8.7 the following should be performed:

- Diet and exercise counselling according to local standards (Visits 2, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 20, 22, 24 and 25). The counselling should be documented in the subject's medical record
- Dispense trial product (including IV/WRS session) (Visits 2, 5, 7, 11, 12, 13, 15, 17, 18, 20, 22 and 24). Trial product must not be dispensed to any person not included in the trial. Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk
- Instruct in the metformin titration to 2000 mg/day or MTD over 3 to 4 weeks at the discretion of the investigator and in metformin maintenance as applicable (titration at visits 2, 3, 4 and maintenance at visit 5). Subjects already treated with metformin 2000 mg/day or more for at least 56 days prior to screening may have their BG meter, urine collection container and diary for Visit 7 provided at Visit 1 and advance directly to Visit 7 see section 5.3. Subjects who are

treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days to advance directly to Visit 7.

- Instruct in the use of the pen-injector for liraglutide administration (Visit 7), instructions should be repeated as needed
- Dose escalation of liraglutide at 0.6 mg increments in weekly intervals (Visits 7, 8, 9 and 10) based on the average of three FPG measurements taken on the three consecutive days preceding Visits 8, 9 and 10. The average FPG must be > 6.1 mmol/L (110 mg/dL) in order for the liraglutide dose to be escalated see section 5.3
- Obtain oral confirmation of compliance according to section 8.9 (Visits 3-25)
- Provide BG meter and instructions for use (Subjects already treated with a stable dose of with metformin 2000 mg/day or more for at least 56 days prior to screening may have their BG meter, for Visit 7 provided at Visit 1). Subjects who are treated with basal insulin should in addition to the stable dose of metformin have a stable dose of basal insulin for at least 56 days to advance directly to Visit 7)
- Provide urine collection containers for collection of urine (Visits 1, 5, 12, 15 and 24). Subjects already treated with a stable dose of with metformin 2000 mg/day or more for at least 56 days prior to screening may have their urine collection container for Visit 7 provided at Visit 1
- Provide diary and instruct in the use of the diary (Visits 1, 2, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 20, 22 and 24)
- Collect, review and transcribe data from diaries at Visits 2-25. At telephone contacts (TCs) information from the diary as reported by the subject and not the physical diary will be collected
- Perform drug accountability according to section 9.3 (Visits 5, 7, 11, 12, 13, 15, 17, 18, 20, 22, 24 and 25)
- Complete relevant IV/WRS calls according to section 10 (Visits 1, 2, 5, 7, 9, 11, 12, 13, 15, 17, 18, 20, 24 and 25)
- Review rescue (Visits 10-24) and withdrawal criteria (Visits 2-24) according to section 6.5 and 6.6.

### 8.8.1 Blood samples - pharmacokinetic

Blood samples for measuring the concentration of liraglutide in the blood will be drawn at Visits 8, 9, 11, 13 and 17. Date, time and dose of liraglutide injections two days prior to Visits 8, 9, 11, 13 and 17 should be recorded in the subject diary. Liraglutide injections should be withheld on the day of the visits until the blood sampling has been performed.

The PK samples will be analysed at a special laboratory (please refer to Attachment I for details). A detailed description of the assay and the results will be reported in a separate bioanalytical report.

The results of the PK samples will only be reported to the investigator upon request.

## 8.9 Subject compliance

At each visit the investigator will emphasise the necessity for the subject to adhere to trial procedures in order to encourage subject compliance.

The investigator must assess the compliance of the subject at each visit based on a review of glycaemic control, adherence to the visit schedule and completion of the subject's diary including previous day's doses of metformin and liraglutide. At Visits 3-25 compliance must be assessed by oral confirmation from the subject and the subject's LAR, the compliance assessment must be documented in subject's medical record and transferred to the eCRF.

In addition, subject compliance will be assessed by monitoring of drug accountability. The unused amount of IMP and NIMP will be assessed against the dispensed amount and, in case of discrepancies, the subject must be asked.

For metformin compliance is defined as taking between 80%-120% of the prescribed dose. There is no fixed compliance range for liraglutide.

If a subject is discovered to be non-compliant, the investigator must inform the subject of the importance of taking IMP and NIMP as directed. Substantial failure to comply with the prescribed dose regimen should be discussed with Novo Nordisk and can lead to withdrawal.

# 9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies

Trial products comprise IMPs, including liraglutide placebo and NIMP.

Auxiliary supplies comprise supplies other than trial products, e.g. needles and blood glucose meters.

Procedures for supply, handling and storage of trial product will be described in the Trial Materials Manual (TMM) provided by Novo Nordisk. The TMM will be distributed to investigational sites.

## 9.1 Trial products

The IMPs used in this trial are:

- liraglutide solution for s.c. injection (6.0 mg/mL)
- liraglutide placebo solution for s.c. injection

Liraglutide and liraglutide placebo solutions for s.c. injection will be supplied by Novo Nordisk in a 3 mL pre-filled pen injector.

The administration of liraglutide and liraglutide placebo will be as outlined in section 5.3.2 . The liraglutide placebo and active drug are visually identical and identical with regards to smell.

The investigator will provide each subject with direction for use of the pre-filled pen injector at the dispensing visits.

IMP dispensing units will be distributed to the sites according to enrolment. Please refer to the TMM provided by Novo Nordisk for further details.

### 9.1.1 Non-investigational medicinal product(s)

Metformin tablets (NIMP) will be purchased by Novo Nordisk and provided to sites for subject treatment during the trial. Metformin tablets will be provided in a metformin hydrochloride tablet form containing 500 mg.

The investigator will provide each subject with verbal instruction in the use of metformin at the dispensing visits.

NIMP dispensing units will be distributed to the sites according to enrolment. Please refer to the TMM provided by Novo Nordisk for further details.

Insulin (Concomitant and rescue treatment) is regarded as NIMPs and will not be supplied by Novo Nordisk.

## 9.2 Labelling

All trial products will be packed and labelled by Novo Nordisk and provided in non subject specific boxes.

Labelling of the IMPs will be in accordance with Annex 13[35], local law and trial requirements.

Labelling of the NIMP will be in accordance with local requirements.

Labelling will include the product related requirements and precautions.

## 9.3 Storage, accountability and destruction

**Storage**

The investigator must ensure availability of proper storage conditions, and record and evaluate the temperature (at least once every working day). Storage facilities should be checked frequently. A log to document the temperature and the date of temperature must be kept. Trial products that have been stored improperly must not be dispensed to any subject before it has been re-evaluated and approved for further use by Novo Nordisk. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside defined conditions (i.e. temperature ranges). The investigator's first point of contact is the monitor.

**Liraglutide and liraglutide placebo**

Storage condition for liraglutide and liraglutide placebo:

Not in use:

- Store in a refrigerator (+2ºC to +8ºC [+36ºF to +46ºF])
- Do not freeze
- Protect from light
- Store away from the freezer compartment

In use:

- After first use of the prefilled pen, the product can be stored for 1 month at room temperature (below +30°C/86ºF) or in a refrigerator (+2ºC to +8ºC [+36ºF to +46ºF])
  - **US**: 30 days at room temperature (+15°C to +30°C [+59ºF to +86ºF]) or in a refrigerator (+2ºC to +8ºC [+36ºF to +46ºF])
- Keep the pen cap on when the prefilled pen is not in use in order to protect from light

- Store away from the freezer compartment

**Metformin**

Storage and handling of metformin must be in accordance with labelling.

**Dispensing and return of medication**

Trial products will be dispensed to each subject as required according to treatment group. The IV/WRS will allocate trial product dispensing unit numbers (DUN) to the appropriate subject at each dispensing visit. All DUNs must be dispensed to the appropriate subject.

Liraglutide and liraglutide placebo must not be used if it does not appear clear and colourless.

Liraglutide, liraglutide placebo or metformin must not be dispensed to any person not participating in the trial.

Subjects must return the dispensed liraglutide, liraglutide placebo and metformin (used/ partly used and unused trial products including empty packaging material). Returned trial products (used/ partly used and unused trial products including empty packaging material) must be stored separately from non-allocated trial product(s).

**Accountability and destruction**

The person delegated by the investigator must keep track of all received, used, partly used and unused trial products and if possible, all empty packaging, by using the drug accountability module in the IV/WRS. There should be performed full accountability for all IMPs (per pen) and NIMPs (per tablet).

Subjects are instructed to return all used, partly used and unused trial products including empty packaging material.

The investigator must keep all returned trial products until the monitor has performed drug accountability. Destruction of trial products will be done according to local procedures and after agreement with the monitor. Destruction of trial products must be documented.

## 9.4 Auxiliary supply

The following may be supplied by Novo Nordisk and in some countries bought locally:

- Needles, for pre-filled pen injector
- Blood glucose meters, incl. lancets, plasma calibrated test strips and control solutions

Further details will be described in the TMM.

# 10 Interactive voice and web response system

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

IV/WRS is used for:

- Screening
- Screening failure (incl. run-in failure)
- Randomisation and stratification
- Medication arrival
- Run-in dispensing
- Dispensing (incl. unblinding at Visit 17)
- Withdrawal
- Completion (treatment)
- Code break
- Drug accountability
- Data change

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

# 11 Randomisation and unblinding procedures

At the randomisation visit (Visit 7) the subjects will be randomised to one of two parallel treatment groups:

- Liraglutide and metformin with or without basal insulin or
- Liraglutide placebo and metformin with or without basal insulin

The trial is a double-blind trial for the first 26 weeks. The randomisation will be carried out in a 1:1 manner using IV/WRS.

Subjects will be stratified at randomisation by sex and according to their age at end of treatment (≤ 14 and > 14 years of age) (see section 5.1 for definition of ≤ 14). Stratification will be controlled by the IV/WRS system.

## 11.1 Breaking of blinded codes

If the trial site needs to break the code, Novo Nordisk should, if possible, be contacted before the code is broken. 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.

If the subject is withdrawn after the code has been broken, a withdrawal session should be completed in the IV/WRS.

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 vendor helpdesk should be contacted. Contact details are listed in attachment II.

## 11.2 Unblinding procedure and laboratory access to blinded data

Subjects' treatment will be blinded during the first 26 weeks of randomised treatment (Visit 7 to Visit 17). At Visit 17 a subject's treatment allocation will be revealed via the IV/WRS.

The special laboratories analysing the samples for anti-liraglutide antibodies and concentration of liraglutide (PK) will be provided with a randomisation list.

# 12 Adverse events, and technical complaints and pregnancies

## 12.1 Definition of adverse events

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.
Note: This includes events from the first trial related activity after the subject has signed the informed consent and until Visit 26 (for subjects treated with liraglutide for more than 3 months until Visit 28).

AEs include:

- 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 medical history or 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 are AEs, but are reported on hypoglycaemic forms instead of on AE forms.

## 12.2 Definition of serious adverse events and non-serious adverse events

An AE is either categorised as a serious AE (SAE) or a non-serious AE.

An 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 this definition.[d]

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
- 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.

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 dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

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

### 12.3 Definition of medical events 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 should be reported according to the same reporting requirements and timelines as for SAEs (see section 12.5) irrespective of whether the MESI fulfils any SAE criterion.

The following are defined as MESIs in this trial (further defined in Appendix C):

1. Medication errors concerning trial products:
    - Administration of wrong drug
    - Wrong route of administration, such as intramuscular instead of subcutaneous
    - Administration of a high dose with the intention to cause harm (e.g. suicide attempt)

- Administration of an accidental overdose:
  - An accidental overdose is defined as the subject having received dosing which exceeds the maximum intended dose 1.8 mg daily

2. Suspected transmission of an infectious agent via a trial product
3. Altered renal function
4. Acute pancreatitis and the suspicion of acute pancreatitis
5. Elevated lipase or amylase >3x UNR
6. Any confirmed episode of calcitonin value ≥20 ng/L (see Appendix D)
7. Neoplasm excluding thyroid neoplasm
8. Thyroid disease including thyroid neoplasm
9. Severe hypoglycaemia
10. Immunogenicity (immune-complex disease and allergic reactions including allergic reactions at injection sites)
11. AEs leading to withdrawal

### 12.4 Severity, relationship and outcome of adverse events

**Severity assessment definitions:**

- **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.

The following terms and definitions are used when assessing the relationship between each 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

**Outcome categories and definitions**

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered** - 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** - This term is only applicable if the subject has completed the trial or has died from another AE. The condition is improving and the subject is expected to recover from the event.
- **Recovered** 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** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- **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", "recovering", "recovered with sequelae" or "not recovered". 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.

### 12.5 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 until the end of the post-treatment follow-up period (Visit 26). The events must be recorded in the applicable forms in a timely manner.

During each contact with the trial site staff (site visits and telephone contacts), the subject must be asked about AEs and technical complaints. This could be done by asking for example: "Have you experienced any problems since the last contact?". Collection on technical complaints will start from the randomisation visit (Visit 7) which is the first visit where the subject will use liraglutide and the pen-injector.

At the follow-up Visits 27-28 the site will record reported AEs and SAE (based on the subject's memory) and the associated concomitant medication. The SAE reporting must follow the timelines set for SAE reporting, please see below.

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

- Novo Nordisk IMPs (liraglutide): Current version of the company core data sheet (CCDS) or any updates hereof.

The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as an individual AE.

All AEs, SAEs and MESIs must be recorded by the investigator on the AE form in the eCRF. A separate AE form should be used for each diagnosis or sign and symptom. For each SAE a safety information form (SIF) should be completed in addition to the AE form in the eCRF. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF may be used to describe all the SAEs.

The SIF will be a paper based form. The completed form will be faxed or emailed to Novo Nordisk according to the below timelines.

MESIs, regardless of seriousness, must be reported using the AE form and the SIF.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial.

**The reporting timelines for SAEs**

- The investigator must enter the AE in the eCRF and tick the seriousness box within 24 hours of obtaining knowledge of the SAE. If the SAE is fulfilling the MESI criteria also tick the MESI box.
- The paper-based SIF must be completed and forwarded to Novo Nordisk **within 5 calendar days** of obtaining knowledge of the SAE preferably electronically in PDF format or by fax.
- The AE form in the eCRF must be signed within 7 calendar days from the date the information was entered in the eCRF.

**The reporting timelines for non-serious AE fulfilling the MESI criteria**

- The investigator must enter the AE in the eCRF, tick the MESI box and complete the paper-based SIF within 14 calendar days of obtaining knowledge of the MESI.

If for some reason the eCRF is unavailable, the AE information should be reported to Novo Nordisk by fax, e-mail or courier within the same timelines.

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

All laboratory results outside of the pre-defined normal limits will automatically be reported to the investigator and Novo Nordisk and the laboratory results will be monitored by Novo Nordisk on a regular basis.

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP[33]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change to any trial procedure.

Novo Nordisk must inform the Institutional Regional Boards/Independent Ethics Committees (IRBs/IECs) in accordance with local requirement and GCP, unless locally this is an obligation of the investigator, as for example in the US.

Novo Nordisk must always inform the regulatory authorities in accordance with local requirements and GCP.

## 12.6 Follow-up of adverse events

All SAEs and MESIs must be followed up until the outcome of the event is "recovered", "recovered 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" or "not recovered", when the subject has completed the follow up period. The follow-up period for this trial is one week (Visit 26).

The follow-up information on SAEs should only include new (corrections or new or additional) information and should be reported **within 24 hours** of obtaining knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

The follow-up information on MESIs should only include new (corrections or new or additional) information and must be reported within 14 calendar days of the investigators first knowledge of the information. This is also the case for previously reported non serious AEs which subsequently fulfil the MESI criteria.

Non-serious AEs must be followed until the outcome of the event is "recovering", "recovered" or "recovered 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 or cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering" or "not recovered".

Queries or follow-up requests from Novo Nordisk should be responded to within 13 calendar days.

The investigator must forward follow-up information on SAEs within 24 hours and MESIs within 14 days of obtaining the follow-up information by updating the AE form in the eCRF and/or completing a new SIF marked follow-up, and forward this to Novo Nordisk. If for any reason the eCRF is unavailable or, after access to edit the eCRF is revoked, the investigator must record any SAE and MESI follow-up information on the provided paper CRFs and/or SIF and send the information by fax, e-mail or courier to Novo Nordisk.

The investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF. If the eCRF is revoked after access to edit, the investigator must record any follow-up information on the provided paper CRFs. Information on AEs, SAEs and MESIs for Visit 27 and 28 must be recorded on the provided paper CRFs.

## 12.7 Technical complaints and technical complaint samples

A technical complaint is any communication that alleges defects on trial supplies. 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 pen and needles (e.g., to the injection mechanism, needles, dose setting mechanism, push button or interface between the pen and the needle)

### 12.7.1 Reporting of technical complaints

All technical complaints on any of the following products liraglutide or liraglutide placebo and metformin which occur from the time of first usage of trial supplies until the time of the last usage of trial supplies must be collected and reported to Novo Nordisk.

The investigator must assess whether the technical complaint is related to any AE(s), SAE(s) and/or MESI(s).

Technical complaints must be reported on a separate technical complaint form and must be completed for each IMP (liraglutide and liraglutide placebo) Novo Nordisk provided NIMP (metformin) and for auxiliary supplies listed on the technical complaint form. If the technical complaint involves more than one batch number, a technical complaint form for each batch number must be completed.

The investigator must complete and forward the technical complaint form by fax, e-mail or courier to Novo Nordisk, within the same timelines as for reporting AEs, SAEs and MESIs as follows:

- Technical complaint assessed as related to an SAE within 24 hours of the trial site obtaining knowledge of the complaint
- All other technical complaints within 5 calendar days

The technical complaint from will be a paper based form.

### 12.7.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor within 5 calendar days. The monitor must initiate the shipment to Novo Nordisk and ensure the sample is sent in accordance with local regulations and as soon as possible to Novo Nordisk complaint centre. A copy or a print of the technical complaint form should be sent with the sample.

The investigator should ensure that the technical complaint sample contains the batch 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 and shipment of the technical complaint sample must be done in accordance with the conditions prescribed for the product (see section 9.3).

### 12.8 Pregnancies

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. Treatment in pregnant trial subjects must be stopped immediately.

**Only applicable to US:** subjects must be instructed to notify the Investigator immediately if they or their partner become pregnant during the trial.

The investigator must report any pregnancy in subjects who received Novo Nordisk provided trial product. **Only applicable to US:** Pregnancies in partners of male subjects must be reported also (see section 12.8.1)

When an abnormality is reported in the foetus or newborn infant and information is needed from the male partner an informed consent must be obtained prior to this.

The investigator must report all information on pregnancies, including AEs in the subject, foetus, and newborn infant on the trial related pregnancy forms. Novo Nordisk will provide investigators with paper pregnancy forms. The pregnancy forms must be forwarded to Novo Nordisk preferably electronically in PDF format or by fax, see Attachment II.

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant(s) until the age of one month. The investigator must collect information on the pregnancy and pregnancy complications as well as the pregnancy outcome including the health of the newborn infant(s) on the pregnancy forms.

The following must be collected:

- Initial information **within 14 calendar days of the investigator's first knowledge of the pregnancy**
- Information on the outcome of her pregnancy - including the health status of the newborn infant at the age of one month **within 14 calendar days of the investigator's knowledge of the pregnancy outcome**
- All non-serious **AEs** in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms within 14 calendar days of the investigator's knowledge. It must be clear in the description if the event occurs in the subject, the foetus or the newborn infant.

- All **SAEs** in connection with the pregnancy and pregnancy outcome must be reported on the pregnancy forms following the **same timelines as required for other SAEs** (see section 12.5). It must be clear in the description if the event occurs in the subject foetus or the newborn infant.
  - The SAEs that must be reported include abnormal outcome - such as congenital anomalies, foetal death and termination of pregnancy (spontaneous or elective abortion), including any anomalies of the foetus observed at gross examination or during autopsy - as well as other pregnancy complications fulfilling the criteria of an SAE.

### 12.8.1 Pregnancies in partners of trial subjects (only applicable to US)

In case of an SAE (with a causal relationship evaluated as possible or probable by the Investigator) in the fetus, newborn infant(s) or infant(s)/toddler(s) of a trial subject's partner, who is potentially exposed to the trial product via the trial subject, the pregnancy and the SAE should be reported on the same forms and within the same timelines as for a subject in the trial. Prior to obtaining any data on the pregnancy, "pregnant partner consent" must be completed by the male subject's partner.

## 12.9 Precautions and/or overdose

When initiating treatment with liraglutide, the subject may in some cases experience side effects.

In the clinical trials of liraglutide, one subject with type 2 diabetes experienced a single overdose of 17.4 mg subcutaneous (10 times the maximal recommended maintenance dose of 1.8 mg). Effects of the overdose included severe nausea and vomiting. No hypoglycaemia was reported. The patient recovered without complications.
For further details please refer to latest version of the IB for liraglutide[15] or any updates thereof.

## 12.10 Committees related to safety

### 12.10.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance. The safety committee will conduct ongoing monitoring of blinded safety data. The 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.

### 12.10.2 The external data monitoring committee

An external data monitoring committee (DMC) is established to independently review and evaluate accumulated unblinded safety data from the trial in order to protect the safety of the subjects and to evaluate the evolving risk-benefit if required.

The DMC is composed of permanent members who are independent of Novo Nordisk and will cover relevant specialities (specialists in paediatrics and endocrinology) and they may request assistance from a number of additional ad hoc members, if needed.

The DMC is established as agreed with PDCO to review unblinded safety data after the first 12 subjects have been randomised to liraglutide and undergone dose escalation starting with a 0.6 mg dose. The DMC will also monitor safety throughout the trial on an ongoing basis, and recommend to Novo Nordisk whether to continue, modify, or terminate the trial as necessary. The composition of the DMC, objectives of the surveillance, meeting frequency and type, data to be analysed at the meetings and responsibilities with regard to information (such as meeting minutes) will be described in a DMC charter.

Novo Nordisk Global Safety must be the only point of contact between the DMC and Novo Nordisk. Other departments can participate in DMC meetings if deemed relevant by Novo Nordisk Global Safety. The DMC recommendations should be addressed directly to Novo Nordisk Global Safety and the internal Novo Nordisk safety committee. It is the responsibility of the internal Novo Nordisk safety committee to take action for subject safety based on the DMC recommendations. DMC concerns relating to trial processes will be communicated to trial management via Novo Nordisk Global Safety.

# 13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF) and provide paper case report forms (CRF) to site. The electronic system and support services to the system will be supplied by a vendor. The subject visit data will be captured in the eCRFs for subject Visit 1-26. The follow-up data for Visit 27-28 will be captured on paper CRFs.

The safety information forms which are used to capture information for SAEs and MESIs and the pregnancy forms (pregnancy A and pregnancy B) are paper based CRFs. The investigator must ensure that data are recorded in these forms as soon as possible and ensure that Novo Nordisk receives these forms within the required timeline (see section 12.5).

**Data entry for eCRFs**
The investigator or delegated staff must 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.

**Data entry for paper CRFs**
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.

**Signing the CRFs**
The investigator must ensure that all information derived from source documentation is consistent with the source information. By electronically signing the case book the investigator confirms, that the information in the CRFs for the trial until Visit 26 including related forms, are completed and correct. Likewise by signing the affirmation statement for each of the Visits 27 and 28 the investigator confirms that the information in the CRFs for these visits including related forms are complete and correct.

## 13.1 Corrections to case report forms

**Correction procedure for eCRFs**
Corrections to the CRF data may be made by the investigator or the investigator’s authorised staff. An audit trail will be maintained in the CRF 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 authorised staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

**Correction procedure 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 were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff. If corrections are made by the investigator's authorised staff after the date of the investigator's signature on the affirmation statement, the affirmation statement must be signed and dated again by the investigator.

Corrections necessary after the CRFs have been removed from the investigator's site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his authorised staff. If the affirmation statement for the subject has already been signed, the investigator must approve any correction.

## 13.2 Case report form flow

The investigator must ensure that data are recorded in the eCRF as soon as possible after the visit, preferably within 3 business days. Once data have been entered, they will be available to Novo Nordisk for data verification and validation purposes.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than business 3 days after the last subject's last visit at the site in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the Investigator after the trial database is released, and access to update the trial data in electronic data capture (EDC) system has been removed. This data will be retained by the site.

When the final CTR is available the data will be archived by Novo Nordisk.

# 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 paper or EDC source data verification, to monitor drug accountability and collect completed CRF pages. The visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 8 weeks for sites with subjects between Visits 1 and 26 (inclusive).

## 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 CRFs.

For screening failures the monitor will ensure that relevant eCRF pages and other trial related forms containing data from screening failures are completed. For screening failures the following data should be source verified: informed consent, reason for screening failure and AEs if any.

The subject diaries will be collected at each subject visit to the clinic and must be kept as source data by the investigator. The diary will be source data verified by the monitor according to guidance for reduced source data verification (SDV) in the monitoring guideline. 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. Therefore, transcription to the diary from the blood glucose meter is considered the source document for recordings of blood glucose.

For all data recorded in the CRFs the source document must be defined in a source document agreement at each site. The list must be detailed and there should only be one source defined at any time for any data element.

The monitor must ensure that the CRFs and eCRFs are completed by site staff.

Monitors must review the medical records and other source data (e.g. the diaries) to ensure consistency and/or identify omissions compared to the CRF or eCRF. If discrepancies are found, the investigator must be questioned about these.

# 15 Data management

Data management is always the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a data management unit within Novo Nordisk or an external 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.

Laboratory data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where laboratory data are transferred via non-secure electronic networks, data will be encrypted during transfer. The laboratory will provide all laboratory reports to the investigator for storage at the trial site.

The subject and any biological material obtained from the subject will be identified by subject ID and trial identification number. 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 (SOPs) 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 the practical use of these systems within the conduct of this clinical trial.

# 17 Statistical considerations

**General considerations**

Novo Nordisk will be responsible for the statistical analysis and reporting. Analysis and reporting will be based on pooled data from all sites.

The statistical analyses will be performed with a significance level of 5% (two-sided tests).

For all endpoints analysed statistically, estimated mean treatment differences will be presented together with two-sided 95% confidence intervals and p-values.

**Handling of missing data**

If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If the value measured at the randomisation visit is missing and the assessment also has been made at screening, then the screening value will be used as the baseline value.

For efficacy variables missing values will be imputed as described in section 17.3 and 17.4.

Data collected after treatment discontinuation or initiation of rescue treatment (see section 5.3.5) will be considered missing in some of the efficacy analyses as described in section 17.3 and 17.4. Data collected after treatment discontinuation will be data from withdrawals collected at either Visit 17 or Visit 25 (see section 8.1.7) in case the measurement is within the visit window (± 5 days) of a planned visit.

For safety variables missing values (including intermittent missing values) will be imputed using the last observation carried forward (LOCF) method on post-baseline measurements. All data for subjects receiving rescue treatment will be included.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

## 17.1 Sample size calculation

The sample size has been determined in order to demonstrate superiority of liraglutide in combination with metformin with or without basal insulin treatment vs. liraglutide placebo with metformin with or without basal insulin treatment, with regards to change in $HbA_{1C}$ from baseline after 26 weeks, using a significance level of 5% and a two-sided test.

The sample size is based on calculations for the primary endpoint alone. Assumptions for the sample size calculations are as follows:

Change in $HbA_{1C}$: a mean difference of 0.9% of liraglutide in combination with metformin with or without basal insulin treatment vs. liraglutide placebo with metformin with or without basal insulin treatment; Standard deviation (SD) =1.2%.The change in mean difference was chosen based on the effect of liraglutide vs. placebo observed in the adult population (LEAD 1, 2, 4 and 5 trials)[15] and a paediatric PK/PD trial which included $HbA_{1c}$ after 5 weeks of treatment as an exploratory endpoint (NN2211-1800)[36].

The chosen withdrawal rates (see table 17.1) are based on the withdrawal rates seen in the LEAD 2 trial[15] where the withdrawal rate was approximately 40% for the placebo group and approximately 20% for the active groups. A slightly higher withdrawal rate is assumed as the trial is performed in a paediatric population. Therefore, the withdrawal rate for the active group is assumed to be 22%. The primary analysis will impute measurements for withdrawn placebo subjects based on placebo completers, and thus the sample size is not adjusted for placebo withdrawal rate.

Based on these assumptions, the sample size is set to 47 in each of the liraglutide and liraglutide placebo arms for the full analysis set (FAS) in order to achieve 80% power see Table 17–1.

Assuming a screening failure rate of 65%, 269 subjects will need to be screened.

**Table 17–1 Total sample size for a 1:1 randomisation**

| | | **Difference to detect in subjects with week 26 data** | | | | |
|---|---|---|---|---|---|---|
| **Withdrawal rate** | | 0.6% | 0.7% | 0.8% | 0.9% | 1.0% |
| 20 | Adjusted difference | 0.48% | 0.56% | 0.64% | 0.72% | 0.80% |
| | Sample size | 200 | 148 | 114 | 90 | 74 |
| 22 | Adjusted difference | 0.47% | 0.55% | 0.62% | 0.70% | 0.78% |
| | Sample size | 210 | 154 | 120 | **94** | 78 |
| 25 | Adjusted difference | 0.45% | 0.53% | 0.60% | 0.68% | 0.75% |
| | Sample size | 226 | 166 | 128 | 102 | 84 |

Power: 80%
Standard deviation of change in $HbA_{1c}$ (%) from baseline at week 26 assumed to be 1.2%
The withdrawn subjects treated with liraglutide are assumed to have an estimated change in HbA1c(%) of zero when compared to placebo.
Difference to detect: Minimum detectable difference between the changes in $HbA_{1c}$ from baseline to week 26, between two treatment arms

## 17.2 Definition of analysis sets

**Full analysis set (FAS)**: includes all randomised subjects receiving at least one dose of liraglutide/liraglutide placebo. In exceptional cases subjects or observations from the FAS may be eliminated. The subjects or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The subjects and observations excluded from FAS, and the reason for this, will be described in the CTR. The statistical evaluation of the FAS will follow the intention-to-treat principle and subjects will contribute to the evaluation "as randomised".

**Safety Analysis Set**: includes all subjects receiving at least one dose of the trial product. Subjects in the safety set will contribute to the evaluation "as treated".

Randomised subjects who are lost to follow up and where no exposure information of the investigational product or comparators is available after randomisation will be handled as unexposed.

## 17.3 Primary endpoint

The primary endpoint is the change from baseline to week 26 in $HbA_{1c}$. The FAS will be used for this analysis. All available data will be used, including data collected after treatment discontinuation and rescue initiation. A pattern mixture model using multiple imputation will be used.

The null hypothesis is no difference between the changes from baseline in $HbA_{1c}$ (%) after 26 weeks of randomised treatment with liraglutide + metformin with or without basal insulin and liraglutide placebo + metformin with or without basal insulin (H0: d= liraglutide – placebo =0). The alternative hypothesis is that there is a difference between the two treatment arms ($H_A$: d≠0). Superiority of liraglutide over liraglutide placebo will be concluded if the 95% confidence interval for the treatment difference for change from baseline in $HbA_{1c}$ (%) after 26 weeks of randomised treatment lies entirely below 0%; implying that the two sided p-value is less than 5%.

The multiple imputation procedure will be as follows:

For subjects in the liraglutide arm who are missing their week 26 $HbA_{1c}$ measurement, measurements will be imputed using the subjects' baseline $HbA_{1c}$ under a regression model based on the completers from the liraglutide placebo arm. Likewise, the same imputation model will be used for subjects in the liraglutide placebo arm with missing week 26 data. Multiple imputation of missing week 26 $HbA_{1c}$ data will be performed by utilizing the relationship between $HbA_{1c}$ measured at baseline and weeks 10 and 14 with that measured at week 26 in placebo patients.

The following four regression models will be built from the liraglutide placebo completers group for this purpose:

- Model 1: Only baseline covariates (baseline $HbA_{1c}$, stratification group (gender*age group), concomitant diabetes treatment at baseline (diet and exercise alone vs. diet and exercise plus metformin and/or basal insulin))
- Model 2: Baseline covariates and week 10 $HbA_{1c}$ as covariates
- Model 3: Baseline covariates and week 14 $HbA_{1c}$ as covariates
- Model 4: Baseline covariates, week 10 $HbA_{1c}$, and week 14 $HbA_{1c}$ as covariates

Missing week 26 data will be imputed by selecting a random observation from a normal distribution centered at the value predicted by the regression model and with variance analogous to predicting a new observation in regression analysis. For subjects on the placebo arm, the model used will be dependent on the subjects' available $HbA_{1c}$ data throughout the trial. For example, if a subject had $HbA_{1c}$ measurements only at baseline and week 14, then model 3 would be used. For subjects on the liraglutide arm, the measurements will be imputed using only the subjects' baseline $HbA_{1c}$ (model 1).

The imputation procedure will be iterated 10,000 times, thus generating 10,000 complete data sets including observed and imputed values.

For each of the imputed data sets the change in $HbA_{1c}$ from baseline to week 26 will be analysed using an ANCOVA with treatment and stratification groups (gender*age group) as categorical fixed effects and baseline $HbA_{1c}$ as covariate. The results obtained from analysing the datasets will be combined using Rubin's rule[37] to draw inference.

The estimated treatment difference between liraglutide and liraglutide placebo together with two-sided 95% CI and p-value for the test of no difference in effect will be presented.

Sensitivity analyses will be performed for the primary efficacy endpoint. They will include:

- an analysis of covariance (ANCOVA) model with LOCF imputation for missing data. Data collected after treatment discontinuation or initiation of rescue medication will be handled as missing data. Effects in the model are treatment, stratification groups (gender*age group), and baseline $HbA_{1c}$ as a covariate.
- an ANCOVA model including data after treatment discontinuation or initiation of rescue treatment and LOCF imputation for missing data. Effects in the model are treatment, stratification groups (gender*age group), and baseline $HbA_{1c}$ as a covariate.
- multiple imputation of missing values in both treatment groups (data collected after treatment discontinuation or initiation of rescue treatment considered as missing) based on parameters estimated from the placebo group. The same model as for the primary analysis will be used.
- a RMA model using all data points for all visits, but excluding data collected after treatment discontinuation or initiation of rescue medication. Fixed effects in the

model are treatment, stratification groups (gender*age group), and baseline $HbA_{1c}$ as a covariate, all nested within visit.

- a RMA model as described above, but including age of the subjects at baseline as covariate, as well as concomitant diabetes treatment at baseline and region (North America, Asia including Russia, Europe including Israel, South America including Mexico).

## 17.4 Secondary endpoints

### 17.4.1 Confirmatory secondary endpoint

All confirmatory secondary endpoints will be presented and analysed using FAS, unless otherwise specified.

**Change from baseline in FPG after 26 weeks of treatment**

The change from baseline in FPG after 26 weeks of treatment will be analysed with the same method as the primary efficacy endpoint. Baseline FPG will be included in the analyses instead of baseline $HbA_{1c}$.

**$HbA_{1c}$ < 7.0% after 26 weeks of treatment (yes/no)**

This dichotomous endpoint will be analysed by a logistic regression model. Effects in the model are treatment, stratification groups (gender*age group), and baseline $HbA_{1c}$ as a covariate. The results will include the 95% confidence interval for the odds ratio (liraglutide over liraglutide placebo) and the p-value for test of no difference between the groups as part of the presentation.

Missing data at week 26 will be imputed from the multiple imputation procedure for the primary endpoint.

**Change from baseline in BMI SDS after 26 weeks of treatment**

The change from baseline in BMI SDS after 26 weeks of treatment will be analysed with the same method as the primary efficacy endpoint. Baseline BMI SDS will be included in the analyses instead of baseline $HbA_{1c,}$

**Hierarchical testing**

The primary endpoint and confirmatory secondary endpoints will be analysed in a hierarchical manner in the following order:

- Primary efficacy endpoint
- Change from baseline in FPG after 26 weeks of treatment
- $HbA_{1c}$ < 7.0% after 26 weeks of treatment (yes/no)
- Change from baseline in BMI SDS after 26 weeks of treatment

In order to be able to conclude significance for an endpoint in the hierarchical list above, the test for that endpoint and the tests for the endpoints higher up in the hierarchy must all be concluded significant with a difference in favour of the liraglutide group.

The hierarchically testing is chosen to maintain the family wise type I error of 5%.

### 17.4.2 Supportive secondary endpoints

All supportive endpoints will be presented and analysed using FAS.

**The following dichotomous endpoints are defined:**
At 26 and 52 weeks of treatment unless otherwise stated:
$HbA_{1c}$ <7.0% (yes/no) at 52 weeks
$HbA_{1c}$ ≤6.5% (yes/no)
$HbA_{1c}$ <7.0% without severe or minor hypoglycaemic episodes (yes/no)
$HbA_{1c}$ <7.5% (yes/no)

The dichotomous endpoints will be analysed by a logistic regression model. Effects in the model are treatment, stratification groups (gender*age group), and baseline HbA1c as a covariate. The results will include the 95% confidence interval for the odds ratio (liraglutide over liraglutide placebo) and the p-value for test of no difference between the groups as part of the presentation.

Missing data at week 26 will be imputed from the RMA of the primary endpoint.

**The following continuous endpoints are defined:**

- Change from baseline at 26 and 52 weeks of treatment unless otherwise stated:
- $HbA_{1c}$ at 52 weeks
- FPG at 52 weeks
- 7-point SMPG

- mean 7-point SMPG, defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time

- post-prandial increments after breakfast, lunch and dinner respectively (from before meal to 90 min after breakfast, lunch and dinner respectively)
    - Fasting insulin, fasting pro-insulin, pro-insulin to insulin ratio, fasting glucagon, fasting C-peptide, and homeostasis model assessment (HOMA-B and HOMA-IR). If there is evidence for a skewed distribution of an endpoint, the values will be logarithmic transformed, and the actual values will be modelled instead of change from baseline.
    - Fasting lipid profile (cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, triglycerides and free fatty acids. If there is evidence for a skewed distribution of an endpoint**,** the values will be logarithmic transformed, and the actual values will be modelled instead of change from baseline.
    - Body weight
    - Waist circumference
    - BMI
    - BMI SDS at 52 weeks
    - BMI percentile (age and gender adjusted)
    - Systolic and diastolic blood pressure
    - Basal insulin dose

These continuous endpoints will be analysed with a similar method as the primary endpoint, except for change in basal insulin dose that will be presented only by descriptive statistics.

### 17.4.3 Safety endpoints

All safety endpoints will be presented using the safety analysis set. Unless otherwise specified safety endpoints will be presented only by descriptive statistics.

**Change from baseline at 26 and 52 weeks of treatment unless otherwise stated**

- Clinical evaluations (physical examination including fundoscopy [fundoscopy at 26 and 52 weeks])
- ECG with rhythm strip (at 26 and 52 weeks)
- Laboratory tests:
    - Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes and differential count (eosinophils, neutrophils, basophils, lymphocytes and monocytes)
    - Biochemistry (creatinine, creatine kinase, urea, albumin, bilirubins (total), ALAT, ASAT, sodium, potassium, alkaline phosphatase, calcium, calcium (albumin corrected), amylase and lipase)
    - Hormones (calcitonin, prolactin, FSH, estradiol, LH, testosterone, DHEAS, CEA and TSH, IGF-1, IGFBP-3

- First morning urinalysis (Micro albumin, creatinine, albumin:creatinine ratio calculated, protein, ketone, glucose, pH)
- Biochemical parameters of bone metabolism: Alkaline Phosphatase, NTX, CPX, P1NP
- Formation of anti-liraglutide antibodies (at 26 and 53 weeks)

- Pulse
- Pubertal assessment/ progression (Tanner staging) , DHEAS, LH, FSH, estradiol in females and testosterone in males
- Height SDS versus baseline at 26 and 52 weeks
- Bone age assessment (x-ray of left hand and wrist) at 52 weeks

In addition the following will be assessed at 26, and 52 weeks:

- Assessment of compliance (questioning of subjects and subjects legally acceptable representative)
- Growth velocity in cm/year and height velocity SDS (if subject is still growing). A growth velocity < 1.0 cm/year is defined as no longer growing.
- Hypoglycaemic episodes
- AEs and serious adverse events (SAEs)

**Pulse**
Pulse will be analysed with a similar method as for the primary endpoint.

**Hypoglycaemic episodes**
Hypoglycaemic episodes are recorded by subjects in their trial diaries throughout the trial. The information collected includes PG before treating the episode and whether the subject was able to treat him/herself. This information is used by Novo Nordisk to classify an episode according to the ADA definition (severe, documented symptomatic, asymptomatic, probable symptomatic and relative) and the additional minor category. A hypoglycaemic episode is defined as treatment emergent if the onset of the episode is on or after the first day of exposure to randomised treatment and no later than one day after the last day on randomised treatment. All hypoglycaemic episodes will be summarised by treatment and severity

**Adverse events**
All AEs will be coded using the most recent version of the Medical Dictionary for regulatory Activities (MedDRA) coding. A treatment emergent adverse event is defined as an event that has onset date (or increase in severity) on or after the first day of exposure to randomised treatment and no later than seven days after the last day of randomised treatment.

**Safety follow-up at 1 and 2 years after trial drug cessation at week 52 (only applicable for subjects on active liraglutide treatment for more than 3 months)**

- AEs and SAEs
- Growth velocity in cm/year (if subject is still growing)
- Height velocity SDS (if subject is still growing)

Change in:

- Height SDS
- Pubertal assessment/progression by Tanner staging
- Bone age assessment (x-ray of left hand and wrist)

### 17.5 PK modelling

The objective for this population PK analysis is to investigate potential covariates for liraglutide plasma exposure in children and adolescents with type 2 diabetes and compare it to adults. Blood samples for liraglutide PK drawn at site visits (Visits 8, 9, 11, 13 and 17) will be included in the analysis. The exact dosing time and dose for the 2 last liraglutide doses prior to the PK sample will be recorded in the subject diary, as well as the metformin dosing regimen used prior to the visit. The time of blood sampling (time of day not pre-specified) relative to the last time of dosing will be used in the analysis. Relevant adult data from previous studies will be included in the analysis to allow for a comparison with adults.

The population PK analysis will be performed by Novo Nordisk. The pre-specified analysis will explore the effect of covariates on liraglutide exposure. A compartmental model with first-order absorption in the central compartment and first-order elimination will be used. The absorption rate constant (Ka) will be estimated if feasible. If this is not feasible, Ka will be set to the value estimated previously in adult subjects with type 2 diabetes. Two other parameters will be estimated: apparent clearance (CL/F) and apparent volume of distribution (Vd/F).

The influence of covariates on exposure relative to a typical subject will be summarized in a forest plot showing the estimated mean (90% confidence interval) effect and comparing it with the bioequivalence criterion of 80-125% for PK relevance.

The population PK analysis will be described in greater detail in the modelling analysis plan (MAP) and reported separately from the CTR.

# 18 Ethics

The trial will be conducted in compliance with ICH GCP[33] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[38].

Subjects will only be included after a thorough evaluation of the inclusion, exclusion and randomisation criteria. The trial has been designed to provide a treatment which is assumed to adequately control the subject's blood glucose. This is expected to be achieved by treating all randomised subjects with metformin in addition to randomised treatment. In addition subjects treated with basal insulin may continue their basal insulin treatment. Furthermore subjects may have addition of rescue treatment if needed.

Rescue and withdrawal criteria are defined to ensure that subjects are considered for rescue treatment or withdrawal if the level of glycaemic control exceeds acceptable limits during both the blinded and un-blinded periods.

Subjects treated with basal insulin at screening should reduce their insulin dose by 20% at randomisation to limit the potential risk of hypoglycaemic episodes induced by the combined therapy of basal insulin and liraglutide. Once reaching the maximum dose of liraglutide/liraglutide placebo basal insulin treatment can be titrated up to no higher than pre-trial dose levels to ensure that treatment in the placebo arm is comparable to the pre-randomisation treatment.

Throughout the trial, subjects will be in regular contact (by telephone or visits) with the investigator or designated persons. Blood sampling and contacts with the clinic are considered an inconvenience for the children and adolescents participating in the trial. On the other hand, the intensified treatment may help to improve glycaemic control.

During the trial (incl. 2 year's follow-up period) up to 4 x-rays of left hand and wrist will be performed. When performing the x-rays the subject will be exposed to x-ray radiation. The amount of x-ray radiation when performing the x-rays is comparable to the amount of background radiation received from the surroundings in the United States during a period of approximately 3 days. This means that the risk of cancer will increase with 0.000125% for the x-rays performed.

Currently liraglutide does not have regulatory approval for treatment of paediatric subjects. However liraglutide has been approved by the authorities for use in adults in more than 60 countries including the US, China and the EU.

The trial product may be associated with AEs, but relevant precautions have been implemented in the design and planned conduct of the trial in order to minimise the risks and inconveniences of trial participation. These precautions include providing thorough information regarding the correct administration of the trial drugs and gradual dose adjustment. Furthermore, subjects and subjects'

LAR are fully informed about possible AEs and inconveniences and will be instructed to contact the investigator in case of any concerns regarding the trial participation.

It is assumed that the risks and benefits associated with liraglutide treatment will be the same for the paediatric population as for the adult populations (see section 3.1.3) with the exception of any unforeseen effects on growth and pubertal development.

When treatment with trial products ends, the subject and investigator will decide on the best available treatment for the subject. Novo Nordisk will not offer investigational drug(s) after the end of trial.

Subjects participating in the trial and their parents may be reimbursed for documented reasonable travelling expenses and loss of income, as according to local law. All agreements on compensation should be approved by the IRB/Ethical committee.

## 18.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[33] and the requirements in the Declaration of Helsinki[38].

Before any trial-related activity, the investigator must give the subject and subject's LAR oral and written information about the trial in a form that the subject and the subject's LAR can read and understand. This process may include the use of an impartial witness where required.

The investigator must ensure the subject and the subject's LAR ample time to come to a decision whether or not to participate in the trial. The subject must only be included in the trial if both the subject and the subject's LAR agree to have the subject participating.

A voluntary, signed and personally dated informed consent and assent form will be obtained from the subject's LAR and the subject respectively before any trial-related activity is performed.

The responsibility for seeking informed consent and assent must remain with the investigator, but the task may be delegated by the investigator to a medically qualified person, in accordance with local requirements. The written informed consent and assent must be signed and personally dated by the person who seeks the consent and assent.

The informed consent may be signed up to 30 days before Visit 1, unless a modification to the informed consent is approved during that period of time.

If information becomes available that may be relevant to the subject's or subject's LAR's willingness to continue participating in the trial, the investigator must inform the subject and the

subject's LAR in a timely manner, and a revised written informed consent and assent must be obtained.

Local laws and requirements may differ from the procedures described above and must be followed.

**Only applicable to Israel:** child assent form is not applicable.

### 18.2 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 will be retained by Novo Nordisk, entered into the database and used for the trial report
- Safety events will be reported to the Novo Nordisk and regulatory authorities according to local/national requirements

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

### 18.3 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, 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 should also promptly inform the IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities should be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation should 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 does have 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.

Investigator must document and explain protocol deviations 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 all protocol deviations must be kept in the investigator's trial file and Novo Nordisk 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 and after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in such audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the 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 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
- Curricula vitae of investigator and sub-investigator(s) and other relevant staff (current, dated and signed and/or supported by an official regulatory document. Must include documented GCP training or a certificate)
- Signed receipt of IB and summary of product characteristics
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any substantial protocol amendment, if applicable
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any substantial 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
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated investigator Agreement
- Financial disclosure form for all investigators

For US: verification under disclosures per Code of Federal regulation (CFR) of Financial Conflict of Interest.

For US sites: FDA form 1572 must be completed and signed for each investigator.

***FDA form 1572:***

For US sites:

- Intended for US sites
- Conducted under the investigational new drug application (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.

As documented in writing by protocol signature, each investigator agrees to comply fully with ICH standards of current GCP, applicable regulatory requirements and the declaration of Helsinki.

# 22 Responsibilities

All staff (Novo Nordisk, site, laboratory, CRO etc) will conduct the trial in compliance with ICH GCP[33], applicable regulatory requirements and the Declaration of Helsinki[38].

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator should 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's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The subject ID list should be kept securely and separate from the personal 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 should 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 of investigator (e.g. if he/she retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and site personal 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 Novo Nordisk for regulatory purposes and 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.

Novo Nordisk will be responsible for preparation of the CTR. The CTR will be reviewed and signed by one or more investigator(s) (signatory investigator) appointed by Novo Nordisk based on their experience in clinical research and input during the analysis phase.

## 23.1 Communication of results

No permission to publish shall be granted to any clinical research organisation involved in the trial.

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.

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

At the end of the trial, one or more public disclosures 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.

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

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 support 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.

In a multi-centre trial based on the collaboration of all trial sites, any publication of results in a journal article must acknowledge all trial sites. Where required by the journal, the principal investigator from each site will be named in the acknowledgement.

### 23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the ICMJE (sometimes referred to as the Vancouver Criteria[39]).

The investigator(s) offered authorship will be asked to comment and approve the publication. No permission to publish will be granted to any CRO involved in the trial described in this protocol. The authorship of publications of all trial results will be determined by the Publication group.

### 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 and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

## 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 participants' data, and will be provided with the randomisation code after results are available.

# 24 Retention of clinical trial documentation

Subject 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 site. If the Novo Nordisk provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy, as 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 investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by national regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local requirements.

# 25 Institutional review boards/independent ethics committees and regulatory authorities

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

During the trial, the investigator or sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial protocol amendments, non-substantial 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 risk/benefit 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.

Substantial protocol amendments must not be implemented before approval or favourable opinion, 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 should be filed in the investigator's trial file and copies must be sent to Novo Nordisk.

**Regulatory Authorities**

Regulatory authorities will receive the clinical trial application (CTA), substantial/non-substantial protocol amendments, reports on SAEs, and the CTR according to national requirements.

# 26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability is 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 by the clinics or doctors conducting experiments, or by persons for whom the said clinic or doctors are responsible.

Novo Nordisk accepts liability in accordance with:

**Austria:** Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl Nr. 63/2009

**Belgium:** Law concerning experiments on the human person of 07 May 2004.

**France:** The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

**Germany:** The German drug law dated August 24, 1976 last amended by Article 1 of the ordinance of July 19, 2011.

**Netherlands:** Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit van 23 juni 2003, houdende regels inzake de verplichte verzekering bij medischwetenschappelijk onderzoek met mensen (Decree of 23 June 2003, containing rules for compulsory insurance in medical research involving human subjects (Medical Research (Human Subjects) Compulsory Insurance Decree).

**Poland**: Pharmaceutical Law of 6 September 2001 (Journal of Laws 08.45.271, as amended) – definitions + Chapter 2a, Law of 5 December 1996 on the profession of doctor and dentist doctor (Journal of Laws 08.136.857, as amended) – Chapter 4, Law of 27 July 2001 on the Office for Registration of Medicinal Products, Medical Devices, and Biocides (Journal of Laws 01.126.1379) – lists competences of the President of the Office and the Office

**Russia**: Federal law “On Medical Products” #86-FZ dated 22 June 1998 (last amendments dated 30 December 2008. Federal Law of 12 April 2010 No. 61-FZ "On Medicinal Drugs' Cerculation"

**Spain**: Royal decree 223/2004, of 6th February, establishing the requisites concerning clinical trials.

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