Effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes

A 56 week randomised, double-blind, placebo-controlled, three armed parallel group, multi-centre, multinational trial with a 12 week observational follow-up period

Trial phase: 3a
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Date: 06 March 2012</th>
<th>Novo Nordisk</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>Liraglutide</td>
<td>Version: 6.0</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Trial ID: NN8022-1922</td>
<td>Status: Final</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Protocol - Revised edition</td>
<td>Page: 2 of 133</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>EudraCT No.: 2008-002199-88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.
# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Summary</td>
<td>12</td>
</tr>
<tr>
<td>2 Flow chart</td>
<td>15</td>
</tr>
<tr>
<td>3 Introduction</td>
<td>20</td>
</tr>
<tr>
<td>4 Objectives and endpoints</td>
<td>24</td>
</tr>
<tr>
<td>5 Trial design</td>
<td>27</td>
</tr>
<tr>
<td>6 Trial population</td>
<td>35</td>
</tr>
<tr>
<td>7 Trial schedule</td>
<td>41</td>
</tr>
<tr>
<td>8 Methods and assessments</td>
<td>42</td>
</tr>
<tr>
<td>9 Appendix</td>
<td></td>
</tr>
</tbody>
</table>

### 1 Summary

- Rationale for the trial: 22
- Basic information: 20
- Glucagon-like peptide-1 (GLP-1): 20
- Liraglutide: 20
- Rationale for trial design: 28
- Subject replacement: 39
- Calculation of estimated total energy expenditure: 33
- Rationale for treatment: 33
- Number of subjects to be studied: 35
- Inclusion criteria: 35
- Exclusion criteria: 35
- Randomisation criteria: 37
- Rescue criteria: 38
- Withdrawal criteria: 38
- Subject replacement: 39
- Rationale for trial population: 40
- Visit Procedures: 42
- Visit Schedule: 44
- Visit 1, Screening visit: 44
- Visit 2, Randomisation visit: 46
- Visit 3, Dose escalation visit: 48

---

**Note:**
- EudraCT No.: 2008-002199-88
- Trial ID: NN8022-1922
- Protocol - Revised edition
- Liraglutide
- Flow chart
- Calculation of estimated total energy expenditure
- Rationale for treatment
- Number of subjects to be studied
- Inclusion criteria
- Exclusion criteria
- Randomisation criteria
- Rescue criteria
- Withdrawal criteria
- Subject replacement
- Visit Procedures
- Visit Schedule
- Visit 1, Screening visit
- Visit 2, Randomisation visit
- Visit 3, Dose escalation visit

---

**Novo Nordisk**

**Date:** 06 March 2012

**Version:** 6.0

**Status:** Final

**Page:** 3 of 133
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2.1.1</td>
<td>Weight and height</td>
</tr>
<tr>
<td>8.2.1.2</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>8.2.2</td>
<td>HbA₁c</td>
</tr>
<tr>
<td>8.2.3</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>8.2.4</td>
<td>Self-monitored fasting plasma glucose</td>
</tr>
<tr>
<td>8.2.4.1</td>
<td>7-Point plasma glucose profiles</td>
</tr>
<tr>
<td>8.2.5</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>8.2.6</td>
<td>Vital signs</td>
</tr>
<tr>
<td>8.2.6.1</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>8.2.6.2</td>
<td>Pulse</td>
</tr>
<tr>
<td>8.2.7</td>
<td>Lipids</td>
</tr>
<tr>
<td>8.2.8</td>
<td>Cardiovascular biomarkers</td>
</tr>
<tr>
<td>8.2.9</td>
<td>Patient reported outcomes (PRO) questionnaires</td>
</tr>
<tr>
<td>8.2.9.1</td>
<td>IWOoL-Lite</td>
</tr>
<tr>
<td>8.2.9.2</td>
<td>Diabetes treatment satisfaction questionnaire</td>
</tr>
<tr>
<td>8.2.10</td>
<td>Urinary Albumin-to-Creatinine ratio</td>
</tr>
<tr>
<td>8.3.1</td>
<td>Physical examination</td>
</tr>
<tr>
<td>8.3.2</td>
<td>Hypoglycaemic episodes</td>
</tr>
<tr>
<td>8.3.3</td>
<td>ECG 12 lead</td>
</tr>
<tr>
<td>8.3.4</td>
<td>Adverse events (AEs)</td>
</tr>
<tr>
<td>8.3.5</td>
<td>Haematology and biochemistry</td>
</tr>
<tr>
<td>8.3.6</td>
<td>Pregnancy test</td>
</tr>
<tr>
<td>8.3.7</td>
<td>Liraglutide antibodies</td>
</tr>
<tr>
<td>8.3.8</td>
<td>Suspicion of Acute Hypersensitivity (allergic reaction) to Trial Product</td>
</tr>
<tr>
<td>8.3.9</td>
<td>Suspicion of Immune-complex Disease</td>
</tr>
<tr>
<td>Page</td>
<td>Section</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>184</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>185</td>
<td>Trial ID: NN022-1922</td>
</tr>
<tr>
<td>186</td>
<td>Protocol - Revised edition</td>
</tr>
<tr>
<td>187</td>
<td>EudraCT No.: 2008-002199-88</td>
</tr>
<tr>
<td></td>
<td>Date: 06 March 2012</td>
</tr>
<tr>
<td></td>
<td>Version: 6.0</td>
</tr>
<tr>
<td></td>
<td>Status: Final</td>
</tr>
<tr>
<td></td>
<td>Page: 5 of 133</td>
</tr>
<tr>
<td>197</td>
<td>8.3.10 Mental Health questionnaires</td>
</tr>
<tr>
<td>198</td>
<td>8.3.10.1 C-SSRS</td>
</tr>
<tr>
<td>199</td>
<td>8.3.10.2 PHQ-9</td>
</tr>
<tr>
<td>200</td>
<td>8.3.11 Thyroidectomy Pathology Slides</td>
</tr>
<tr>
<td>201</td>
<td>8.3.12 Thyroid Tissue Sample Collection in Case of Thyroidectomy</td>
</tr>
<tr>
<td>202</td>
<td>8.3.13 Genetic Testing in case of Confirmed C-cell Pathology</td>
</tr>
<tr>
<td>203</td>
<td>8.3.14 Eye examination</td>
</tr>
<tr>
<td>204</td>
<td>8.3.15 Binge Eating Scale questionnaire</td>
</tr>
<tr>
<td>205</td>
<td>8.4 Other assessments</td>
</tr>
<tr>
<td>206</td>
<td>8.4.1 Smoking habits</td>
</tr>
<tr>
<td>207</td>
<td>8.4.2 Diabetes diary</td>
</tr>
<tr>
<td>208</td>
<td>8.4.3 3-day food diary</td>
</tr>
<tr>
<td>209</td>
<td>8.4.4 Dietary compliance and physical activity</td>
</tr>
<tr>
<td>210</td>
<td>8.4.5 Liraglutide concentration (population PK)</td>
</tr>
<tr>
<td>211</td>
<td>8.4.6 History of diabetes complications</td>
</tr>
<tr>
<td>212</td>
<td>8.4.7 History of Concomitant Cardiovascular Disease</td>
</tr>
<tr>
<td>213</td>
<td>8.4.8 History of Gallbladder Disease</td>
</tr>
<tr>
<td>214</td>
<td>8.4.9 History of Psychiatric Disorders</td>
</tr>
<tr>
<td>215</td>
<td>8.5 Subject compliance</td>
</tr>
<tr>
<td>216</td>
<td>9 Trial supplies</td>
</tr>
<tr>
<td>217</td>
<td>9.1 Trial product(s)</td>
</tr>
<tr>
<td>218</td>
<td>9.2 Packaging and labelling of trial product(s)</td>
</tr>
<tr>
<td>219</td>
<td>9.3 Storage and drug accountability of trial product(s)</td>
</tr>
<tr>
<td>220</td>
<td>9.4 Auxiliary supply</td>
</tr>
<tr>
<td>221</td>
<td>10 Randomisation, breaking of blinded codes and interactive voice/wr response system (IV/WRS)</td>
</tr>
<tr>
<td>222</td>
<td>10.1 Randomisation</td>
</tr>
<tr>
<td>223</td>
<td>10.2 Breaking of blinded codes</td>
</tr>
<tr>
<td>224</td>
<td>10.3 Interactive voice/web response system (IV/WRS)</td>
</tr>
<tr>
<td>225</td>
<td>11 Concomitant illnesses/Medical history and concomitant medication</td>
</tr>
<tr>
<td>226</td>
<td>12 Adverse events and Pregnancies</td>
</tr>
<tr>
<td>227</td>
<td>12.1 Definitions</td>
</tr>
<tr>
<td>228</td>
<td>12.1.1 Technical complaints</td>
</tr>
<tr>
<td>229</td>
<td>12.2 Collection, recording and reporting of adverse events</td>
</tr>
<tr>
<td>230</td>
<td>12.2.1 Medical events of special interest</td>
</tr>
<tr>
<td>231</td>
<td>12.2.2 External independent event adjudication committee</td>
</tr>
<tr>
<td>232</td>
<td>12.3 Follow-up of adverse events</td>
</tr>
<tr>
<td>233</td>
<td>12.3.1 Collection and reporting of technical complaints</td>
</tr>
<tr>
<td>234</td>
<td>12.3.2 Collection, storage and shipment of technical complaint samples</td>
</tr>
<tr>
<td>235</td>
<td>12.4 Pregnancy</td>
</tr>
<tr>
<td>236</td>
<td>12.5 Precautions/over-dosage</td>
</tr>
<tr>
<td>237</td>
<td>12.6 Safety committee</td>
</tr>
<tr>
<td>238</td>
<td>12.6.1 Internal Novo Nordisk safety committee</td>
</tr>
<tr>
<td>239</td>
<td>12.6.2 Calcitonin Monitoring Committee</td>
</tr>
<tr>
<td>240</td>
<td>13 Case report forms</td>
</tr>
<tr>
<td>Page</td>
<td>Section</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>245</td>
<td>EudraCT No.: 2008-002199-88</td>
</tr>
<tr>
<td>256</td>
<td>13.1 Rules for completing eCRFs</td>
</tr>
<tr>
<td>257</td>
<td>13.2 Corrections to eCRFs</td>
</tr>
<tr>
<td>258</td>
<td>13.3 eCRF flow</td>
</tr>
<tr>
<td>259</td>
<td>14 Monitoring procedures</td>
</tr>
<tr>
<td>260</td>
<td>15 Data management</td>
</tr>
<tr>
<td>261</td>
<td>16 Computerised systems</td>
</tr>
<tr>
<td>262</td>
<td>17 Evaluability of subjects for analysis</td>
</tr>
<tr>
<td>263</td>
<td>18 Statistical considerations</td>
</tr>
<tr>
<td>264</td>
<td>18.1 Sample size calculation</td>
</tr>
<tr>
<td>265</td>
<td>18.2 Statistical methods</td>
</tr>
<tr>
<td>266</td>
<td>18.2.1 Primary efficacy endpoints</td>
</tr>
<tr>
<td>267</td>
<td>18.2.1.1 Primary analysis of the co-primary endpoints</td>
</tr>
<tr>
<td>268</td>
<td>18.2.1.2 Sensitivities of the co-primary endpoints</td>
</tr>
<tr>
<td>269</td>
<td>18.2.2 Analysis of secondary efficacy endpoints</td>
</tr>
<tr>
<td>270</td>
<td>18.2.3 Analysis of safety endpoints</td>
</tr>
<tr>
<td>271</td>
<td>18.3 Interim analysis</td>
</tr>
<tr>
<td>272</td>
<td>18.4 Sequential safety analysis/safety monitoring</td>
</tr>
<tr>
<td>273</td>
<td>18.5 Exploratory statistical analysis for pharmacogenetics and biomarkers</td>
</tr>
<tr>
<td>274</td>
<td>18.6 Health economics and/or subject reported outcome</td>
</tr>
<tr>
<td>275</td>
<td>18.7 PK and/or PD modelling</td>
</tr>
<tr>
<td>276</td>
<td>19 Ethics</td>
</tr>
<tr>
<td>277</td>
<td>19.1 Informed consent form for trial subjects</td>
</tr>
<tr>
<td>278</td>
<td>19.2 Data Handling</td>
</tr>
<tr>
<td>279</td>
<td>19.3 Institutional review boards/independent ethics committee</td>
</tr>
<tr>
<td>280</td>
<td>19.4 Regulatory authorities</td>
</tr>
<tr>
<td>281</td>
<td>20 Premature termination of the trial/trial site</td>
</tr>
<tr>
<td>282</td>
<td>21 Protocol compliance</td>
</tr>
<tr>
<td>283</td>
<td>21.1 Audits and inspections</td>
</tr>
<tr>
<td>284</td>
<td>22 Critical documents</td>
</tr>
<tr>
<td>285</td>
<td>23 Responsibilities</td>
</tr>
<tr>
<td>286</td>
<td>24 Reports and publications</td>
</tr>
<tr>
<td>287</td>
<td>24.1 Communication and publication</td>
</tr>
<tr>
<td>288</td>
<td>24.1.1 Authorship</td>
</tr>
<tr>
<td>289</td>
<td>24.1.2 Publication(s)</td>
</tr>
<tr>
<td>290</td>
<td>24.1.3 Site-specific publication(s) by Investigator(s)</td>
</tr>
<tr>
<td>291</td>
<td>24.2 Investigator access to data and review of results</td>
</tr>
<tr>
<td>292</td>
<td>25 Retention of clinical trial documentation</td>
</tr>
<tr>
<td>293</td>
<td>26 Indemnity statement</td>
</tr>
<tr>
<td>294</td>
<td>References</td>
</tr>
</tbody>
</table>
Appendix A  Approval of final protocol (Not applicable for consolidated protocol)
Appendix B  Agreement on the final protocol
Appendix C  New York Heart Association Criteria for Functional Capacity
Appendix D  Instruction for Blood Pressure Measurement
Appendix E  Extended Flow Chart
Appendix F  PRO questionnaires
Appendix G  Mental Health questionnaires
Appendix H  Medical Events of Special Interest (MESI)
Appendix I  Calcitonin Monitoring Committee
**Table of tables**

<table>
<thead>
<tr>
<th>Page</th>
<th>Table</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>5–1</td>
<td>Treatment of subjects</td>
</tr>
<tr>
<td>33</td>
<td>5–2</td>
<td>Equations for estimating basal metabolic rate (BMR) in kcal/day*</td>
</tr>
<tr>
<td>44</td>
<td>8–1</td>
<td>Visit schedule</td>
</tr>
</tbody>
</table>
List of abbreviations

ADA American Diabetes Association
AE adverse event
ALAT alanine aminotransferase
ANCOVA Analysis of Covariance
ASAT aspartate aminotransferase
ATP-III adult treatment panel III
BES binge eating scale
BMI body mass index
BMR basal metabolic rate
BP blood pressure
CABG coronary artery bypass graft surgery
C-cell parafollicular cell
DFU Direction for Use
CPK creatine phosphokinase (creatinine kinase)
CRD Novo Nordisk clinical research department
eCRF electronic case report form
C-SSRS Columbia suicidality severity rating scale
CTA clinical trial application
CTR clinical trial report
DPP-4 dipeptidyl peptidase-4
DTSQs diabetes treatment satisfaction questionnaire (status version)
DUN dispensing unit number
ECG electrocardiogram
EDC electronic data capture
EOT end of trial
EAP Events Adjudication Panel
FAS full analysis set
FDA Food and Drug Administration
FFA free fatty acids
FMTC familial medullary thyroid carcinoma
FPFV first patient first visit
FPG fasting plasma glucose (fasting glucose)
GCP good clinical practice
GI gastro intestinal
GLP-1 glucagon-like peptide-1
HbA1c glycosylated haemoglobin
hCG human chorionic gonadotropin
HDL high density lipoprotein
HOMA homeostasis model assessment
hsCRP high sensitivity C reactive protein
i.v. intravenous
IB investigator brochure
Liraglutide

Trial ID: NN8022-1922

Protocol - Revised edition

EudraCT No.: 2008-002199-88

Date: 06 March 2012

Novo Nordisk

Version: 6.0

Status: Final

Page: 11 of 133

TSH thyroid-stimulating hormone

TVP trial validation plan

UNR upper normal range

VLDL very low density lipoprotein
1 Summary

Primary objective:
To investigate the efficacy of liraglutide compared to liraglutide placebo in inducing and maintaining weight loss in overweight or obese subjects with type 2 diabetes after 56 weeks.

Secondary objectives:
To assess and compare the effect of liraglutide versus liraglutide placebo on parameters of glycaemic control, waist circumference, cardiovascular risk factors and patient reported outcomes (PRO) in overweight or obese subjects with type 2 diabetes.

Safety objective:
To evaluate the safety and tolerability of liraglutide.

Trial design:
This is a 56 week, randomised, double-blind, placebo-controlled, three armed, parallel group, multi-centre, multinational trial with a 12-week observational follow-up period.

This paragraph applies to all countries except France: Subjects will be randomised in a 2:1:1 manner to receive 3.0 mg of liraglutide, 1.8 mg of liraglutide or liraglutide placebo (1.8 mg or 3.0 mg) as an add-on to their background diabetes treatment of either diet and exercise only or single compound oral antidiabetic drug (OAD) treatment (metformin, sulphonylurea [SU] or glitazone) or any combination OAD treatment (metformin+SU, metformin+glitazone, SU+glitazone, metformin+SU+glitazone).

This paragraph is only applicable to France: Subjects will be randomised in a 2:1:1 manner to receive 3.0 mg of liraglutide, 1.8 mg of liraglutide or liraglutide placebo (1.8 mg or 3.0 mg) as an add-on to their background diabetes treatment of single compound oral antidiabetic drug (OAD) treatment (metformin as single agent therapy, SU as single agent therapy (if presence of metformin contraindication or intolerance), glitazone as single agent therapy (if presence of metformin contraindication or intolerance)) or combination of two of the above mentioned OAD treatments (metformin+SU, metformin+glitazone, SU+glitazone).

The background treatment must be stable (same drug(s), dose and dosing frequency) for at least 3 months prior to screening.

The maximum overall duration of the trial will be 70 weeks including the screening period and the 12-week observational follow-up period. The trial consists of a screening visit, a randomisation visit, 15 treatment visits and 4 follow-up visits. Furthermore, subjects that have discontinued the trial prematurely (before Visit 16) will be asked to attend a weight recording visit (16x) which will take place 56 weeks after the randomisation visit.

PRO recordings will be performed in France, Germany, Spain, Sweden, United Kingdom and USA.
Trial population:

It is planned to randomise 800 subjects from 9 different countries.

Key inclusion criteria:

- Informed consent obtained
- Subjects diagnosed with type 2 diabetes and treated with either diet and exercise alone, metformin, SU, glitazone as single agent therapy or any combination of the previously mentioned compounds (metformin+SU, metformin+glitazone, SU+glitazone, metformin+SU+glitazone)
- Only applicable to France: Subjects diagnosed with type 2 diabetes and treated with either metformin as single agent therapy, SU as single agent therapy (if presence of metformin contraindication or intolerance), glitazone as single agent therapy (if presence of metformin contraindication or intolerance) or combination of two of the above mentioned compounds: metformin+SU, metformin+glitazone, SU+glitazone
- HbA1c 7.0-10.0% (both inclusive)
- Body Mass Index (BMI) ≥ 27.0 kg/m²
- Stable body weight
- Preceding failed dietary effort

Key exclusion criteria:

- Treatment with glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors or insulin within the last 3 months
- Known proliferative retinopathy or maculopathy
- History of acute or chronic pancreatitis
- Obesity induced by drug treatment
- Use of approved weight lowering pharmacotherapy
- Previous surgical treatment of obesity
- History of major depressive disorder or suicide attempt
- Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg)
- Screening calcitonin ≥ 50 ng/L
- Familial or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)
- Personal history of non-familial medullary thyroid carcinoma
- Only applicable to France: Abnormality of the thyroid identified during the physical exam at screening

Assessments:

The primary efficacy assessment is change in fasting body weight at 56 weeks. The secondary efficacy assessments are HbA1c and other parameters of glycaemic control (proportion of subjects reaching target HbA1c, fasting plasma glucose [FPG], 7-point plasma glucose profile, proportion of subjects with change in concomitant medication (anti-hypertensives, lipid lowering agents, oral antidabetic drugs) at 56 weeks), glucose metabolism related parameters incl. β-cell function, lipid profile, waist circumference, cardiovascular biomarkers, vital signs, and PRO.
The key assessments of safety are physical examination, hypoglycaemic episodes, ECG, adverse events (AE)s, haematology, biochemistry, formation of liraglutide antibodies and mental health assessments.

**Trial product(s):**

Novo Nordisk, Denmark will supply the following trial products:

- Liraglutide 6.0 mg/mL, 3 mL FlexPen® for subcutaneous (s.c.) injection
- Liraglutide placebo, 3 mL FlexPen® for subcutaneous (s.c.) injection
## 2 Flow chart

<table>
<thead>
<tr>
<th>Screen</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance</th>
<th>End of treatment</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5a</td>
</tr>
<tr>
<td>Weeks in relation to Visit 2</td>
<td>-2</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Visit Window, days</td>
<td>±5</td>
<td>±3</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
</tbody>
</table>

**SUBJECTS**

- Informed consent
- In/exclusion criteria
- Randomisation criteria
- Rescue criteria
- Withdrawal criteria
- Demography
- Date of diagnosis of diabetes
- History of diabetes complications
- Diabetes treatment history
- Medical history and Concomitant illness
- History of Concomitant Cardiovascular Disease
- History of Gallbladder Disease
- History of Psychiatric Disorders
- Concomitant medication
- Smoking habits
- Attend visit fasting

**EFFICACY**

- Body measurements
- HbA1c
- Fasting plasma glucose
- 7-point plasma profile (self-measured)
- Glucose metabolism
<table>
<thead>
<tr>
<th>Screen</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance</th>
<th>End of treatment</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5a</td>
</tr>
<tr>
<td>Weeks in relation to Visit 2</td>
<td>-2</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Visit Window, days</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
<tr>
<td>Urinary Albumin-to-Creatinine ratio</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lipids</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular biomarkers</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO questionnaires</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAFETY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemic episodes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Haematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>X</td>
<td>(X)</td>
<td>(X)</td>
<td></td>
<td>(X)</td>
</tr>
<tr>
<td>Liraglutide antibodies</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health questionnaires</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>OTHER ASSESSMENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK (liraglutide plasma concentration)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIAL MATERIAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense trial card</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes diary</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3-day food diary</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Diet and physical activity counselling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Recording of dietary compliance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Visit Number</td>
<td>Screen</td>
<td>Randomisation</td>
<td>Dose escalation period</td>
<td>Maintenance</td>
<td>End of treatment</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 2 3 4 5a 5b 6 7 8 9 10 11 12 13 14 15 16 16x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks in relation to Visit 2</td>
<td>-2</td>
<td>0 2 4 6 8 12 16 20 24 28 32 36 40 44 50</td>
<td>56</td>
<td>58 60 64 68</td>
<td></td>
</tr>
<tr>
<td>Visit Window, days</td>
<td>± 5</td>
<td>± 3 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5 ± 5</td>
<td>± 3 ± 5 ± 5 ± 5 ± 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Only subjects discontinuing the trial prematurely before Visit 16 will be asked to attend Visit 16x 56 weeks after their randomisation date for the assessment of body weight and Mesi.

2 Height will only be measured at Visit 1. Waist circumference will not be measured at Visit 16x.

3 On a normal representative day of the week (not on a day when they anticipate unusual strenuous exercise), preferably within one week prior to the visit.

4 Applicable for subjects in France, Germany, Spain, Sweden, United Kingdom and USA.

5 The investigator or his delegate must review patient reported outcome(s) for completeness and AEs immediately following administration. For subjects discontinuing the trial prematurely before Visit 16 the questionnaire should be completed at the end of treatment visit (Visit 16).

6 For all women of childbearing potential: a serum pregnancy test will be performed at Visit 1, 16 and 20. Furthermore, pregnancy urine tests will be performed at any other clinic visits during the trial if a menstrual period is missed or as required by local law.

7 For subjects discontinuing the trial prematurely before Visit 16, liraglutide antibodies will be measured at the end of treatment visit (Visit 16) while subjects that complete the treatment will have liraglutide antibodies measured at the first follow-up (Visit 17).

8 Mental health will be assessed by the use of PHQ-9 and C-SSRS at all site visits. The Investigator must assess the scores at Visit 1 (screening visit) and Visit 2 (randomisation visit) to exclude subjects with major depression (PHQ-9 ≥ 15) and/or any suicidal ideation (of type 4 or type 5) (see section 8.3.10).

9 For subjects discontinuing the trial prematurely before Visit 16 the mental health questionnaires will be completed at the end of treatment visit (Visit 16) while subjects that complete the treatment will have mental health questionnaires completed at the first follow-up (Visit 17).

10 Dispense diabetes diary at Visit 1 to 19 and transcribe into eCRF at Visit 2 to 20.

11 Dispense 3-day food diary at Visit 1, 4, 6, 8, 10, 12, 15 and 18. Collect 3-day food diary at Visit 2, 5b, 7, 9, 11, 13, 16 and 19.

12 Diet counselling based on a 3-day food diary.

13 At Visit 2 only physical activity will be recorded.
Glucose meter will be dispensed at Visit 1 and pedometer will be dispensed at Visit 2.

Subjects discontinuing the trial prematurely before Visit 16 will be asked to attend a last visit at which procedures according to Visit 16 will be performed and the EOT form completed. For subjects discontinuing the trial prematurely after Visit 16 the following will apply; at Visit 17: procedures according to Visit 17 will be performed and the EOT form completed - after Visit 17; procedures according to Visit 20 will be performed and the EOT form completed.
2.1 Trial design diagram:
3 Introduction

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

3.1 Basic information

The prevalence of both obesity and diabetes continues to increase worldwide. More than one billion adults worldwide are overweight and at least 300 million are obese. The prevalence of diabetes is also rising, with worldwide prevalence estimated at 4.0% in 2007, and still rising. Eighty to ninety percent of people with type 2 diabetes are overweight and obesity worsens the metabolic and physiologic abnormalities associated with diabetes, particularly hyperglycaemia, hyperlipidemia, and hypertension. Weight loss is a cornerstone of diabetes care for overweight people, as it improves insulin sensitivity and glycaemic control and in addition improves blood pressure and lipid profiles by decreasing triglycerides and low-density lipoprotein levels.

3.1.1 Glucagon-like peptide-1 (GLP-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 blood glucagon levels and reduces gastric emptying by decreasing gastric motility and increasing satiety and subsequently reducing food intake, and has been shown to promote β-cell growth and proliferation in animal models. GLP-1 reduces appetite in lean and normal weight individuals, as well as in obese individuals, and has been shown to reduce body weight in people with type 2 diabetes. The underlying mechanism mediating the weight-reducing effects of GLP-1 is most likely a combination of effects on the gastrointestinal tract and the central nervous system, i.e. decreased gastric motility and reduced appetite/increased satiety with a subsequent reduction in food intake.

The combination of these mechanisms makes GLP-1 receptor stimulation an attractive mechanism to investigate for weight management and blood glucose lowering.

3.1.2 Liraglutide

Liraglutide is a long-acting GLP-1 analogue under development by Novo Nordisk and recently approved for the treatment of type 2 diabetes in the US, EU, Japan and other countries worldwide under the brand name Victoza. 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 subcutaneously, these structural modifications result in a compound with protracted kinetic properties suitable for one time daily injection. In vitro receptor studies have shown that liraglutide is a selective, potent and full agonist of the cloned human GLP-1 receptor. The effects of liraglutide include delayed gastric emptying, reduced sensation of hunger and increased satiety leading to decreased food intake and subsequent weight loss.

A total of 50 clinical trials with liraglutide have been completed (includes doses up to 3.0 mg). The trials were conducted world-wide, with most being conducted in Europe. Out of more than 10000 subjects, more
than 7500 subjects were exposed to liraglutide (including 850 subjects treated for 104 weeks in completed trials). A total of 986 obese subjects without type 2 diabetes (<9% of all subjects) have been included to date in the obesity clinical development programme for liraglutide in the completed phase 2 trial NN8022-1807 and the completed phase 3a trial NN8022-1923 (of which 305 subjects were randomised to liraglutide 3.0 mg). A further 48 obese subjects were randomised in the ongoing phase 1 trial NN8022-3630.

Data from finalised trials have shown liraglutide to have a pharmacokinetic profile suitable for one time daily administration, as evidenced by a relatively slow absorption ([\(t_{\text{max}}\) =8-12 hours]) with a terminal elimination half-life ([\(t_{\frac{1}{2}}\)] of approximately 13 hours. The pharmacokinetic profile is comparable between healthy subjects and subjects with type 2 diabetes.

Results from a phase 2 trial in obese subjects without type 2 diabetes (NN8022-1807) showed a dose-dependent weight loss ranging from 3.8 to 7.8 kg with liraglutide doses of 1.2-3.0 mg administered for 52 weeks (20 weeks as double-blind and 32 weeks of open-label treatment (sponsor unblinded at 20 weeks). In addition to weight lowering, there was a decrease in systolic blood pressure and an impact on the number of subjects with pre-diabetes. In addition, of the approximately 30% of subjects who had pre-diabetes at baseline, 85% did not have pre-diabetes after 20 weeks compared to 45% of placebo subjects. Of the 70% of subjects without pre-diabetes at baseline, 20% of placebo subjects developed pre-diabetes, whereas only 2-4% of liraglutide-treated subjects had pre-diabetes after 20 weeks. The safety evaluation was favourable with the main tolerability finding being gastrointestinal side effects (please refer to liraglutide obesity Investigators Brochure (IB), 3rd Edition, 2010).

The first of three confirmatory phase 3 trials within the liraglutide obesity development programme (Trial NN8022-1923, or SCALE™-Maintenance) was recently completed. Reporting is ongoing. The trial was a 56-week randomised, double-blind, placebo-controlled trial investigating treatment of liraglutide 3.0 mg versus placebo as an adjunct to diet and exercise in obese subjects or overweight subjects with co-morbidities who had already lost at least 5% of their body weight during a 4 to 12-week run-in period on a low calorie diet. The mean weight loss for subjects in the run-in period was approximately 6 kg. From a body weight of approximately 100 kg at randomisation, treatment with liraglutide for 56 weeks provided an additional estimated mean weight loss of 6.11% (~5.7 kg), compared to weight-neutrality or maintenance in the placebo group (+0.16 kg vs. baseline). Eighty one (81) percent of liraglutide-treated subjects maintained their run-in weight loss compared to 48% in the placebo group. Moreover, 51% of liraglutide-treated subjects lost additional 5% or more of their baseline body weight, compared to 22% in the placebo group. Treatment with liraglutide maintained and in some instances further improved beneficial effects on markers of glycaemic control and cardiovascular risk.

Treatment with liraglutide was generally well-tolerated, with high completion rates in groups (75% in liraglutide group, 70% in placebo group). The number of withdrawals due to adverse events was evenly distributed between groups (8.5% in the liraglutide group vs. 8.6% in placebo group). Serious adverse events were relatively uncommon, but were more frequent in liraglutide-treated subjects (4.2%) compared to placebo (2.4%). There were no events of pancreatitis or medullary thyroid cancer, and no treatment-related increases in blood calcitonin levels. Consistent with previous trials with liraglutide, the most commonly reported adverse events were from the gastrointestinal system, with nausea reported by 47% of subjects in the liraglutide group compared to 17% in the placebo groups, and vomiting by 17% vs. 2%, respectively. As
in previous trials, the majority of events were reported in the first 6-8 weeks, were mild or moderate in severity and transient in nature. Please refer to liraglutide obesity Investigators Brochure, 3rd Edition, 2010, or any updates hereof.

Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in patients treated with liraglutide. Patients 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 surveillance identified at least 30 cases of pancreatitis with exenatide (14). However, a health services registry-based study found no increased frequency of pancreatitis among exenatide users (15).

If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory tests have been conducted, and appropriate treatment should be initiated. Subjects diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3x UNR or characteristic findings on CT/MRI) should be withdrawn from the study.

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. Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). 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.

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).

Further information can be obtained in the Liraglutide Investigator's Brochure Obesity, 3rd Edition, 2010 or any updates hereof.

### 3.2 Rationale for the trial

The currently available treatment modalities for inducing weight loss in overweight or obese subjects with type 2 diabetes (i.e. life style interventions and pharmacologic therapy) are still not satisfactory, as they seldom offer adequate glycaemic control, or are associated with safety issues, undesired side effects or offer no improvement in cardiovascular risk factors. Hence, there is a need and a strong incentive for development
of improved weight management agents for subjects with type 2 diabetes that address the unmet medical needs.

Subjects with type 2 diabetes often have multiple unmet medical needs related to cardiovascular risk, including hypertension and dyslipidemia. It has been consistently demonstrated that weight loss in subjects with type 2 diabetes has a beneficial impact not only on glycaemic control, but also on other cardiovascular risk markers. The present trial has been designed to show the effects of liraglutide in inducing weight loss in overweight or obese subjects with type 2 diabetes, while improving glycaemic control and potentially improving other markers of cardiovascular risk.

Treatment duration of 56 weeks is considered appropriate to demonstrate weight loss and subsequent weight maintenance. In order to assess the effects of drug cessation on appetite and weight control, possible withdrawal effects and rebound will be ascertained in the 12-week observational follow-up period.
4 Objectives and endpoints

4.1 Objectives

Hypothesis:
Liraglutide will induce and maintain weight loss significantly better than liraglutide placebo in overweight or obese subjects with type 2 diabetes.

Primary objective:
To investigate the efficacy of liraglutide compared to liraglutide placebo in inducing and maintaining weight loss in overweight or obese subjects with type 2 diabetes after 56 weeks.

Secondary objectives:
To compare liraglutide and liraglutide placebo regarding the effect on:
- Parameters of glycaemic control
- Waist circumference
- Cardiovascular risk factors
- Attaining treatment targets of risk factors for subjects with type 2 diabetes
- Patient reported outcomes (PRO)
- Weight maintenance in the 12-week observational follow-up period

Safety objectives:
- To evaluate the safety and tolerability of liraglutide

4.2 Endpoint(s)

Primary efficacy endpoints:
- Change from baseline in body weight (fasting body weight) at 56 weeks
- Proportion of subjects losing at least 5% of baseline body weight at 56 weeks
- Proportion of subjects losing more than 10% of baseline body weight at 56 weeks

Secondary efficacy endpoints:
- Parameters of glycaemic control
  - Change from baseline (Week 0) to Week 56 in:
    - HbA1c
    - FPG
    - 7-point plasma glucose profile (self-measured)
    - Glucose metabolism related parameters incl. β-cell function (fasting glucagon, fasting insulin, fasting C-peptide, pro-insulin: insulin ratio and homeostasis model assessment [HOMA] parameters (16))
- Parameters of glycaemic control
Observational follow-up efficacy endpoints:

- Weight change from baseline (Week 0) to Week 68 (fasting body weight)
- Weight change from Week 56 to Week 68
- Change in waist circumference from baseline (Week 0) to Week 68
- Change in waist circumference from Week 56 to Week 68
- Change in fasting plasma glucose from baseline (Week 0) to Week 68
- Change in vital signs from baseline (Week 0) to Week 68
- Change in vital signs from Week 56 to Week 68
- Change in Urinary Albumin-to-Creatinine ratio from Week 0 to Week 68
- Change in Urinary Albumin-to-Creatinine ratio from Week 56 to Week 68

Safety endpoints:

- Physical examination (cardiovascular system, respiratory system, abdomen, central and peripheral nervous system, musculo-skeletal system and the thyroid gland)
- Hypoglycaemic episodes
- Electrocardiogram (ECG)
- Adverse events
- Haematology and biochemistry including amylase, lipase and calcitonin
- Pulse (Vital signs)
- Formation of liraglutide antibodies
• Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Health Questionnaire (PHQ-9)

Observational follow-up safety endpoints:
- Hypoglycaemic episodes
- Adverse events
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential count)
- Biochemistry (creatinine, CPK, urea, albumin, bilirubins (total), ALAT, ASAT, alkaline phosphatase, sodium, potassium, calcium [total], amylase, lipase, calcitonin)
- In a subset of subjects: Change from baseline (Week 0) in Binge Eating (assessed by Binge Eating Scale [BES]) to Week 56 and 58
- Mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient Health Questionnaire (PHQ-9)

Other endpoints:
- Plasma concentrations of liraglutide (PK sampling)
5 Trial design

5.1 Type of trial

This is a 56-week, randomised, double-blind, placebo-controlled, three armed, parallel group, multi-centre, multi-national trial comparing once daily administration of 3.0 mg and 1.8 mg of liraglutide with liraglutide placebo in overweight or obese subjects with type 2 diabetes.

A planned total of 800 subjects will be randomised. Based on an assumption of a 50% screening failure rate, 1600 subjects will be screened. Subjects will be randomised in a 2:1:1 manner to receive 3.0 mg of liraglutide, 1.8 mg of liraglutide or liraglutide placebo as an add-on to their background diabetes treatment. The placebo arm will be further subdivided into two arms with different injection volumes corresponding to the different dose levels of liraglutide (see table Table 5–1).

This paragraph applies to all countries except France: The background treatment (diet and exercise only or single compound OAD treatment [metformin, SU or glitazone] or any combination OAD treatment [metformin+SU, metformin+glitazone, SU+glitazone, metformin+SU+glitazone]) must be stable (same drug or drugs [same INN(s) (International Non-proprietary Name)], dose and dosing frequency) for at least 3 months prior to screening.

This paragraph is only applicable to France: The background treatment (single compound OAD treatment [metformin; SU (if presence of metformin contraindication or intolerance) or glitazone (if presence of metformin contraindication or intolerance)]) or combination of two of the above mentioned OAD treatments [metformin+SU, metformin+glitazone, SU+glitazone] must be stable (same drug or drugs [same INN(s) (International Non-proprietary Name)], dose and dosing frequency) for at least 3 months prior to screening.

To mitigate sulphonylurea induced hypoglycaemia, subjects treated with SU (either alone or in combination with other oral antidiabetic drugs [OADs]) will at screening (Visit 1) be asked to reduce the SU dose by 50%. If already on minimum labelled dose at screening, a subject should remain on that dose unless unacceptable hypoglycaemia occurs, in which case the subject must be withdrawn.

In case of consistent hyperglycaemia as described in section 6.5 glycaemic rescue i.e. intensification of background OAD treatment or addition of new background OADs should be implemented, but how specifically is at the discretion of the Investigator.

At the time of randomisation (Visit 2) the subjects will be stratified using an Interactive Voice/Web response system (IV/WRS) according to the following background diabetes treatment categories:

1) diet and exercise only or single compound metformin treatment or
2) single compound OAD treatment (sulphonylurea or glitazone) or combination OAD treatment (metformin+SU, metformin+glitazone, SU+glitazone, metformin+SU+glitazone). Subjects treated with SU or any combination of SU must not comprise more than 30% of total subjects

Subjects in the two stratification groups will be further stratified into 2 groups by screening value of HbA1c (A. <8.5% or B. ≥8.5%).
Proportion of subjects treated with SU mono- or combination therapy will be restricted to a maximum of 30% of total randomised subjects. When target is reached, subjects treated with SU as background treatment may not be randomised in the trial.

The duration of the trial from screening to follow up will be 70 weeks per subject with a liraglutide/liraglutide placebo treatment duration of 56 weeks. The trial will consist of a screening visit (Visit 1), a 4-week dose escalation period, a 52-week maintenance period and a 12-week observational follow-up period after last treatment.

Subjects that have discontinued the trial prematurely (before Visit 16) will be asked to attend the premature discontinuation Visit 16 and a visit 56 weeks after the randomisation date (Visit 16x). The purpose of this visit will be recording of the body weight and assessment of MESI. The assessment will be done by asking the subject if he/she has experienced any MESI (see section 12.2.1 and appendix H) since the last contact.

If the subject is not willing to attend Visit 16x, it should be documented in the patient medical record that the subject has refused to attend the visit.

PRO recordings will be performed in France, Germany, Spain, Sweden, United Kingdom and USA.

5.2 Rationale for trial design

Obesity is a serious medical condition that is increasing in incidence worldwide. Obesity induces metabolic abnormalities that contribute to the development of diabetes mellitus and cardiovascular disease, and it is associated with increased morbidity and mortality risk. The treatment modalities currently available for the treatment of obesity (i.e. lifestyle interventions, pharmacotherapy and surgery) have limited long-lasting success in producing major and sustained weight loss and are often associated with undesirable side effects. A need therefore exists for new and effective therapeutic strategies to prevent and reduce obesity.

Within the last decade, the ability of GLP-1 to decrease appetite and energy intake has been demonstrated in both lean and obese as well as diabetic and non-diabetic subjects. Furthermore, studies have shown that obese subjects have attenuated GLP-1 release in response to meals.

Results from a phase 2 trial in obese subjects without type 2 diabetes (NN8022-1807) showed a dose dependent weight loss ranging from 3.8 to 7.8 kg with liraglutide doses of 1.2-3.0 mg administered for 52 weeks (20 weeks as double-blind and 32 weeks of open-label treatment (sponsor unblinded at 20 weeks). In addition to weight lowering, there was a decrease in systolic blood pressure and an impact on the number of subjects with pre-diabetes. In addition, of the approximately 30% of subjects who had pre-diabetes at baseline, 85% did not have pre-diabetes after 20 weeks compared to 45% of placebo subjects. Of the 70% of subjects without pre-diabetes at baseline, 20% of placebo subjects developed pre-diabetes, whereas only 2-4% of liraglutide-treated subjects had pre-diabetes after 20 weeks. The safety evaluation was favourable with the main tolerability finding being gastrointestinal side effects (please refer to liraglutide obesity Investigators Brochure (IB), 3rd Edition, 2010)
The present trial is randomised and conducted as a double-blind trial to avoid bias in subject selection and the clinical evaluations/assessments. The trial design has been chosen to further investigate the potential of liraglutide to safely induce long term weight loss in overweight or obese type 2 diabetes. Treatment duration of 56 weeks is considered appropriate to demonstrate weight loss and subsequent weight maintenance. In order to assess the effects of drug cessation on appetite and weight control, possible withdrawal effects and rebound will be ascertained in the 12-week observational follow-up period.

A multi-centre design has been chosen to obtain the required number of subjects within the scheduled recruitment period.

A placebo-controlled trial design has been chosen to show that liraglutide (as an add-on to background diabetes treatment) is more effective in type 2 diabetes than lifestyle changes alone.

In order to comply with a regulatory request for bridging the safety and efficacy findings of the upper liraglutide dose of 3.0 mg in this study to the previously studied safety and efficacy of liraglutide 1.8 mg for the treatment of type 2 diabetes, a bridging arm consisting of 200 subjects randomised to liraglutide 1.8 mg per day has been included. The 1.8 mg dose of liraglutide has been demonstrated to be safe and efficacious for achieving glycaemic control in subjects with type 2 diabetes, but has not generated adequate weight loss to be selected as the optimal dose (3.0 mg) for weight management.

Subjects will be randomly assigned to one of the three treatment arms, and stratification with regards to the background treatment will rule out any bias linked to these treatment modalities.

To ensure sufficient exposure to liraglutide is obtained in subjects treated with non-SU based antidiabetic regimens, the proportion of randomised subjects treated with SU mono- or –combination therapy will be restricted to a maximum of 30%.

Subjects must have a stable body weight and be in a stable treatment with their background diabetes medication over a period of at least 3 months prior to screening. This will be done to rule out that change in safety and efficacy data will be due to changes in weight or background diabetes treatment.

Only subjects sub-optimally controlled on their background therapy are included, as defined by the requirement for an HbA1c value between 7.0 and 10.0% (both inclusive) at screening (Visit 1).

At screening, subjects treated with an SU, either as monotherapy or in combination with other oral antidiabetic drugs, will be required to reduce their SU dose by 50% or as close to 50% as possible based on dose options locally available. This is done to prevent hypoglycaemia induced by the combination of an SU and liraglutide, and possibly accentuated by weight loss. As a consequence, some subjects may experience early deterioration of glycaemic control, and to limit the number of subjects who would otherwise meet the FPG rescue criteria early in the study (and be excluded from analysis), a FPG randomisation criteria of 220 mg/dL (12.2 mmol/L) has been included.
5.3 Treatment of subjects

Subjects will attend Visit 1 (screening visit) to assess their eligibility. If found eligible the subjects will return at Visit 2 (randomisation visit, Week 0) where they will be randomised in a 2:1:1 (3.0 mg of liraglutide, 1.8 mg of liraglutide or liraglutide placebo respectively) manner to one of the three treatment arms using a telephone/web randomisation system (IV/WRS). The placebo arm will be further subdivided into two arms with different injection volumes (clicks on the FlexPen®) corresponding to the different dose levels of liraglutide. See Table 5–1.

Table 5–1 Treatment of subjects

<table>
<thead>
<tr>
<th>Trial periods</th>
<th>Scree-</th>
<th>Rando-</th>
<th>Dose escalation period/ Maintenance</th>
<th>Main-</th>
<th>Follow-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ning</td>
<td>misatio</td>
<td>n</td>
<td>tenance/</td>
<td>up</td>
</tr>
<tr>
<td><strong>Weeks in relation to Visit 2</strong></td>
<td>-2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>(randomisation)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit number</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Liraglutide 3.0 mg</td>
<td>N = 400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scree-ning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo 300 µL</td>
<td>N = 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg</td>
<td>N = 200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo 500 µL</td>
<td>N = 150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Following the end of the treatment, all trial drug treatment will be discontinued and the trial drug collected. Subjects will be advised with regards to the best possible post-trial treatment option for their weight management and type 2 diabetes at the discretion of the Investigator (with the exception of treatments listed in withdrawl criterion no.4 (see section 6.6) in the follow-up period).

5.3.1 Liraglutide/liraglutide placebo

Treatment with liraglutide or liraglutide placebo will be blinded to the subjects, the Investigator and the Novo Nordisk throughout the trial.

Liraglutide will be available at a concentration of 6.0 mg/mL. Liraglutide and liraglutide placebo will be supplied in a 3 mL FlexPen®.

Dosing with the liraglutide/liraglutide placebo FlexPen® is controlled by turning the dose selector until the dose indicator shows the relevant dose (10, 20, 30, 40 or 50 clicks equivalent to 0.6, 1.2, 1.8, 2.4 or 3.0 mg, respectively or placebo). 1 click equals 0.06 mg. Therefore, the dose level (injection volume) of liraglutide or placebo is open labelled.
Liraglutide or liraglutide placebo is administered once daily by subcutaneous injections with the FlexPen®, either in the abdomen, thigh or upper arm. Injections can be done at any time of day irrespective of meals. However, it is preferable that liraglutide be injected during the same overall time period on a day to day basis.

Subjects will be instructed to perform an air shot before the first injection with the FlexPen®. For further information, please see the direction for use (DFU) for the liraglutide FlexPen®. These DFUs will be provided in local language together with the trial product. The Investigator must instruct subjects in how to inject liraglutide or liraglutide placebo, and must ensure that the subjects are familiar with the DFU. It must be documented in the subject’s medical record that the subject has been instructed in the use of the FlexPen®.

Subjects will follow a fixed dose escalation and in order to reduce the level of side effects, liraglutide is gradually escalated up to the maintenance dose. Subjects will be instructed to escalate the liraglutide (active or placebo) dose to 3.0 mg/day over a 4 week period or to 1.8 mg/day over a 2 week period, following an initial dose of 0.6 mg/day and weekly dose escalation steps of 0.6 mg/day.

If subjects do not tolerate an increase in dose during dose-escalation, the Investigator has the option to individualise the dose escalation with a total delay of up to 7 days. All subjects must be at the target dose of 50 clicks/day (3.0 mg liraglutide or liraglutide placebo) at the latest 35 days after randomisation or 30 clicks per day (1.8 mg liraglutide or liraglutide placebo) at the latest 21 days after randomisation.

After reaching the target dose of 50 clicks per day (3.0 mg liraglutide or liraglutide placebo) or 30 clicks per day (1.8 mg liraglutide or liraglutide placebo), dose and dosing frequency should not be changed at any time during the treatment period. If any dose is missed by the subject up to and including 3 consecutive days it must be documented in the medical record and the Investigator should discuss the importance of treatment compliance with the subject. After a potential discontinuation up to 3 days the subject must be re-initiated on trial drug on target dose of 50 clicks per day (3.0 mg liraglutide or liraglutide placebo) or 30 clicks per day (1.8 mg liraglutide or liraglutide placebo). Missed doses for more than 3 consecutive days should be discussed with Sponsor and it will be up to Investigator’s judgement if the subject can continue on target dose or should be withdrawn.

It is always important that the Investigator emphasises to subjects the necessity of compliance with regard to taking trial drug as described in the protocol. It is the responsibility of the Investigator to access the subject’s overall compliance throughout the trial and subjects deemed to be non-compliant subjects should be withdrawn at the Investigator’s discretion. If subjects do not tolerate the target dose, they must be withdrawn from the trial except if withdrawal criteria no. 7 and/or no. 8 are suspected.

If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory tests have been conducted. If tests reveal that a subject does not have acute pancreatitis, the subject can remain in the trial with re-initiation of titration until the target dose is reached.

The exact date, time, dose and site of injection of the 3 doses of trial product immediately prior to Visit 3, 6, and Visit 10, must be noted in the eCRF for evaluation of PK.
5.3.2 Metformin, sulphonylurea and glitazone

In this trial, metformin, sulphonylurea and glitazone are characterised as background medication (non-investigational products) and will be used open-labelled throughout the trial. The drugs will not be provided by Novo Nordisk.

If FPG is repeatedly above the limits of hyperglycaemia as described in section 6.5, glycaemic rescue with intensification of background OAD treatment or addition of new background OADs should be implemented, but how specifically is at the discretion of the Investigator.

Subjects treated with SU (either alone or in combination with other OADs), will at screening (Visit 1) be required to reduce the SU dose by 50% or as close to 50% as possible based on dose options locally available. If already on minimum labelled dose at screening, a subject should remain on that dose unless unacceptable hypoglycaemia occurs, in which case the subject must be withdrawn.

In case a subject is on an OAD (metformin, SU, glitazone) which becomes unavailable during the course of the trial it is allowed as per the discretion of the investigator to shift to an alternative treatment within the other OAD classes allowed in the protocol.

If the FPG falls below 6.1 mmol/L (110 mg/dL) as analysed by the central laboratory, it should be considered to reduce the OAD treatment at the Investigator’s discretion.

The subject should receive the best standard of care at the discretion of the Investigator. Glycaemic goals should follow recommendations laid out in “Standards of Medical Care in Diabetes”(17), i.e. HbA1c <7%. If Investigator determines that insulin, GLP-1 receptor agonist (e.g., Byetta® or Victoza®), or DPP-IV inhibitor, is the best treatment option, the subject must be withdrawn (withdrawal criterion no. 4, see section 6.6).

5.3.3 Counselling on Diet and Physical Activity

At Visit 2 subjects will receive dietary counselling (either in a group or individually) by a qualified dietician according to local standard and placed on a hypo caloric diet containing max. 30% of energy from fat, approximately 20% of energy from protein, approximately 50% of energy from carbohydrates and an energy deficit of approximately 500 kcal/day compared to the subjects’ estimated total energy expenditure (TEE) (See section 5.3.3.1).

The hypo-caloric diet is continued after randomisation and throughout the treatment period. If after 28 weeks of treatment the subjects are unable to lose additional weight despite having a BMI ≥25, re-calculation of the recommended energy intake with no calorie deficit (maintenance diet) is accepted. If a BMI ≤22 is reached the recommended energy intake should be re-calculated with no calorie deficit (maintenance diet) for the remainder of the trial.

Counselling on diet and physical activity (either in a group or individually) will be provided every month, with the exception of Visit 15 and 16 where visits are 6 weeks apart.
Adherence to the visit schedule is a recommendation as counselling can be done either in a group or individually at the dietician’s discretion.

All subjects are instructed by dieticians to keep a 3-day diary of food intake between Visits 1 and 2, Visits 4 and 5b, Visits 6 and 7, Visits 8 and 9, Visits 10 and 11, Visits 12 and 13, Visits 15 and 16, Visits 18 and 19. The 3-day food diaries will be used for counselling at Visit 2, 5b, 7, 9, 11, 13, 16 and 19.

The subject’s dietary compliance and the average daily level of physical activity will be recorded at Visit 2 (only average daily level of physical activity), 5b, 7, 9, 11, 13, 16, and 19. The subject will be questioned whether they performed less than half an hour, between half an hour and one hour or more than 1 hour of physical activity per day. An increase in physical activity (recommended minimum 150 minutes/week) will be encouraged and re-enforced by use of pedometers.

Whether or not the subject is in compliance with the prescribed diet is at the discretion of the dietician after review of the 3-day food diaries.

### 5.3.3.1 Calculation of estimated total energy expenditure

The TEE is calculated by multiplying the estimated Basal Metabolic Rate (BMR) (see Table 5–2) with a Physical Activity Level (PAL) value of 1.3\(^{(18)}\):

\[
\text{Total Energy Expenditure (TEE) (kcal/day)} = \text{BMR} \times 1.3
\]

#### Table 5–2 Equations for estimating basal metabolic rate (BMR) in kcal/day*

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>BMR (kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>18-30 years</td>
<td>15.057 x actual weight in kg + 692.2</td>
</tr>
<tr>
<td></td>
<td>31-60 years</td>
<td>11.472 x actual weight in kg + 873.1</td>
</tr>
<tr>
<td></td>
<td>≥ 60 years</td>
<td>11.711 x actual weight in kg + 587.7</td>
</tr>
<tr>
<td>Women</td>
<td>18-30 years</td>
<td>14.818 x actual weight in kg + 486.6</td>
</tr>
<tr>
<td></td>
<td>31-60 years</td>
<td>8.126 x actual weight in kg + 845.6</td>
</tr>
<tr>
<td></td>
<td>≥ 60 years</td>
<td>9.082 x actual weight in kg + 658.5</td>
</tr>
</tbody>
</table>

* Revised WHO equations\(^{(18)}\).

### 5.4 Rationale for treatment

Based on a balanced evaluation of the efficacy and safety/tolerability results from the double-blinded phase 2 dose-range finding trial (NN8022-1807) and subsequent 32 week open label extension, a dose of 3.0 mg has been chosen as the optimal dose for the weight management indication for liraglutide and will therefore be further investigated in this confirmatory trial. Liraglutide 3.0 mg induced a clinically relevant weight loss from baseline, while improving weight-related risk factors, such as waist circumference, systolic blood pressure and glucose control. The safety of 3.0 mg liraglutide was satisfactory with the main tolerability issue identified being gastro-intestinal side-effects (nausea, diarrhoea and vomiting). The gastro-intestinal...
side effects were predominantly mild to moderate in severity, were mostly transient in nature and were
primarily present during the first 6-8 weeks of treatment.

Liraglutide titration in weekly steps to achieve the target dose of 50 clicks (3.0 mg or placebo) or 30 clicks
(1.8 mg or placebo) is applied in order to reduce the incidence and severity of gastrointestinal side effects.

To increase safety, subjects will be seen more frequently during the initial part of the trial, and they will be
informed to contact the Investigator in the event of any safety issues. Subjects may at all times be withdrawn
from the trial for safety reasons.

All subjects will continue pre-trial treatment. To ensure adequate exposure in subjects treated with other
(non-SU) antidiabetic regimens a proportion of subjects treated with SU mono- or combination therapy at
screening is restricted to a maximum of 30% of randomised subjects. Subjects treated with sulphonylureas
will be asked to reduce the dose by 50% to prevent SU-induced hypoglycaemia. Even though this may
worsen glycaemic control initially, reinforcement of rescue criteria (see section 6.5) to reinstate pre-trial dose
levels and addition of rescue medication should ensure adequate glycaemic control even for subjects on SUs
randomised to liraglutide placebo.

Based on data from the ongoing clinical development program of liraglutide, the current trial is anticipated to
confirm the safety and efficacy of liraglutide in inducing body weight reduction in overweight or obese
subjects with type 2 diabetes.

For further information please refer to the liraglutide obesity Investigators Brochure 3rd edition 2010 and any
subsequent updates thereof.
6 Trial population

6.1 Number of subjects to be studied

Countries planned to participate: France, Germany, Israel, South Africa, Spain, Sweden, Turkey, United Kingdom and USA.

Planned number of subjects to be screened: 1600

Planned number of subjects to be randomised/started on trial products: 800

Planned number of subjects to complete the trial: 480

Anticipated number of trial sites: 130

The anticipated screening failure rate of 50% and the anticipated drop-out rate at 56 weeks of 40% are based on reported rates from obesity and diabetes trials.

6.2 Inclusion criteria

1. Informed consent obtained before any trial-related activities (trial related activities are any procedure that would not have been performed during the normal management of the subject)

2. Subjects diagnosed with type 2 diabetes and treated with either diet and exercise alone, metformin, sulphonylurea, glitazone as single agent therapy or any combination of the previously mentioned compounds (metformin+SU, metformin+glitazone, SU+glitazone, metformin+SU+glitazone). Treatment should have been stable for at least 3 months prior to screening

Only applicable to France: Subjects diagnosed with type 2 diabetes and treated with either metformin as single agent therapy, SU as single agent therapy (if presence of metformin contraindication or intolerance), glitazone as single agent therapy (if presence of metformin contraindication or intolerance), or combination therapy of two of the above mentioned compounds: metformin+SU, metformin+glitazone, SU+glitazone. Treatment should have been stable for at least 3 months prior to screening

3. HbA1c 7.0-10.0% (both inclusive)

4. Body Mass Index (BMI) ≥ 27.0 kg/m²

5. Stable body weight (less than 5 kg self-reported change during the previous 3 months)

6. Preceding failed dietary effort

7. Age 18 years and above (or as allowed according to local labelling for metformin and sulphonylurea treatment)

6.3 Exclusion criteria

1. Treatment with GLP-1 receptor agonists (including liraglutide or exenatide), DPP-4 inhibitors or insulin within the last 3 months
2. Treatment with any hypoglycaemic agent(s) other than metformin, sulphonylurea and glitazone in the 3 months prior to screening

3. Recurrent major hypoglycaemia or hypoglycaemic unawareness as judged by the Investigator

4. Use of any drug (except for metformin, sulphonylurea or glitazone), which in the Investigator’s opinion could interfere with glucose level (e.g. systemic corticosteroids)

5. Receipt of any other anti-diabetic investigational drug within 3 months prior to screening for this trial, or receipt of any investigational drugs not affecting diabetes within 1 month prior to screening for this trial

6. Known proliferative retinopathy or maculopathy requiring acute treatment, as judged by the Investigator

7. Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as TSH > 6 mIU/L or < 0.4 mIU/L

8. History of chronic pancreatitis or idiopathic acute pancreatitis

9. Obesity induced by other endocrinologic disorders (e.g. Cushing Syndrome)

10. Current or history of treatment with medications that may cause significant weight gain, within 3 months prior to screening for this trial, including systemic corticosteroids (except for a short course of treatment, i.e., 7-10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (e.g., imipramine, amitryptiline, mirtazapin, paroxetine, phenelzine, clorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium)

11. Diet attempts using herbal supplements or over-the-counter medications within 3 months prior to screening into this trial

12. Current participation in an organised weight reduction program (or within the last 3 months) and/or are currently using or have used within three months prior to screening for this trial: pramlintide, sibutramine, orlistat, zonisamide, topiramate or phenteremine (either by prescription or as part of a clinical trial)

13. Participation in a clinical trial within the last 3 months prior to screening for this trial

14. Previous surgical treatment for obesity (excluding liposuction if performed > one year before trial entry)

15. Screening calcitonin value ≥ 50 ng/L

16. Familial or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma

17. Personal history of non-familial medullary thyroid carcinoma

18. Simultaneous participation in any other clinical trial of an investigational drug

19. History of Major Depressive Disorder within the last 2 years

20. A PHQ-9 score of ≥ 15

21. History of other severe psychiatric disorders, e.g., schizophrenia, bipolar disorder

22. Any lifetime history of a suicide attempt

23. A history of any suicidal behaviour in the last month prior to randomisation

24. Any suicidal ideation of type 4 or 5 on the C-SSRS in the last month prior to randomisation

25. Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the Investigator

26. Uncontrolled treated/untreated hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg). If white coat hypertension is suspected at the screening visit (Visit 1) a repeated measurement at Visit 2 prior to other trial related activities is allowed

27. Cancer (past or present except basal cell skin cancer or squamous cell skin cancer), which in the Investigator’s opinion could interfere with the results of the trial

28. Known or suspected hypersensitivity to trial product(s) or related product(s)
29. Previous participation in the randomised phase of this trial. Re-screening is allowed once within the limits of the recruitment period

30. Known or suspected abuse of alcohol or narcotics

31. Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete the mental health questionnaires in the provided language

32. Subjects from the same house hold participating in the trial

33. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice) US: abstinence and the following methods: diaphragm with spermicide, condom with spermicide (by male partner), intrauterine device, sponge, spermicide, Norplant®, Depo-Provera® or oral contraceptives. Germany: adequate contraceptive measures are implants, injectables, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomised partner). UK: adequate contraceptive measures are defined as sterilisation, intra-uterine device, oral contraceptives, consistent use of barrier methods, male sterilisation or true abstinence

34. The receipt of any investigational product within four weeks prior to screening for this trial (Visit 1)

Only applicable to France: The following exclusion criteria are applicable for France in addition to the criteria listed above:

- Treatment with diet and exercise only
- Treatment with sulphonylurea as single agent therapy or glitazone as single agent therapy, unless the patient has metformin contraindication or metformin intolerance
- Treatment with triple oral antidiabetic therapy
- Abnormality of the thyroid identified during the physical exam at screening

Proportion of subjects treated with SU mono- or combination therapy will be restricted to a maximum of 30% of total randomised subjects. When target is reached, subjects treated with SU as background treatment may not be randomised in the trial.

Subjects who are non-compliant with any of the eligibility criteria, but included in the trial, should be withdrawn immediately. If extraordinary circumstances speak in favour of maintaining the subject in the trial then this is only acceptable if justified and approved by the Independents Ethics Committee (IEC)/Institutional Review Board (IRB), and if the regulatory authorities are notified according to local requirements

Investigators are recommended to refer screening failure subjects having a calcitonin value of \( \geq 50 \) ng/L to an endocrinologist for follow-up.

### 6.4 Randomisation criteria

In order to be eligible for randomisation in the trial, subjects must comply with the following:

1. At the randomisation visit (Visit 2) the fasting plasma glucose (FPG) must be <12.2 mmol/L (220 mg/dL) as measured by the Investigator at the clinic, by use of a glucose meter. A mean of two
consecutive measurements (using two strips) should be used. If FPG is above or equal to the limit stated above the randomisation may be postponed once within the Visit 2 visit window.

6.5  Rescue criteria

1. If self-measured FPG on three consecutive days/occasions exceeds the limits set below, the subject should contact the Investigator and come in for an unscheduled visit as soon as possible. The next scheduled visit should not be awaited. A FPG should be obtained and analysed by the central laboratory. If this FPG exceeds the limits set below, the background medication dose should initially be escalated to the maximal approved dose, followed by addition of one of the other allowed background OADs (for subjects on diet/exercise alone, treatment with a permitted OAD should be initiated at the discretion of the Investigator):

   - From baseline to Week 6: FPG > 15 mmol/L (270 mg/dL)
   - From Week 7 to Week 12: FPG > 13.3 mmol/L (240 mg/dL)
   - From Week 13 to Week 56: FPG > 11.1 mmol/L (200 mg/dL)

2. If any of the FPG or HbA1c samples analysed by the central laboratory exceeds the limits set below, the subject should immediately be called in for an unscheduled visit as soon as the result has come to the knowledge of the Investigator. The next scheduled visit should not be awaited. A new FPG should be obtained and analysed by the central laboratory and if this FPG exceeds the limits set below the background medication dose should initially be escalated to the maximal approved dose, followed by addition of one of the other allowed background OADs (for subjects on diet/exercise alone, treatment with a permitted OAD should be initiated at the discretion of the Investigator):

   - From baseline to Week 6: FPG > 15 mmol/L (270 mg/dL)
   - From Week 7 to Week 12: FPG > 13.3 mmol/L (240 mg/dL)
   - From Week 13 to Week 56: FPG > 11.1 mmol/L (200 mg/dL) or HbA1c > 8%

6.6  Withdrawal criteria

The subject may be withdrawn from the trial at the discretion of the Investigator or Novo Nordisk due to a safety concern or if judged non-compliant with trial procedures.

A subject must be withdrawn if the following applies:

1. The subject may withdraw from the trial at will at any time.
2. If the target treatment dose of the randomised trial product is not tolerated by the subject.
3. Pregnancy or intention to become pregnant.
4. If insulin, GLP-1 receptor agonist (e.g. Byetta® or Victoza®) or DPP-4 inhibitor treatment is initiated.
5. If adaptation of background OADs does not result in fasting plasma glucose or HbA1c levels below those specified as rescue criteria (section 6.5) within 8 weeks.
6. If a subject despite lowering of background anti-diabetic treatment experiences severe episodes of major hypoglycaemia or repeated minor hypoglycaemic episodes (as judged by the investigator).

7. If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory tests have been conducted and appropriate treatment should be initiated. Subjects that are diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3x UNR or characteristic findings on CT/MRI), must be withdrawn from the trial.

8. A subject must be referred to a Mental Health Professional (MHP) if he/she has

- a PHQ-9 score ≥ 10, OR,
- any suicidal behaviour, OR,
- any suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) on any C-SSRS assessment.

- A referral to a Mental Health Professional (MHP) should also be made if in the opinion of the Investigator it is necessary for the safety of the subject. If a subject’s psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the subject, at the discretion of the Investigator (in agreement with the MHP), may be continued in the trial on randomised therapy, otherwise, the subject must be withdrawn.

The Investigator should carefully explain to the subject why the referral and psychiatric evaluation by a MHP is needed if one or more referral criteria are met. If the subject refuses to be referred to a MHP after the recommendation and explanation from the Investigator, the subject’s decision should be documented in the medical record and the Investigator must assess if it is safe for the subject to continue in the trial or if the subject should be withdrawn.

Only applicable to France:

9. Confirmed calcitonin value ≥ 50 ng/L

In case of withdrawal, the End of Trial (EOT) Form in the case report form (eCRF) must be completed and if possible, the subject should be called in for a final visit. Procedures according to Visit 16 should be performed.

Subjects who have discontinued the trial prematurely will be asked to attend a visit taking place 56 weeks after the randomisation date (Visit 2). The purpose of this visit will be recording of the body weight and reporting of MESI.

6.7 Subject replacement

Withdrawn subjects will not be replaced. However, re-screening is allowed once within the limits of the recruitment period, at the Investigator’s discretion.

If a subject is re-screened, a new subject number has to be assigned and new informed consent must be completed, all screening visit 1 blood sampling and assessments have to be repeated.
6.8 Rationale for trial population

Overweight or obese subjects with type 2 diabetes have been selected for this trial in line with the trial objectives of investigating the efficacy of liraglutide compared to placebo with regard to weight loss and glycaemic control in this population. The intended treatment population is any overweight or obese subject with type 2 diabetes (treated with either: diet and exercise alone, with a single OAD or combination OAD (Only applicable to France: treated with a single OAD or dual combination OAD)). To ensure adequate exposure in subjects treated with other (non-SU) antidiabetic regimens a proportion of subjects treated with SU mono- or combination therapy at screening is restricted to a maximum of 30% of randomised subjects. The inclusion criterion defining HbA1c levels will ensure that at the start of the trial, the glycaemic control of participating subjects is appropriate for treatment intensification. Furthermore, rescue criteria are defined to ensure that subjects are considered for glycaemic rescue if plasma glucose levels exceed acceptable limits during trial participation.

The requirement for stable body weight and stable background type 2 diabetes treatment for at least 3 months prior to screening is implemented in order to ensure that change in glycaemic control and body weight observed during the trial is solely caused by the trial treatments.
7  Trial schedule

Planned duration of recruitment period 16 weeks

Planned date for first subject (FPFV) 01-Jun-2011

Planned completion of the last subject (LPLV) Jan-2013

Planned completion of clinical trial report Jun-2013

The end of the clinical trial is defined as the last visit of the last subject (LPLV) globally.

The recruitment will be evaluated by Novo Nordisk on a continuous basis and country and regional specific contingency measures may be applied. A Competitive recruitment may be applied if deemed needed.

To ensure that only the required number of subjects is randomised, screened subjects will be monitored closely via IV/WRS.

All Investigators will be notified immediately when the enrolment period comes to an end, after which no subjects must be screened, and the IV/WRS will be closed for further screening and randomisation.

Protocol information for this trial will be subject to public disclosure at external web sites (www.clinicaltrials.gov and www.novonordisk-trials.com) according to international regulations e.g. the International Committee of Medical Journal Editors (ICMJE) (19), the Food and Drug Administration Amendments Act (FDAAA) (20), as reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure.
8 Methods and assessments

8.1 Visit Procedures

Before screening takes place subjects will be provided with written and verbal information about the trial and the procedures involved. Qualified site staff in accordance with local law will ensure that subjects are fully informed both verbally and in writing about the practical consequences of participating, of their rights and responsibilities while participating in the trial as well as any possible advantages and disadvantages in being treated with the trial products. Subjects will have the opportunity to ask questions to a medically qualified person and have ample time to consider participation. Subjects who wish to participate must give signed and dated informed consent. This must be done prior to any trial related activities, i.e. procedures that would not have been performed during normal management of the subject.

It must be stated in the medical record that the subject is participating in the current trial. Subjects enrolled in the trial will be provided with a subject ID card, stating that they are participating in a trial and whom to contact (site address, Investigator’s name and telephone number) for further information, if necessary. The subjects should be reminded to show the card to other health care providers, as applicable. The subjects should be instructed to return the card to the Investigator at the last visit of the subject or destroy the card after the last visit.

The Investigator must keep a subject screening log and a subject enrolment log. These can be combined in one document.

For screening failures (subjects who have given informed consent but who do not meet the inclusion, exclusion and/or randomisation criteria and hence are not randomised), all data for completed trial procedures should be recorded in the eCRF, and the reason for exclusion from the trial should be recorded on the screening failure form. The screening failure form will be entered into the clinical database. Serious and non-serious adverse events from screening failures will be entered by the Investigator into the electronic CRFs and consequently transferred to the clinical database. When trial related procedures have been finalised for screening failures, no more adverse events should be entered in the eCRF. Follow-up of AEs should be made according to section 12. In addition screening failures should be registered in the IV/WRS. As a minimum, the reason for screening failure must be recorded in the eCRF.

Investigators are recommended to refer screening failure subjects having a calcitonin value of ≥ 50 ng/L to an endocrinologist for follow-up.

Trial product should be taken once daily at a time convenient to the subject; however, it is preferable that liraglutide/liraglutide placebo be injected during the same overall time period on a day to day basis. The injection site does not have to be consistent throughout the trial.

At Visit 2, 3, 4, 5b, 7, 8, 10, 13, 15, 16, 16x, 17 and 20 the subject must attend the clinic in a fasting condition in the morning (i.e., at least eight hours overnight fast without food and/or drink intake, except for water).
Background medication and the trial product should be withheld on the day of the fasting Visits 2, 3, 4, 5b, 7, 8, 10, 13, 15, 16, 17, and Visit 20, until blood sampling has been done. At all other visits the background medication and trial product should be taken as usual during the conduct of the trial.

Weight will be measured at all visits to the clinic, hence at those visits subjects attend fasting, weight will be measured in a fasting state, whereas at all other visits weight will be measured in a non-fasting state.

Trial product will be dispensed at visits 2, 4 and 5b-15. Subjects will be asked to bring all empty, partly used and unused trial product at visits 4 and 5b-16 for drug accountability. The IV/WRS should be contacted for trial product dispensing. If the subject attends the clinic for a visit not described in the protocol, then an Unscheduled Visit Form must be completed. The Unscheduled Visit Form should not be completed if the sole purpose of the visit is trial product dispensing. If an unscheduled visit is made for the purpose of dispensing trial products to the subjects then an unscheduled dispensing session must be completed in the IV/WRS. If the subject attends a fasting visit in a non-fasting state the subject should preferably be called in for a new visit within the visit window to have the fasting weight and fasting circumference measured and the fasting blood samples drawn. All other assessments can be performed even though the subject is not fasting. If it is not possible to attend the new visit within the visit window, the subjects should be called in for an Unscheduled Visit and the original visit page in the eCRF should be used to obtain information on fasting weight, fasting circumference and fasting blood samples by overwriting the original date and readings.

In case a subject is being prematurely withdrawn from the trial before or at visit 16, the Investigator will ensure that the procedures for the End of Treatment visit (Visit 16) are undertaken, if possible. If a subject is being prematurely withdrawn from the trial after visit 16 or at Visit 17, the Investigator will ensure that the procedures for Visit 17 are undertaken, if possible. If a subject is being prematurely withdrawn from the trial after Visit 16 or Visit 17, the Investigator will ensure that the procedures for the follow-up visit (Visit 20) are undertaken, if possible. The primary reason (adverse event, non-compliance with protocol or other) for discontinuation must be specified in the eCRF and an IV/WRS withdrawal session should be completed. Even if the subject is not able to attend a final visit, the End of Trial Form (EOT) must be completed.

Subjects that have discontinued the trial prematurely before Visit 16 will be asked to attend a visit (Visit 16x) taking place 56 weeks after the randomisation date. The purpose of this visit will be recording of the body weight and assessment of MESI. The assessment will be done by asking the subject if he/she has experienced any MESI (see section 12.2.1 and appendix H) since the last contact.

If the subject is not willing to attend Visit 16x, it should be documented in the patient medical record that the subject has refused to attend the visit.

As liraglutide is not available on prescription for the obesity indication after the end of the trial, the subjects will not be able to receive it when the trial ends. This means that Novo Nordisk will not offer investigational drug after the end of the trial. At the End of Treatment visit (Visit 16) the Investigator or delegate should provide counselling on the management of weight control and advise the subjects to commence the appropriate antidiabetic therapy at her/his discretion (with the exception of the treatments listed in withdrawal criterion no.4).
8.1.1 Visit Schedule

Subjects will attend the clinic as stated in Table 8–1.

### Table 8–1 Visit schedule

<table>
<thead>
<tr>
<th>Visit no.</th>
<th>Time of Visit</th>
<th>Type of Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>Week -2 ± 5 days</td>
<td>Screening</td>
</tr>
<tr>
<td>Visit 2</td>
<td>Day 0, baseline</td>
<td>Randomisation, start of liraglutide 0.6 mg/liraglutide placebo</td>
</tr>
<tr>
<td>Visit 3</td>
<td>Week 2 ± 3 days</td>
<td>Dose escalation visit</td>
</tr>
<tr>
<td>Visit 4</td>
<td>Week 4 ± 5 days</td>
<td>Dose escalation visit/Maintenance visit</td>
</tr>
<tr>
<td>Visit 5a</td>
<td>Week 6 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 5b</td>
<td>Week 8 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 6</td>
<td>Week 12 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 7</td>
<td>Week 16 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 8</td>
<td>Week 20 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 9</td>
<td>Week 24 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 10</td>
<td>Week 28 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 11</td>
<td>Week 32 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 12</td>
<td>Week 36 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 13</td>
<td>Week 40 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 14</td>
<td>Week 44 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 15</td>
<td>Week 50 ± 5 days</td>
<td>Maintenance visit</td>
</tr>
<tr>
<td>Visit 16x</td>
<td>Week 56 ± 5 days</td>
<td>Body weight/MESI recording visit</td>
</tr>
<tr>
<td>Visit 16</td>
<td>Week 56 ± 3 days</td>
<td>End of treatment visit/ premature discontinuation before or at Visit 16</td>
</tr>
<tr>
<td>Visit 17</td>
<td>Week 58 ± 3 days</td>
<td>Follow-up visit/premature discontinuation at Visit 17</td>
</tr>
<tr>
<td>Visit 18</td>
<td>Week 60 ± 5 days</td>
<td>Follow-up visit</td>
</tr>
<tr>
<td>Visit 19</td>
<td>Week 64 ± 5 days</td>
<td>Follow-up visit</td>
</tr>
<tr>
<td>Visit 20</td>
<td>Week 68 ± 5 days</td>
<td>Follow-up visit/premature discontinuation after Visit 17</td>
</tr>
</tbody>
</table>

The total duration of the trial (for a subject completing the trial) will be up to 70 weeks and will comprise a total of 21 visits.

8.1.2 Visit 1, Screening visit

Visit 1 will take place 2 weeks ± 5 days before Visit 2.

Subjects must give signed and dated informed consent prior to any trial-related activities. All subjects will be provided with a copy of the subject information and a copy of their own signed and dated Informed Consent Form.

The subjects will be allocated the unique lowest consecutive 6 digit subject number available from the range of subject numbers. The subject number is composed of three digits unique for each trial site and three digits for each enrolled subject at the trial site. The subject number is maintained throughout the trial.
The IV/WRS should be called/entered to register the subject as screened (see section 10.3) and the subject will be provided with a study card indicating that the subject is participating in a trial.

To mitigate SU induced hypoglycaemia, subjects treated with SU (either alone or in combination with other OADs), will at screening be required to reduce the SU dose by 50% or as close to 50% as possible based on dose options locally available. If already on minimum labelled dose at screening, a subject should remain on that dose unless unacceptable hypoglycaemia occurs, in which case the subject must be withdrawn. Other OAD treatment should remain stable throughout the trial (same drug or drugs [same INN(s)], dose and dosing frequencies).

The following will be performed and/or recorded in the eCRF:

- Informed consent, signed and dated (see section 19.1)
- Inclusion and exclusion criteria (see section 6.2 and 6.3)
- Demographic information registered in the IV/WRS and/or recorded in the eCRF (date of birth, sex and race and ethnicity, according to local requirements)
- Diagnosis of type 2 diabetes
- Diabetes treatment history (see section 11)
- Medical history/concomitant illnesses (see section 11)
- Concomitant medication (see section 11)
- Smoking habits (see section 8.4)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Physical examination (see section 8.3.1)
- ECG (see section 8.3.3)
- Eye examination (see section 8.3.14)
- Mental Health questionnaires (see section 8.3.10)
- Dispense study card
- Dispense diabetes diary and instruct in the use hereof (see section 8.4.2 and 14)
- History of diabetes complications (see section 8.4.6)
- History of Concomitant Cardiovascular Disease (see section 8.4.7)
- History of Gallbladder Disease (see section 8.4.8)
- History of Psychiatric Disorders (see section 8.4.9)
- Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
- Dispense glucose meter and instruct in the use hereof (see section 8.2.4 and 8.3.2)
- Provide collection cup for urine sample
- Record the subjects on the subject screening log or the informed consent log according to local practice

Blood sampling for measurements of:

- HbA1c (see section 8.2.2)
- Lipids (see section 8.2.6)
- Haematology and biochemistry (see section 8.3.5)
- For females of childbearing potential: serum pregnancy test (see section 8.3.6)
Interact with the IV/WRS to:

- Complete screening session (see section 10.3)

Once all data relating to Visit 1 (screening visit) have been obtained, they must be reviewed by the
Investigator to ensure that the subject is eligible to continue in the trial (see also section 6.2 and 6.3). If the
subject is not eligible to continue, the subject is a screening failure and the IV/WRS must be contacted to
register the subject as a screening failure, and the reason for exclusion must be recorded.

Reminders:

- An appointment for Visit 2 (2 weeks after Visit 1) should be made
- Subjects should be reminded to:
  - Continue treatment with background diabetes medication throughout the trial
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 2 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 2
  - Bring the urine sample at Visit 2
  - Complete their 3-day food diary and return it at Visit 2 (see section 5.3.3 and 8.4.3)
  - Attend Visit 2 fasting (i.e., at least eight hours overnight fast without food and/or drink intake,
    except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 2 until blood
    sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure
    measurement at Visit 2

- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - A 7-point plasma glucose profile on a normal representative day within a week prior to Visit 2 (see
    section 8.2.4)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including
    details about hypoglycaemia (see section 8.3.2)

8.1.3 Visit 2, Randomisation visit

The visit will take place 2 weeks after Visit 1.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink
intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood
sampling and body measurements should be made within the visit window.

The subject will receive dietary counselling by a qualified dietician and placed on a hypo caloric diet (see
section 5.3.1).

If the subject is found eligible after review of inclusion, exclusion and randomisation criteria at Visit 2, the
subject will be randomised into one of the three treatment arms (see section 5.1) using IV/WRS (see section
Subjects will have trial products supplied according to randomisation and will be instructed in administration of daily injections of liraglutide/liraglutide placebo. Injections can be done at anytime of day irrespective of meals. However, it is preferable that liraglutide/liraglutide placebo be injected during the same overall time period on a day to day basis. The injection site does not have to be kept consistent throughout the trial. The trial products dispensed will cover the dose escalation period. Subjects will follow a fixed dose escalation. The dose will be gradually escalated to 3.0 mg or 1.8 mg starting with 0.6 mg and with a dose level increment of 0.6 mg every 7 days (see section 5.3.1).

If the subject is not eligible for randomisation, the subject is considered a screening failure and the IV/WRS must be contacted to register the subject as a screening failure.

The following will be performed and/or recorded in the eCRF:

- Check in- and exclusion criteria (see section 6.1 and 6.2)
- Check randomisation criteria (see section 6.4)
- Stratification group (see section 5.1)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Adverse events since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Mental Health questionnaires (see section 8.3.10)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (using the 3-day food diary) (see section 5.3.3)
- Record the subject’s physical activity (see section 5.3.3)
- Dispense pedometer and instruct the subject in the use hereof (see section 5.3.3)
- For subjects in France, Germany, Spain, Sweden, United Kingdom and USA: PRO questionnaires (see section 8.2.9 and 8.3.15)

Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Self-measured 7-point plasma glucose profile (see section 8.2.4)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:

- HbA1c (see section 8.2.2)
- FPG (see section 8.2.3)
- Glucose metabolism (see section 8.2.5)
- Lipids (see section 8.2.6)
- Cardiovascular biomarkers (see section 8.2.8)
- Haematology and biochemistry (see section 8.3.5)
- Liraglutide antibodies (see section 8.3.7)

**Urine sampling for measurement of:**
- Urinary Albumin-to-Creatinine ratio (see section 8.2.10)

**Interact with the IV/WRS to:**
- Complete screening failure session, if applicable
- Complete randomisation session
- Complete trial product dispensing session (see section 9.3)

**Reminders:**
- An appointment for Visit 3 (2 weeks ± 3 days after Visit 2) should be made
- Attend Visit 3 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water).
- To withhold treatment with background medication and trial product on the day of Visit 3 until blood sampling has been done
- Subjects should be reminded to:
  - Increase the dose by 0.6 mg/day every week until the target dose of 3.0 or 1.8 mg/day has been reached
  - Measure FPG on a regular basis, at the Investigators discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 3 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 3
- Subjects should be reminded to record the following in their diabetes diary:
  - The date of first administration of trial product
  - Injection date and time, dose and injection site for the three doses prior to Visit 3
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

**8.1.4 Visit 3, Dose escalation visit**

Visit 3 will take place 2 weeks ± 3 days after Visit 2.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

**The following will be performed and/or recorded in the eCRF:**
- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)
- Injection date and time, dose and injection site for the three doses prior to visit 3 (see section 8.4.5)

Blood sampling for measurement of:

- FPG (see section 8.2.3)
- Liraglutide plasma concentration (see section 8.4.5)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable

Reminders:

- An appointment for Visit 4 (4 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Increase the dose 0.6 mg/day every week until the target dose has been reached
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 4 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 4
  - Attend Visit 4 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 4 until blood sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 4
  - Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 4
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.5 Visit 4, Dose escalation visit/maintenance visit

Visit 4 will take place 4 weeks ± 5 days after Visit 2.
The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (see section 5.3.3)
- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:

- HbA1c (see section 8.2.2)
- FPG (see section 8.2.3)
- Haematology and biochemistry (see section 8.3.5)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable
- Complete trial product dispensing session (see section 9.3)
- Interact with Drug Accountability module (see section 10.3)

Reminders:

- An appointment for Visit 5a (6 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 5a (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 5a
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 5a
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
8.1.6 Visit 5a, maintenance visit

Visit 5a will take place 6 weeks ± 5 days after Visit 2.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- AEs since last visit (see section 12)
- Mental Health questionnaires (see section 8.3.10)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)

Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable

Reminders:

- An appointment for Visit 5b (8 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 5b (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 5b
  - Complete their 3-day food diary and return it at Visit 5b (see section 5.3.3 and 8.4.3)
  - Attend Visit 5b fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 5b until blood sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 5b
  - Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 5b
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.7 Visit 5b, maintenance visit

Visit 5b will take place 8 weeks ± 5 days after Visit 2.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (using the 3-day food diary) (see section 5.3.3)
- Record the subject’s dietary compliance and physical activity (see section 5.3.3)

Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurement of:

- FPG (see section 8.2.3)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable
- Complete trial product dispensing session (see section 9.3)
- Interact with Drug Accountability module (see section 10.3)

Reminders:

- An appointment for Visit 6 (12 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 6 (see section 8.4.2 and 14)
− Bring their glucose meter at Visit 6
− Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 6
− Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 6

Subjects should be reminded to record the following in their diabetes diary:
− Changes in concomitant medication (see section 11)
− Injection date and time, dose and injection site for the three doses prior to visit 6
− Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.8 Visit 6, maintenance visit
Visit 6 will take place 12 weeks ± 5 days after Visit 2.

The following will be performed and/or recorded in the eCRF:

• Rescue criteria (see section 6.5)
• Withdrawal criteria (see section 6.6)
• Subject compliance (see section 8.5)
• Concomitant medication (see section 11)
• Body measurements (see section 8.2.1)
• Vital signs (see section 8.2.6)
• Mental Health questionnaires (see section 8.3.10)
• Date and actual time of blood sampling for the measurement of liraglutide plasma concentration (see section 8.4.5)
• AEs since last visit (see section 12)
• For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
• Diet and physical activity counselling (see section 5.3.3)

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Hypoglycaemic episodes since last visit (see section 8.3.2)
• Injection date and time, dose and injection site for the three doses prior to visit 6 (see section 8.4.5)

Blood sampling for measurement of:
• Liraglutide plasma concentration (see section 8.4.5)

Interact with the IV/WRS to:
• Complete withdrawal session, if applicable
• Complete trial product dispensing session (see section 9.3)
• Interact with Drug Accountability module (see section 10.3)
Reminders:

- An appointment for Visit 7 (16 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 7 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 7
  - Complete their 3-day food diary and return it at Visit 7 (see section 5.3.3 and 8.4.3)
  - Attend Visit 7 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 7 until blood sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 7
  - Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 7
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.9 Visit 7, maintenance visit

Visit 7 will take place 16 weeks ± 5 days after Visit 2.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Mental Health questionnaires (see section 8.3.10)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (based on the 3-day food diary) (see section 5.3.3)
- Record the subject’s dietary compliance and physical activity (see section 5.3.3)
Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:

- HbA1c (see section 8.2.2)
- FPG (see section 8.2.3)
- Haematology and biochemistry (see section 8.3.5)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable
- Complete trial product dispensing session (see section 9.3)
- Interact with Drug Accountability module (see section 10.3)

Reminders:

- An appointment for Visit 8 (20 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 8 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 8
  - Attend Visit 8 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 8
  - To withhold treatment with background medication and trial product on the day of Visit 8 until blood sampling has been done
  - Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 8
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.10 Visit 8, maintenance visit

Visit 8 will take place 20 weeks ± 5 days after Visit 2.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
• Withdrawal criteria (see section 6.6)
• Subject compliance (see section 8.5)
• Concomitant medication (see section 11)
• Body measurements (see section 8.2.1)
• Vital signs (see section 8.2.6)
• Mental Health questionnaires (see section 8.3.10)
• AEs since last visit (see section 12)
• For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
• Diet and physical activity counselling (see section 5.3.3)

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurement of:
• FPG (see section 8.2.3)

Interact with the IV/WRS to:
• Complete withdrawal session, if applicable
• Complete trial product dispensing session (see section 9.3)
• Interact with Drug Accountability module (see section 10.3)

Reminders:
• An appointment for Visit 9 (24 weeks ± 5 days after Visit 2) should be made
• Subjects should be reminded to:
  – Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  – Complete their diabetes diary and return it at Visit 9 (see section 8.4.2 and 14)
  – Bring their glucose meter at Visit 9
  – Complete their 3-day food diary and return it at Visit 9 (see section 5.3.3 and 8.4.3)
  – Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 9
  – Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 9
• Subjects should be reminded to record the following in their diabetes diary:
  – Changes in concomitant medication (see section 11)
  – Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.11 Visit 9, maintenance visit
Visit 9 will take place 24 weeks ± 5 days after Visit 2.
The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (based on the 3-day food diary) (see section 5.3.3)
- Record the subject’s dietary compliance and physical activity (see section 5.3.3)
- Provide collection cup for urine sample
- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Transcription from the diabetes diary:

- Complete withdrawal session, if applicable
- Complete trial product dispensing session (see section 9.3)
- Interact with Drug Accountability module (see section 10.3)

Reminders:

- An appointment for Visit 10 (28 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 10 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 10
  - Bring the urine sample at Visit 10
  - Attend Visit 10 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 10 until blood sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 10
  - Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 10
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
− A 7-point plasma glucose profile on a normal representative day within a week prior to Visit 10 (see section 8.2.4)
− Injection date and time, dose and injection site for the three doses prior to visit 10
− Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.12 Visit 10, maintenance visit
Visit 10 will take place 28 weeks ± 5 days after Visit 2.
The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:
• Rescue criteria (see section 6.5)
• Withdrawal criteria (see section 6.6)
• Subject compliance (see section 8.5)
• Concomitant medication (see section 11)
• Body measurements (see section 8.2.1)
• Vital signs (see section 8.2.6)
• Mental Health questionnaires (see section 8.3.10)
• Date and actual time of blood sampling for the measurement of liraglutide plasma concentration (see section 8.4.5)
• AEs since last visit (see section 12)
• For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
• Diet and physical activity counselling (see section 5.3.3)
• For subjects in France, Germany, Spain, Sweden, United Kingdom and USA: PRO questionnaires (see section 8.2.9). BES is not performed at Visit 10.

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Self-measured 7-point plasma glucose profile (see section 8.2.4)
• Hypoglycaemic episodes since last visit (see section 8.3.2)
• Injection date and time, dose and injection site for the three doses prior to visit 10 (see section 8.4.5)

Blood sampling for measurements of:
• HbA1c (see section 8.2.2)
• FPG (see section 8.2.3)
• Glucose metabolism (see section 8.2.5)
• Lipids (see section 8.2.6)
• Cardiovascular biomarkers (see section 8.2.8)
8.1.13 Visit 11, maintenance visit

Visit 11 will take place 32 weeks ± 5 days after Visit 2.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Mental Health questionnaires (see section 8.3.10)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (based on the 3-day food diary) (see section 5.3.3)

Reminders:

- An appointment for Visit 11 (32 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 11 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 11
  - Complete their 3-day food diary and return it at Visit 11 (see section 5.3.3 and 8.4.3)
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 11
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)
- Subjects should be reminded to return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 11
• Record the subject’s dietary compliance and physical activity (see section 5.3.3)

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Hypoglycaemic episodes since last visit (see section 8.3.2)

Interact with the IV/WRS to:
• Complete withdrawal session, if applicable
• Complete trial product dispensing session (see section 9.3)
• Interact with Drug Accountability module (see section 10.3)

Reminders:
• An appointment for Visit 12 (36 weeks ± 5 days after Visit 2) should be made
• Subjects should be reminded to:
  – Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  – Complete their diabetes diary and return it at Visit 12 (see section 8.4.2 and 14)
  – Bring their glucose meter at Visit 12
  – Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure
    measurement at Visit 12
  – Return all used, partly used and unused trial products, including empty packing, for drug
    accountability at Visit 12
• Subjects should be reminded to record the following in their diabetes diary:
  – Changes in concomitant medication (see section 11)
  – Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including
    details about hypoglycaemia (see section 8.3.2)

8.1.14 Visit 12, maintenance visit
Visit 12 will take place 36 weeks ± 5 days after Visit 2.

The following will be performed and/or recorded in the eCRF:
• Rescue criteria (see section 6.5)
• Withdrawal criteria (see section 6.6)
• Subject compliance (see section 8.5)
• Concomitant medication (see section 11)
• Body measurements (see section 8.2.1)
• Vital signs (see section 8.2.6)
• Mental Health questionnaires (see section 8.3.10)
• AEs since last visit (see section 12)
• For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
• Diet and physical activity counselling (see section 5.3.3)
Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable
- Complete trial product dispensing session (see section 9.3)
- Interact with Drug Accountability module (see section 10.3)

Reminders:

- An appointment for Visit 13 (40 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 13 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 13
  - Complete their 3-day food diary and return it at Visit 13 (see section 5.3.3 and 8.4.3)
  - Attend Visit 13 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 13 until blood sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 13
  - return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 13
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.15 Visit 13, maintenance visit

Visit 13 will take place 40 weeks ± 5 days after Visit 2.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
• Vital signs (see section 8.2.6)
• Mental Health questionnaires (see section 8.3.10)
• AEs since last visit (see section 12)
• For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
• Diet and physical activity counselling (based on the 3-day food diary) (see section 5.3.3)
• Record the subject’s dietary compliance and physical activity (see section 5.3.3)

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:
• HbA1c (see section 8.2.2)
• FPG (see section 8.2.3)
• Haematology and biochemistry (see section 8.3.5)

Interact with the IV/WRS to:
• Complete withdrawal session, if applicable
• Complete trial product dispensing session (see section 9.3)
• Interact with Drug Accountability module (see section 10.3)

Reminders:
• An appointment for Visit 14 (44 weeks ± 5 days after Visit 2) should be made
• Subjects should be reminded to:
  – Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  – Complete their diabetes diary and return it at Visit 14 (see section 8.4.2 and 14)
  – Bring their glucose meter at Visit 14
  – Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 14
  – return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 14
• Subjects should be reminded to record the following in their diabetes diary:
  – Changes in concomitant medication (see section 11)
  – Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.16 Visit 14, maintenance visit
Visit 14 will take place 44 weeks ± 5 days after Visit 2.
The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Diet and physical activity counselling (see section 5.3.3)

Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable
- Complete trial product dispensing session (see section 9.3)
- Interact with Drug Accountability module (see section 10.3)

Reminders:

- An appointment for Visit 15 (50 weeks ± 5 days after Visit 2) should be made
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.3)
  - Complete their diabetes diary and return it at Visit 15 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 15
  - Attend Visit 15 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 15
  - To withhold treatment with background medication and trial product on the day of Visit 15 until blood sampling has been done
  - Return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 15
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)
8.1.17 Visit 15, maintenance visit

Visit 15 will take place 50 weeks ± 5 days after Visit 2.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

- Rescue criteria (see section 6.5)
- Withdrawal criteria (see section 6.6)
- Subject compliance (see section 8.5)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- AEs since last visit (see section 12)
- For females of childbearing potential: urine pregnancy test as applicable (see section 8.3.6)
- Mental Health questionnaires (see section 8.3.10)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (see section 5.3.3)
- Provide collection cup for urine sample
- Transcription from the diabetes diary:
  - Any change in concomitant medication (see section 11)
  - Hypoglycaemic episodes since last visit (see section 8.3.2)
- Blood sampling for measurement of:
  - FPG (see section 8.2.3)
- Interact with the IV/WRS to:
  - Complete withdrawal session, if applicable
  - Complete trial product dispensing session (see section 9.3)
  - Interact with Drug Accountability module (see section 10.3)
- Reminders:
  - An appointment for Visit 16 (56 weeks ± 3 days after Visit 2) should be made
  - Subjects should be reminded to:
    - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
    - Complete their diabetes diary and return it at Visit 16 (see section 8.4.2 and 14)
    - Complete their 3-day food diary and return it at Visit 16 (see section 5.3.3)
    - Bring their glucose meter at Visit 16
    - Bring the urine sample at Visit 16
Attend Visit 16 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)

To withhold treatment with background medication and trial product on the day of Visit 16 until blood sampling has been done

Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 16

return all used, partly used and unused trial products, including empty packing, for drug accountability at Visit 16

Subjects should be reminded to record the following in their diabetes diary:

Changes in concomitant medication (see section 11)

A 7-point plasma glucose profile on a normal representative day within a week prior to Visit 16 (see section 8.2.4)

Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.18 Visit 16, End of treatment/premature discontinuation before Visit 16

Visit 16 will take place 56 weeks ± 3 days after Visit 2.

Subjects discontinuing (leaving/being withdrawn from) the trial prematurely before or at Visit 16 should have procedures according to Visit 16 performed at their last visit, if possible.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:

Subject compliance (see section 8.5)

Subject main trial completer (Y/N)

Concomitant medication (see section 11)

Body measurements (see section 8.2.1)

Vital signs (see section 8.2.6)

Mental Health questionnaires (see section 8.3.10)

Physical examination (see section 8.3.1)

ECG (see section 8.3.3)

AEs since last visit (see section 12)

Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)

Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)

Diet and physical activity counselling (based on the 3-day food diary).

Provide counselling on the management of weight control and advise the subject to continue on their treatment with background OAD therapy or other treatment modalities (treatments listed in withdrawal criterion no.4 may not be used in the follow-up period, see section 6.6) at the discretion of the Investigator (see section 5.3.3)

Record the subject’s dietary compliance and physical activity (see section 5.3.3)
• Provide collection cup for urine sample

• For subjects in France, Germany, Spain, Sweden, United Kingdom and USA: PRO questionnaires (see section 8.2.9 and 8.3.15).

• For subjects discontinuing the trial prematurely before Visit 16: Complete PRO questionnaires

• For subjects discontinuing the trial prematurely before Visit 16: Complete Mental Health questionnaires

• For subjects who discontinue the trial prematurely before Visit 16: Complete EOT form

Transcription from the diabetes diary:

• Any change in concomitant medication (see section 11)

• Self-measured 7-point plasma glucose profile (see section 8.2.4)

• Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:

• HbA₁c (see section 8.2.2)

• FPG (see section 8.2.3)

• Glucose metabolism (see section 8.2.5)

• Lipids (see section 8.2.6)

• Cardiovascular biomarkers (see section 8.2.8)

• Haematology and biochemistry (see section 8.3.5)

• For females of childbearing potential: serum pregnancy test (see section 8.3.6)

• For subjects who discontinue the trial prematurely before Visit 16: liraglutide antibodies (see section 8.3.7)

Urine sampling for measurements of:

• Urinary Albumin-to-Creatinine ratio (see section 8.2.10)

Interact with the IV/WRS to:

• Complete withdrawal session, if applicable

• Interact with Drug Accountability module (see section 10.3)

Reminders:

• An appointment for Visit 17 should be made 58 weeks ± 3 days after Visit 2

• Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 17 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 17
  - Bring the urine sample at Visit 17
  - Attend Visit 17 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication and trial product on the day of Visit 17 until blood sampling has been done
Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 17.

Subjects should be reminded to record the following in their diabetes diary:
- Changes in concomitant medication (see section 11)
- Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

Subjects that have discontinued the trial prematurely before Visit 16 should be reminded that a body weight recording visit will be performed 56 weeks after the randomisation date.

### 8.1.19 Visit 16x, Body weight/MESI recording visit

Visit 16x will take place 56 weeks ± 5 days after Visit 2.

The body weight recording visit is only applicable for subjects who have discontinued the trial prematurely before Visit 16 and accept that they can be contacted 56 weeks after their randomisation date.

Subjects will be asked to attend this visit 56 weeks after their randomisation date for the purpose of body weight recording and assessment of MESI. The assessment will be done by asking the subject if he/she has experienced any MESI (see section 12.2.1 and appendix H) since the last contact. The subjects should attend Visit 16x fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water).

If the subject is not willing to attend Visit 16x, it should be documented in the patient medical record that the subject has refused to attend the visit.

The following will be performed and/or recorded in the eCRF:
- Body weight (see section 8.2.1)
- MESI, if any (see section 12.2.1)
- Fasting state

### 8.1.20 Visit 17, follow-up visit/premature discontinuation at Visit 17

Visit 17 will take place 58 weeks ± 3 days after Visit 2.

Subjects discontinuing (leaving/being withdrawn from) the trial prematurely after visit 16 or at Visit 17 should have procedures according to Visit 17 performed, if possible.

The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.

The following will be performed and/or recorded in the eCRF:
- Withdrawal criteria (see section 6.6)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
• Mental health questionnaires (see section 8.3.8)
• AEs since last visit (see section 12)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• For subjects who discontinue the trial prematurely after visit 16 or at Visit 17: Complete EOT form
• For subjects in France, Germany, Spain, Sweden, United Kingdom and USA: PRO questionnaires
  (only Binge Eating Scale questionnaire [see section 8.3.15])

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:
• FPG (see section 8.2.3)
• Haematology and biochemistry (see section 8.3.5)
• Liraglutide antibodies (see section 8.3.7)

Urine sampling for measurements of:
• Albumin/creatinine ratio (see section 8.2.10)

Interact with the IV/WRS to:
• Complete withdrawal session, if applicable

Reminders
• An appointment for Visit 18 should be made 60 weeks ± 5 days after Visit 2
• Subjects should be advised to adjust their background type 2 diabetes treatment, at the discretion of the investigator
• Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 18 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 18
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 18
• Subjects should be reminded to record the following in their diabetes diary:
  – Changes in concomitant medication (see section 11)
  – Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.21 Visit 18, follow-up

Visit 18 will take place 60 weeks ± 5 days after Visit 2.
The following will be performed and/or recorded in the eCRF:

- Withdrawal criteria (see section 6.6)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
- AEs since last visit (see section 12)
- Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
- Dispense 3-day food diary and instruct the subject in the completion hereof (see section 5.3.3 and 8.4.3)
- Diet and physical activity counselling (see section 5.3.3)

**Transcription from the diabetes diary:**

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

**Interact with the IV/WRS to:**

- Complete withdrawal session, if applicable

**Reminders**

- An appointment for Visit 19 should be made 64 weeks ± 5 days after Visit 2
- Subjects should be advised to adjust their background type 2 diabetes treatment, at the discretion of the investigator
- Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 19 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 19
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 19
- Subjects should be reminded to record the following in their diabetes diary:
  - Changes in concomitant medication (see section 11)
  - Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

**8.1.22 Visit 19, follow-up**

Visit 19 will take place 64 weeks ± 5 days after Visit 2.

The following will be performed and/or recorded in the eCRF:

- Withdrawal criteria (see section 6.6)
- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
• AEs since last visit (see section 12)
• Collect and review diabetes diary and dispense new diabetes diary (see section 8.4.2 and 14)
• Collect and review 3-day food diary (see section 5.3.3 and 8.4.3)
• Diet and physical activity counselling (based on the 3-day food diary)
• Provide collection cup for urine sample

Transcription from the diabetes diary:
• Any change in concomitant medication (see section 11)
• Hypoglycaemic episodes since last visit (see section 8.3.2)

Interact with the IV/WRS to:
• Complete withdrawal session, if applicable

Reminders
• An appointment for Visit 20 should be made 68 weeks ± 5 days after Visit 2
• Subjects should be advised to adjust their background type 2 diabetes treatment, at the discretion of the investigator
• Subjects should be reminded to:
  - Measure FPG on a regular basis, at the Investigator’s discretion (see section 8.2.4)
  - Complete their diabetes diary and return it at Visit 20 (see section 8.4.2 and 14)
  - Bring their glucose meter at Visit 20
  - Bring the urine sample at Visit 20
  - Attend Visit 20 fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water)
  - To withhold treatment with background medication on the day of Visit 20 until blood sampling has been done
  - Avoid caffeine, smoking and physical activity within 30 minutes prior to the blood pressure measurement at Visit 20
• Subjects should be reminded to record the following in their diabetes diary:
  – Changes in concomitant medication (see section 11)
  – Measurements of plasma glucose in any event(s) of hypoglycaemia or hyperglycaemia, including details about hypoglycaemia (see section 8.3.2)

8.1.23  Visit 20, follow-up/premature discontinuation after Visit 17
Visit 20 will take place 68 weeks ± 5 days after Visit 2.
Subjects discontinuing (leaving/being withdrawn from) the trial prematurely after Visit 17 should have procedures according to Visit 20 performed at their last visit, if possible.
The subject should attend the visit fasting (i.e., at least eight hours overnight fast without food and/or drink intake, except for water). If the subjects attend the visit without being fasting, a new appointment for blood sampling and body measurements should be made within the visit window.
The following will be performed and/or recorded in the eCRF:

- Concomitant medication (see section 11)
- Body measurements (see section 8.2.1)
- Vital signs (see section 8.2.6)
- Mental Health questionnaires (see section 8.3.10)
- AEs since last visit (see section 12)
- Collect and review diabetes diary (see section 8.4.2 and 14)
- Complete the EOT form

Transcription from the diabetes diary:

- Any change in concomitant medication (see section 11)
- Hypoglycaemic episodes since last visit (see section 8.3.2)

Blood sampling for measurements of:

- FPG (see section 8.2.3)
- Haematology and biochemistry (see section 8.3.5)

Urine sampling for measurements of:

- Urinary Albumin-to-Creatinine ratio (see section 8.2.10)

Interact with the IV/WRS to:

- Complete withdrawal session, if applicable
- Make completion call for subjects completing the trial

Reminders

- Subjects should be advised to adjust their background type 2 diabetes treatment, at the discretion of the investigator

8.2 Assessments for efficacy

The laboratory analyses for efficacy and safety will be outsourced to a Central Laboratory unless otherwise specified. Descriptions of assay methods, instrumentation and procedures for obtaining samples, handling and storage of samples will be described in a trial specific laboratory manual provided by the Central Laboratory.

Blood samples that are not drawn on the day of the scheduled visit may be drawn on another day at an additional visit (e.g. if the subject is not fasting), preferably within the visit window.

Samples will be coded with the intention that the subject’s identity will remain encrypted but information such as age, sex, race, health information and response to liraglutide will be correlated. The samples will only be used in relation to the present trial. Novo Nordisk and its representatives and/or regulatory authorities, may have access to this information. However, the subject’s identity will not be revealed.
Laboratory analysis results will be sent to the Investigator on an ongoing basis except for the results of liraglutide antibody analyses and liraglutide plasma concentration. All laboratory reports must be dated and signed by the Investigator on the day of evaluation. If a result is outside the normal range, the Investigator has to judge whether the abnormality is clinically significant or not (see section 12.1). The signed laboratory report is retained at the Investigator site as source documentation.

Any abnormal, clinically significant result identified at screening visit 1 will be recorded as concomitant illnesses.

### 8.2.1 Body measurements

Body measurements include weight, height and waist circumference.

#### 8.2.1.1 Weight and height

Weight will be recorded to the nearest 0.1 kg. Weight should be measured at all visits to the clinic using calibrated scales. At Visit 2, 3, 4, 5b, 7, 8, 10, 13, 15, 16, 16x, 17 and 20 the weight should be measured in the fasting state. If the weight is not measured fasting, the subject should be called in for a new visit within the visit window to have the fasting weight measured (see section 8.1). At the remaining visits the measurement will be performed in a non-fasting state.

The same pair of scales should be used throughout the trial. Weight should be measured with an empty bladder, without shoes and only wearing light clothing. Weight measured at Visit 1 will only be used for the Investigator’s calculation of BMI, whereas weight measured at Visit 2 will be used as baseline for assessment of change in body weight.

Height without shoes will be recorded at Visit 1.

BMI will be calculated as follows: $\text{BMI} = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$

#### 8.2.1.2 Waist circumference

Waist circumference will be determined in a fasting state at Visit 2, 3, 4, 5b, 7, 8, 10, 13, 15, 16, 17 and 20 and in a non-fasting state at the remaining visits according to the procedure below.

Three consecutive measurements will be performed at each visit and will be recorded in the eCRF. The waist circumference will be measured in the horizontal plane to the nearest 0.5 cm using a non-stretchable measuring tape.

Subjects should be measured in the standing position, with an empty bladder and wearing only light clothing. The measuring tape should lie flat against the skin without compressing the soft tissue and need to be removed between each measurement.

The observer should be sitting in front of the subject during the measurement. The subject should be standing with arms at their side and feet together. Subjects should be asked to breathe normally and the measurement should be performed when the subject is breathing out gently.
The waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest.

8.2.2 HbA1c

Samples will be drawn at Visit 1, 2, 4, 7, 10, 13 and 16 for measurement of HbA1c. The assay method used will be a National Glycohemoglobin Standardisation Program (NGSP) certified method.

8.2.3 Fasting plasma glucose

FPG will be determined from central laboratory analyses of blood samples drawn at Visits 2, 3, 4, 5b, 7, 8, 10, 13, 15, 16, 17 and 20.

8.2.4 Self-monitored fasting plasma glucose

Self-monitoring of PG will be performed using a glucose meter, supplied by Novo Nordisk. A sufficient amount of test strips and calibration solutions will be supplied together with the glucose meter.

The subjects will be instructed in the use of the device, and will also be provided with written instructions. The Investigator must ensure that the subject uses the glucose meter correctly. The instructions should include:

- Advice on regular calibration according to the manufacturer’s instructions
- Instruction in performing self-measurement of PG concentration

The glucose meters use test strips calibrated to plasma values. This means that all capillary blood glucose measurements performed with these glucose meters are automatically converted into plasma equivalent glucose values, which will be shown in the display. These values are to be used for evaluation purposes.

All subjects are encouraged to measure their FPG concentrations on a regular basis as agreed with the Investigator. Also subjects should measure their PG at least every time the subject has symptoms of hypoglycaemia or hyperglycaemia. Hypoglycaemic episodes should be recorded in the diary (see section 8.3.2). The Investigator may ask the subject to perform additional PG self-measurements if needed for any safety reason.

If self-measured FPG falls below 6.1 mmol/L (110 mg/dL), or from baseline to 6 weeks, increases above 15 mmol/L (270 mg/dL) or from 7 weeks to 12 weeks, increases above 13.3 mmol/L (240 mg/dL) or from 13 weeks to 56 weeks, increases above 11.1 mmol/L (200 mg/dL) on three consecutive days/occasions, the subject should contact the Investigator. The outcome of the contact will be recorded on an Unscheduled Visit Form in the eCRF.

8.2.4.1 7-Point plasma glucose profiles

Subjects will be instructed on how to perform a 7-point plasma glucose profile on a normal representative day (not on a day when they anticipate unusual strenuous physical activity) within a week prior to Visit 2, 10 and 16. The 7-point profile includes plasma glucose measurements at the following time points:

- Before each main meal (breakfast, lunch and dinner)
Subjects will be instructed how to record the results in the diabetes diaries provided. The record of each measurement should always include the date, actual time and plasma glucose value. The results entered into the diary will be transcribed to the eCRF at the following visit.

8.2.5 Glucose metabolism

Blood samples for determination of glucose metabolism will be taken at Visit 2, 10 and 16.

- Fasting glucagon
- Fasting insulin
- Fasting C-peptide
- Fasting pro-insulin

β-cell function (and insulin resistance) will be derived from FPG and fasting insulin data using the HOMA[16].

8.2.6 Vital signs

8.2.6.1 Blood pressure

Systolic and diastolic blood pressure will be measured at all visits to the clinic except for Visit 3 according to the procedure described in Appendix D.

8.2.6.2 Pulse

Pulse will be recorded after resting for five minutes in a sitting position at all visits to the clinic except for Visit 3.

8.2.7 Lipids

Blood samples for determination of cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, TG and FFA will be drawn in a non-fasting state at Visit 1 and in a fasting state at Visit 2, 10 and 16. When the blood sample is taken in a fasting state it is important that the subject has consumed only water at least 8 hours overnight prior to blood sampling.

8.2.8 Cardiovascular biomarkers

Samples for determination of selected cardiovascular biomarkers will be drawn in a fasting state at Visit 2, 10 and 16:

- hsCRP
- Adiponectin
- Fibrinogen
- PAI-1
8.2.9 Patient reported outcomes (PRO) questionnaires

PRO will be performed in France, Germany, Spain, Sweden, United Kingdom and USA. It will be assessed at Visit 2, 10 and 16 with the IWQoL-Lite and by the use of the DTSQs. The Binge Eating Scale questionnaire will be completed at Visit 2, 16 and 17 (see section 8.3.15).

Subjects discontinuing the trial prematurely before Visit 16 should complete the questionnaires at the end of treatment visit (Visit 16).

The questionnaires are validated and will be translated into local language before being handed out to the subjects participating in the trial. The questionnaires should preferably be completed before any trial related procedures and subjects should be given the opportunity to complete the questionnaires by themselves without interruption. The investigator or his delegate must review patient reported outcome(s) for completeness and AEs immediately following administration.

8.2.9.1 IWQoL-Lite

IWQoL-Lite provides an individual perception of impact of weight on physical function, self-esteem, sexual life, public distress, and work (21). The questionnaire contains 31 items and it takes approximately 10 minutes to complete.

8.2.9.2 Diabetes treatment satisfaction questionnaire

DTSQs is designed to assess the impact of treatment on subjects’ treatment satisfaction. Treatment satisfaction includes assessments of perceived frequency of hyperglycaemia, perceived frequency of hypoglycaemia, and satisfaction with treatment (22). It will take approximately 10 minutes to complete.

8.2.10 Urinary Albumin-to-Creatinine ratio

A urine sample will be taken at site visits 2, 10, 16, 17 and 20 for assessment of Urinary Albumin-to-Creatinine ratio. The subjects will receive materials to collect a sample of their morning urine on the visit prior to the above listed visits and will be asked to bring the sample to the site for central laboratory assessment.

8.3 Assessments for safety

8.3.1 Physical examination

Physical examination will be performed at Visit 1 and 16 according to local procedure. Physical examination should include the cardiovascular system, respiratory system, abdomen, central and peripheral nervous system, musculo-skeletal system and the thyroid gland.

Any abnormal, clinical significant findings at Visit 1 must be recorded as a concomitant illness (see section 11).

Any changes in subsequent visits as compared to Visit 1 which fulfil the criteria for an AE must be recorded as an AE (see section 12).
8.3.2 Hypoglycaemic episodes

Plasma glucose should always be measured when there is the suspicion of a hypoglycaemic episode. All plasma glucose (PG) values ≤ 3.9 mmol/L (70 mg/dL), as well as values > 3.9 mmol/L (70 mg/dL) when hypoglycaemic symptoms have occurred, should be recorded by the subjects in the diaries. Hypoglycaemic episodes will be recorded by the subject in his/her diary throughout the trial and must be transcribed into the eCRF by the Investigator at each site visit throughout the trial from randomisation (site visit 2) to follow-up (site visit 20). The recording should include:

- date of hypoglycaemic episode
- time of hypoglycaemic episode
- time of last trial drug prior to episode trial drug
- date and time of diabetes background treatment prior to episode
- time of last main meal prior to episode
- whether the episode was symptomatic
- whether the episode was in relation to exercise
- whether the subject was able to treat him-herself (if not answered, the Investigator must provide an explanation in the eCRF)
- if the subject was not able to treat him-herself, whether he-she recovered with oral administration of carbohydrates
- the plasma glucose level before treating the episode (if available)

The answer to the question: “Was subject able to treat him/herself?” should be answered “No” if oral carbohydrates, glucagon or intravenous 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 in case the subject is unconscious.

A hypoglycaemic episode will be defined as treatment emergent if the onset of the episode is on or after the first day of trial product, and no later than 14 days after the last day of randomised treatment.

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

A hypoglycaemic episode form and an AE form must be filled in for all hypoglycaemic episodes. If the hypoglycaemic episode fulfils the criteria for a serious AE and/or a MESI, a hypoglycaemic episode form, an AE form and a safety information form must be filled in according to section 12. Severe hypoglycaemic episodes will be recorded as MESIs.

Hypoglycaemic episodes will be summarised based on the ADA classification (23), and also according to an additional definition. Both ADA classification and the additional definition will be applicable to the statistical analysis of the confirmatory endpoints.

ADA hypoglycaemia classification

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.

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).

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).

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)).

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).

**Figure 8–1  Classification of hypoglycaemia**

**Additional definition**

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

**Minor hypoglycaemic episode** is defined as:
8.3.3 ECG 12 lead

ECG will be performed at visits 1, 10, 16 and 20. The ECG will be interpreted, signed and dated by the Investigator.

The interpretation must follow the categories:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

In case of an abnormal ECG, the Investigator must evaluate if the abnormal ECG fulfils the criteria of an AE or a SAE, and if so, should be reported as an AE or a SAE, respectively (see section 12).

An ECG taken within the period starting at Visit 1 and ending at the date of Visit 2 is acceptable. In addition, all ECG will undergo central assessment.

Sites will be informed of the central ECG evaluation in case this evaluation reveals an abnormal ECG reading. If the abnormality represents an unreported AE or SAE it must be reported by the Investigator.

8.3.4 Adverse events (AEs)

All AEs will be recorded at each visit after Visit 1 according to procedures described in section 12.

8.3.5 Haematology and biochemistry

Samples will be drawn in a non-fasting state at Visit 1 and in a fasting state at Visit 2, 4, 7, 10, 13, 16, 17 and 20 and will be analysed by the Central Laboratory. Calcitonin assessments will be made at Visit 1, 2, 4, 7, 10, 13, 16, 17 and 20.

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 additional data is specified in the trial specific laboratory manual. The investigator must review all laboratory results for concomitant illnesses and adverse events and report these according to this protocol.
Haematology

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

Biochemistry

- Creatinine
- Creatine kinase
- Urea
- Albumin
- Bilirubins, total
- ALAT
- ASAT
- Alkaline phosphatase
- Sodium
- Potassium
- Calcium, total
- Amylase
- Lipase
- Calcitonin
- TSH

For subjects with calcitonin \( \geq 20 \text{ ng/L} \) (from visit 2 onwards) a repeat measurement of calcitonin must be performed preferably within four weeks and if confirmed, the event “elevated calcitonin” should be reported as a MESI (i.e., any confirmed episode of calcitonin concentration value \( \geq 20 \text{ ng/L} \), if not already reported as a MESI, see section 12.2.1).

8.3.6 Pregnancy test

Females of childbearing potential will have a serum pregnancy test (hCG) performed in connection with Visit 1 (screening visit), Visit 16 (the end of treatment visit) and Visit 20 (the end of trial visit). Blood drawn for biochemistry will be used (see section 8.3.5).
Urine pregnancy tests will be performed for females of childbearing potential at any time during the trial if a menstrual period is missed or as required by local law. Urine pregnancy kits will be supplied by the Central Laboratory. The test will be performed at the site.

Pregnancy testing will not be required for women who have undergone a hysterectomy or bilateral tubal ligation, or for women above the age of 50, who have been without menses for at least 1 year.

8.3.7 Liraglutide antibodies

Blood samples for serum antibody against liraglutide will be drawn at Visit 2 and 17. For subjects discontinuing (leaving/being withdrawn from) the trial prematurely before Visit 16, the samples will be drawn at Visit 16 instead of Visit 17.

The sample drawn at baseline (Visit 2) will be analysed ongoing with the sample drawn at Visit 16 (only for subjects discontinuing)/Visit 17. Antibody analyses are done by use of a radioimmunoassay. All antibody positive samples will be further characterised for neutralising effect and cross reactivity to native GLP-1 and liraglutide. The neutralising effect of anti-drug antibodies is measured using a cell based assay.

8.3.8 Suspicion of Acute Hypersensitivity (allergic reaction) to Trial Product

If acute hypersensitivity to trial product is suspected, local testing for blood tryptase concentration (total and/or mature tryptase) is recommended.

If trial product is discontinued as a consequence of suspicion of acute hypersensitivity, blood sampling for central assessment of liraglutide antibodies and IgE-isotype of liraglutide antibodies should be conducted, at least 14 days after trial product discontinuation.

Tryptase concentrations (if measured) as well as results of liraglutide antibody and IgE-isotype liraglutide antibodies will be sent to Novo Nordisk and will be included in the final MESI report.

8.3.9 Suspicion of Immune-complex Disease

If immune-complex disease is suspected, blood sampling for central assessment of complement levels (C3 and C4) should be conducted. Results should be included when reporting a MESI.

8.3.10 Mental Health questionnaires

In recent years there has been increasing attention on the influence of seemingly innocuous changes in body chemistry on mental health, and even drugs thought to be largely free of mental effects are now seen as having the potential to affect mental health. Makers of drugs to treat obesity, urinary incontinence, epilepsy, smoking cessation, depression and many other conditions are being asked by regulators to put comprehensive mental health assessments into clinical trials. Therefore, even though liraglutide has not been associated with causing depression or suicidality two mental health questionnaires have been included in the present trial.
Mental Health will be assessed at all site visits by the use of C-SSRS and PHQ-9. Subjects discontinuing the trial prematurely before Visit 16 will complete the mental health questionnaires at Visit 16 (end of treatment visit).

The subject should be given the opportunity to complete the PHQ-9 questionnaire by themselves without interruption.

The investigator or his delegate must review the C-SSRS and PHQ-9 questionnaires for completeness and AEs immediately following administration.

### 8.3.10.1 C-SSRS

The C-SSRS is a detailed questionnaire assessing both suicidal behaviour and suicidal ideation. The questionnaire will be administered as an interview by the Investigator or a sufficiently trained and medically qualified delegate according to local law (14).

The Investigator must assess the C-SSRS score at Visit 1 (screening visit) and Visit 2 (randomisation visit) to exclude subjects with any suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) (see section 6.3).

### 8.3.10.2 PHQ-9

The PHQ-9 is a 9-item self-reported depression screening tool (24). The questionnaire takes approximately 10 minutes to complete.

The Investigator must assess the PHQ-9 score at Visit 1 (screening visit) and Visit 2 (randomisation visit) to exclude subjects with a major depression (PHQ-9 score $\geq 15$) (see section 6.3).

The investigator or his delegate must review the PHQ-9 questionnaire for completeness and AEs immediately following administration.

### 8.3.11 Thyroidectomy Pathology Slides

In case a subject undergoes a thyroidectomy (partial or total) for any reason during the trial, pathology slides of the thyroid tissue will be centrally reviewed in addition to the routine examination at the site level. Both the site pathology report and the central pathology report will be reviewed by an independent Event Adjudication Committee (EAC), see section 12.2.2. A set of pathology slides routinely made after thyroidectomies by the pathology laboratory of the hospital where the operation was performed will be sent centrally for a second reading by a pathologist with expertise in thyroid and C-cell pathology, who will be blinded to both trial treatment and site diagnosis. Once the samples are re-examined they will be sent back to the site laboratory.

The investigator will be informed of the second pathology report, in order to take appropriate action (e.g. in case of a difference to the diagnosis of the site pathology)
8.3.12 Thyroid Tissue Sample Collection in Case of Thyroidectomy

Subjects scheduled for thyroidectomy will be asked to inform the Investigator prior to their operation. These subjects will be asked to consent to have a small sample of the removed thyroid tissue collected for testing of RET Y1062 phosphorylation in the thyroid C-cells. This is only applicable if C-cell pathology is confirmed (i.e., hyperplastic or neoplastic thyroid C-cells), and only if allowed by local law. The tissue sample will be destroyed after examination.

8.3.13 Genetic Testing in case of Confirmed C-cell Pathology

Subjects scheduled for thyroidectomy will be asked to consent to be tested (blood sample) to identify germline RET gene mutations associated with MEN 2 syndrome. This RET gene mutation detection will be conducted in subjects with pathology reports confirming C-cell abnormality (medullary carcinoma or C-cell hyperplasia). Genetic testing will only be performed if allowed by local law and if the subject chooses to consent to it.

8.3.14 Eye examination

Fundoscopy/fundusphotography will be performed preferably at Visit 1 but at the latest before Visit 2 by the Investigator, a local Ophthalmologist or an Optometrist according to local practice. Result of the fundoscopy/fundusphotography will be interpreted locally by the Investigator in relation to the trial. To document this, the Investigator must sign and date the result page. The interpretation must follow the categories:

- “Normal”
- “Abnormal, not clinically significant”
- “Abnormal, clinically significant”

In case of an “abnormal, clinically significant” fundoscopy/fundusphotography, the Investigator must comment in the subject notes and withdraw the subject if exclusion criterion no. 6 (known proliferative retinopathy) is fulfilled.

If a fundoscopy/fundusphotography has been performed within eight weeks before the screening visit (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/fundusphotography. If the fundoscopy/fundusphotography is performed before the subject has signed the informed consent form, it must be documented in the subject notes that the reason for performing the procedure was not related to this trial.

The date of Fundoscopy/fundusphotography must be recorded in the eCRF and be source data verifiable.

8.3.15 Binge Eating Scale questionnaire

The binge eating scale questionnaire is a 16-item self-report diagnostic tool designed to capture both the behavioural and emotional characteristics of binge eating (16-18). It takes approximately 10 minutes to complete the questionnaire.
Subjects discontinuing the trial prematurely before Visit 16 should complete the questionnaires at the end of treatment visit (Visit 16).

The investigator or his delegate must review patient reported outcome(s) for completeness and AEs immediately following administration.

8.4 Other assessments

8.4.1 Smoking habits

At the screening visit (Visit 1) it should be recorded whether the subject is a smoker.

8.4.2 Diabetes diary

A diabetes diary will be handed out to the subjects at Visit 1 to 19. From Visit 2 to Visit 20 the Investigator should collect and review the diaries.

The Investigator should ask the subjects to report the following in the diabetes diary:

- Date of first dose of randomised treatment
- Concomitant medication (dosage changes and new medications) (see section 11)
- Hypoglycaemic episodes (see section 8.3.2)
- 7-point plasma glucose profile (only before Visit 2, 10 and 16) (see section 8.2.4)

8.4.3 3-day food diary

A 3-day food diary will be handed out to the subjects at Visit 1, 4, 6, 8, 10, 12, 15 and 18. Subjects will be instructed by the dietician to register food intake. The dietician should collect and review the diaries. The diary will be used for diet counselling at Visit 2, 5b, 7, 9, 11, 13, 16 and 19.

8.4.4 Dietary compliance and physical activity

The subject’s dietary compliance and the average daily level of physical activity will be recorded every second month at Visit 2 (only average daily level of physical activity), 5b, 7, 9, 11, 13, 16 and 19. The subject will be questioned whether they performed less than half an hour, between half an hour and one hour or more than 1 hour of physical activity per day. An increase in physical activity (recommended minimum 150 minutes/week) will be encouraged and re-enforced by use of pedometers.

Whether or not the subject is in compliance with the prescribed diet is at the discretion of the dietician after review of the 3-day food diaries.

8.4.5 Liraglutide concentration (population PK)

A single blood sample for measurement of plasma liraglutide concentration will be drawn at Visit 3 (dose escalation period), Visit 6 and 10 (maintenance period). The PK assessments will be performed in a fasting state at Visit 3 and Visit 10 and in a non-fasting state at Visit 6. Subjects will be instructed to note the exact date and time of administration, injection site and the dose of liraglutide/liraglutide placebo of the 3 doses
immediately prior to Visit 3, 6 and 10. Injection site, date and time of administration and the dose will be
recorded in the eCRF. Diaries will be used to capture information on the injection date and time, dose as well
as injection site. Exact date, time and injection site of liraglutide/ liraglutide placebo will be transcribed from
the diaries into the eCRF. The date and actual time of blood sampling for the measurement of the liraglutide
plasma concentration should also be recorded in the eCRF at each visit (Visit 3, Visit 6 and Visit 10).

A special laboratory will be responsible for the analysis of the liraglutide plasma concentration. Blood
samples for liraglutide plasma concentration are collected, treated and shipped according to the description in
the laboratory manual supplied by the special laboratory. Samples will be analysed on an ongoing basis
during the trial. Codes with the randomisation number containing information about treatment for the
particular subject will be available to the special laboratory. Novo Nordisk, Investigator and subject will
remain blinded to the treatment until after database lock.

8.4.6 History of diabetes complications

Information related to microvascular complications of diabetes, (i.e. Diabetic retinopathy, Diabetic
neuropathy, Diabetic nephropatly (including Microalbuminuria), Diabetic Macroangiopathy, Foot ulcer) will
be recorded in the eCRF at Visit 1.

8.4.7 History of Concomitant Cardiovascular Disease

Information related to concomitant cardiovascular disease (i.e., myocardial infarction, disorders of rhythm or
conduction, heart failure incl. NYHA class, ischemic heart disease incl. type, PCI and CABG, left ventricular
systolic dysfunction, left ventricular diastolic dysfunction, hypertension, ischemic stroke, transient ischemic
attack, hemorrhagic stroke, intracranial artery stenosis, carotid artery stenosis, peripheral arterial disease incl.
> 50% stenosis on angiography or other imaging) will be recorded in the eCRF at Visit 1.

8.4.8 History of Gallbladder Disease

Information related to gallbladder disease will be recorded in the eCRF at Visit 1.

8.4.9 History of Psychiatric Disorders

Information related to psychiatric disorders (specifically history of depression, suicidal behaviour, anxiety,
mood disorders, insomnia, or other sleep disorders) will be recorded in the eCRF at Visit 1.

8.5 Subject compliance

The Investigator will at each visit remind the subject to follow protocol procedures.

At Visit 4 and 5b-16 (including the end of treatment visit, early discontinuation visit or any unscheduled visit
when drug accountability is performed) the subject will return their partly used or unused trial products
including all empty packaging material. The Investigator will assess the amount of trial product returned
compared to what was dispensed at the last dispensing visit, and ask the subject if the trial product has been
used as prescribed.
If a subject is discovered to be non-compliant, the Investigator should counsel the subject on the importance of taking trial products as directed. Failure to comply can ultimately lead to withdrawal from the trial. This must always be preceded by discussions with and approval by Novo Nordisk.
9   Trial supplies

Procedures for supply, handling and storage of trial materials will be described in a separate Trial Materials Manual (TMM) provided by Novo Nordisk.

The trial products will be dispensed to each subject as required according to treatment group. The IV/WRS will allocate trial product DUN to the subject at each dispensing or randomisation visit. The correct DUN must be dispensed to the subject.

9.1   Trial product(s)

The administration of liraglutide/liraglutide placebo will be as outlined in section 5.3.

The following trial products will be supplied by Novo Nordisk, Denmark.

- Liraglutide 6.0 mg/mL, 3 mL FlexPen® for subcutaneous (s.c.) injection
- Liraglutide placebo 3 mL FlexPen® for subcutaneous (s.c.) injection

9.2   Packaging and labelling of trial product(s)

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

Labelling will be in accordance with Annex 13, local law and trial requirements.

Each investigator site will be supplied with sufficient trial products for the trial on an ongoing basis controlled by the IV/WRS.

Dispensing units will be prepared and distributed to the sites according to enrolment. Please refer to the TMM provided by Novo Nordisk for details regarding trial products standard packages.

The Investigator will provide each subject with a direction for use for liraglutide FlexPen® at each drug dispensing visit.

9.3   Storage and drug accountability of trial product(s)

The Investigator must keep track of all received, used, partly used and unused trial products by the use of the drug accountability module in the IV/WRS.

Store in a refrigerator (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze liraglutide/liraglutide placebo and do not use liraglutide/liraglutide placebo if it has been frozen.

Liraglutide/liraglutide placebo should not be used if it does not appear clear and colourless.
After first use of the liraglutide/liraglutide placebo pen, the product can be stored for 1 month at room temperature (below 30°C) or in a refrigerator (2°C to 8°C).

US: 30 days at room temperature (+15°C to +30°C)/(59°F to 86°F) or in a refrigerator (+2°C to +8°C)/(+36°F to +46°F)

Keep the pen cap on when liraglutide/liraglutide placebo pen is not in use in order to protect from light. Liraglutide/liraglutide placebo should be protected from excessive heat and sunlight.

Always remove the injection needle after each injection and store the liraglutide/liraglutide placebo pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate.

No trial product which has exceeded the expiry date must be used.

The Investigator must ensure the availability of proper storage conditions and record and evaluate the temperature. The temperature must be recorded and evaluated on a daily basis (working days) using as a minimum a calibrated min/max thermometer. A log to document the temperature must be kept. For sites using Elpro Libero storage device a weekly (work week) manual handwritten log must be maintained to confirm by signature and date that the storage temperature is within the acceptable ranges, plus a monthly print out of the loggings (graph/data) must be reviewed, signed and dated.

Storage facilities should be checked frequently (at least once every working day).

In case of incorrect storage the Investigator or site staff must contact the monitor without delay. Trial product must be set on-hold and not dispensed to subjects until notified by the monitor.

No trial product(s) should be dispensed to any person not enrolled in the trial and the IV/WRS should always be contacted when dispensing trial product(s).

Returned trial product(s) (partly used or unused including empty packaging material) must be stored separately from non-allocated trial product(s) until the monitor has performed drug accountability. The monitor will be responsible for retrieval of trial products from the site. Destruction of trial products will be done according to local laws and will be recorded on a Destruction Form, which must be signed by the person responsible for destruction, as agreed with the monitor.

### 9.4 Auxiliary supply

Novo Nordisk will provide the following auxiliary supplies: NovoFine® needles, blood glucose meters (Abbott Diabetes Care), lancets, test strips control solution and pedometers.

For further details please refer to the TMM.
Randomisation, breaking of blinded codes and interactive voice/web response system (IV/WRS)

10.1 Randomisation

Randomisation to the liraglutide 3.0 mg arm, the liraglutide 1.8 mg arm and the liraglutide placebo arm will be carried out in a 2:1:1 manner, respectively. The placebo arm will be further subdivided into two arms with different injection volumes corresponding to the different dose levels of liraglutide i.e. subjects will be randomised to four treatment groups. The trial is a double-blinded trial.

The treatment will be allocated in a centralised manner via the IV/WRS system and will be stratified according to background treatment (see section 5.1) and baseline HbA1c (see section 5.1).

Subjects randomised in the trial will continue with the subject number allocated at screening.

10.2 Breaking of blinded codes

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

If the trial site needs to break the code, Novo Nordisk should, if possible, be contacted prior to breaking the code. Novo Nordisk (Monitor and department responsible for global product safety) will be notified immediately after the code break by the IV/WRS.

If the subject should be withdrawn following a code break, a withdrawal session should be completed in IV/WRS.

When code is broken the treatment allocation will be accessible to the Investigator and the department responsible for global product safety, Novo Nordisk.

In case IV/WRS is not accessible at the time of code break the IV/WRS vendor helpdesk should be contacted.

10.3 Interactive voice/web response system (IV/WRS)

A trial specific IV/WRS will be set-up, and can be accessed at any time by the internet. Some sessions may be available through a toll-free telephone number. Accessibility to the IV/WRS must be restricted to and controlled by authorised persons.

IV/WRS is used for:

- screening
- screening failure
• randomisation
• dispensing
• medication arrival
• withdrawal
• completion
• code break
• drug accountability
• live data change

An IV/WRS user manual will be provided to the trial site.
11 Concomitant illnesses/Medical history and concomitant medication

Definitions:

Concomitant illness: any illness that is present at the start of the trial (i.e. at the first visit).

Medical history: any relevant medical history which is not present at the start of the trial as judged by the Investigator.

Concomitant medication: any medication other than the trial product(s) that is taken during the trial, including the screening period.

Details of all concomitant illnesses and medication must be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication must be recorded at each visit. 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 then the Monitor must be informed.

The information collected for each concomitant medication includes, at a minimum, start date, stop date or continuing and indication.

Proportion of subjects with change in concomitant medication from baseline to Week 56 in:

- Anti-hypertensive agents
- Lipid-lowering agents
- Oral-antidiabetic drugs
12 Adverse events and Pregnancies

12.1 Definitions

Adverse event (AE):

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

Note: This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol (the period from Visit 16 – End of treatment to Visit 20 – End of trial).

The following should not be recorded as AEs:

- 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.
- Pre-existing conditions found as a result of screening procedures. These should be recorded as medical history/concomitant illness.

An AE can also be a clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity which requires active management (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

A worsening in concomitant illness must be recorded as an AE. A worsening of an ongoing AE should be reported on a new AE form by making a new assessment for seriousness and/or severity.

Serious adverse event (SAE):

A Serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening* experience
- In-subject hospitalisation* or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity*
- A congenital anomaly/birth defect
- Important medical events* that may not result in death, be life-threatening*, or require hospitalisation may be considered an SAE when, based upon 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.
* 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 were more severe.

* The term “hospitalisation” is the definition of a subject admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but 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 neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

* The term “disability/incapacity” means that following the event the subject or clinical investigation subject has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life.

* The term “important medical events” means events which may jeopardise the subject or require intervention to prevent a seriousness criterion. It can be adverse events which suggest a significant hazard or put the subject or clinical investigation subject at risk, such as drug-interactions, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.

**Non-serious adverse event:**

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

**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

**Relationship to trial product (liraglutide and liraglutide placebo) assessment definitions:**

- Probable: good reasons 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 an aetiology other than the trial product

**Outcome categories and definitions:**

- **Recovered** - 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** - The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- **Recovered with sequelae** - As a result of the AE the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). If the sequelae meet seriousness criteria, the AE must be reported as an SAE.
12.1.1 Technical complaints

A technical complaint is any written, electronic, or oral communication that alleges defects on trial products - listed as trial products in this protocol (9.1). The technical complaint may be associated with an AE, but does not concern the AE itself.

A technical complaint may for example concern:

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

12.2 Collection, recording and reporting of adverse events

All events meeting the definition of an AE must be collected and reported. At each contact with the trial site (visit or telephone, excluding safety visits, where the subject is not seeing the Investigator or his staff [e.g. visits to the laboratory]), the subject must be asked about adverse events. The subject will be asked about AEs in the following manner: “Have you experienced any problems since the last contact?”. All AEs, either observed by the Investigator or reported by the subject, must be recorded by the Investigator and evaluated.

Novo Nordisk’s assessment of expectedness is done according to the reference documents:

- Liraglutide obesity: IB, 3rd edition, 2010 or any updates hereof

The Investigator should record the diagnosis, if available. If no diagnosis is available the Investigator should record each sign and symptom as individual adverse events.

All AEs, SAEs and MESIs must be recorded by the Investigator on the AE Form in EDC. If more than one sign or symptom is to be reported, create a separate adverse event form for each sign and symptom.

For SAEs and MESIs, the SIF pages also have to be completed for each event in the eCRF. However if several symptoms or diagnosis occur as part of the same clinical picture, only one set of SIF can be used to describe all the SAEs. All concerned AE numbers must be included in the AE number field in the header of the SIF.

For MESIs, the specific MESI follow-up questions have also to be completed in the eCRF. For MESIs qualifying for adjudication, the Source Data Collection Tool has also to be completed in the eCRF.
The Investigator must report initial information on all SAEs and MESIs to Novo Nordisk within 24 hours of obtaining knowledge about the event by completing the following in EDC:

- AE form
- SIF

The investigator must sign the relevant AE form and SIF within 7 calendar days after entering/updating the AE form and SIF for SAEs and MESIs

The specific MESI follow-up questions and source data collection tool also have to be completed if applicable.

If for any reason the EDC application is unavailable, complete the AE form, SIF and if applicable the specific MESI follow-up questions and Source Data Collection Tool on paper CRFs and forward a copy electronically in PDF format by e-mail, or by fax or courier to Novo Nordisk within the same timelines.

The Investigator/Novo Nordisk must inform the regulatory authorities and independent ethics committee (IEC)/institutional review boards (IRB) in accordance with the local requirements in force and International Conference on Harmonisation Good Clinical Practice (ICH GCP) (25).

Novo Nordisk will notify the Investigator of trial product related suspected unexpected serious adverse reactions in accordance with the local requirements (e.g. European Directive 2001/20/EC and International Conference on Harmonisation/Good Clinical Practice [ICH GCP (25)]). In addition, the Investigator will be informed of any trial related procedure SAE which may warrant a change of any trial procedure.

Investigators will be notified of trial-related SAEs in accordance with the local requirements in force and ICH GCP (25).

The monitor must be informed accordingly.

### 12.2.1 Medical events of special interest

A medical event of special interest (MESI) (serious or non-serious) is a noteworthy event of scientific and medical concern that Novo Nordisk continues to monitor.

A MESI does not necessarily have a causal relationship with the Investigational Medicinal Product (IMP).

A MESI should be reported following the same reporting requirements and timelines as for SAEs (see section 12.1), irrespective of the MESI fulfils a SAE criterion.

The following are defined as MESIs in this trial (see Appendix H for further definitions)

- Medication errors concerning trial products
  - administration of wrong drug or use of wrong device
  - 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, i.e. dose which may lead to significant health consequences, as judged by the Investigator, irrespective of whether the SAE criteria are fulfilled or not.

- Suspected transmission of an infectious agent via a trial product
- Death (if not already reported as a cardiovascular MESI)
- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischemic attack)
- Heart failure
- Stent trombosis
- Revascularisation procedure
- Hospitalisation for cardiac arrhythmia
- Pancreatitis or acute, severe, persistent abdominal pain leading to a suspicion of pancreatitis
- Acute gallstone disease (biliary colic or acute cholecystitis)
- Elevated lipase or amylase $\geq 3 \times \text{UNR}$ reported as result of protocol-scheduled visits: Should always be reported as separate MESI, even if followed by diagnosis of pancreatitis (i.e. event/diagnosis not to be updated, new event to be filed)
- Neoplasms (if thyroid neoplasm select Thyroid disease MESI)
- Thyroid disease
- Any confirmed episode of calcitonin value $\geq 20 \text{ ng/L}$ (from Visit 2 and onwards)
- Acute renal failure
- Severe hypoglycaemic events
- Immunogenisity event (allergic reactions including allergic reactions at injection sites, or immune-complex disease)
- AEs leading to withdrawal (if not already reported as any of the listed MESIs)
- Psychiatric Disorders (including psychiatric disorders diagnosed by C-SSRS and PHQ-9 questionnaires)

All events confirmed or suspected to be a MESI must be reported. Additionally, in case the sponsor identifies potentially missed MESIs through predefined review of available data, the Investigator will be asked to reconsider if this is a MESI.

Some events might apply to more than one MESI category. Medical judgement should be exercised when choosing which MESI form to fill out.

For subjects with calcitonin $\geq 20 \text{ ng/L}$ (from visit 2 and onwards) a repeat measurement of calcitonin must be performed preferably within four weeks and if confirmed, the event “elevated calcitonin” should be reported as a MESI (i.e., any confirmed episode of calcitonin concentration value $\geq 20 \text{ ng/L}$, if not already reported as a MESI).

For details on how increased calcitonin levels at follow-up visits should be reported and followed up, please refer to Appendix H for reporting of MESIs and Appendix I describing how the Calcitonin Monitoring Committee works.
In addition the following rules for increased lipase and/or amylase apply:

If the amylase or lipase baseline (at screening) value is > 3xUNR this information will be recorded as medical history for that subject. If at any post baseline visit the amylase or lipase value is > 3xUNR a MESI should be reported.

If the patient is diagnosed with a thyroid neoplasm only the “Thyroid disease” MESI form has to be filled out and not the “Neoplasm” MESI form.

Revascularisation procedures and stent thrombosis’ should always be reported as separate AEs and captured separately on the respective MESI forms.

For all SAE(s)/MESI(s) with a fatal outcome the MESI form “Death” should be filled out unless the death is caused by a cardiovascular MESI. In this case only the cardiovascular MESI should be filled out. If death is a consequence of a cardiovascular MESI previously reported this MESI should be updated with the outcome death.

Certain MESIs will be adjudicated by an external independent event adjudication committee as described in section (12.2.2). For further information regarding definitions of MESIs and an overview of which events that should undergo adjudication, please refer to Appendix H.

Complete the AE form, Safety Information Form (SIF), specific MESI follow-up questions and if applicable Source Data Collection Tool in the eCRF within 7 calendar days.

If for any reason the electronic data capture (EDC) application is unavailable, complete the AE form, SIF, specific MESI follow-up question and if applicable Source Data Collection Tool on paper CRFs and forward a copy electronically in PDF format by e-mail, or by fax or courier to Novo Nordisk within 7 calendar days.

### 12.2.2 External independent event adjudication committee

An external independent Event Adjudication Committee (EAC) is constituted for this trial to perform ongoing adjudication, standardisation and assessment of events listed in Appendix H.

The following events, except for screening failures, (also described in 12.2.1 under MESIs) will be adjudicated and evaluated by the EAC in an independent and blinded manner:

- Death
- Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina)
- Cerebrovascular event (stroke or transient ischemic attack)
- Heart failure requiring hospitalisation
- Stent thrombosis
- Coronary revascularisation procedure
- Pancreatitis or acute, severe, persistent abdominal pain leading to a suspicion of pancreatitis
- Neoplasms
- Thyroid disorders requiring thyroidectomy
The EAC is composed of permanent members who cover required medical specialties. The EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk.

The EAC works in accordance with written guidelines included in the EAC Charter that describes in detail the composition, tasks, responsibilities, and work processes of the committee. The charter will be finalised prior to first patient first visit.

The EAC will perform adjudication based on the criteria and definitions described in the EAC Charter. The cardiovascular events will be classified according to FDA requirements (26).

The EAC will review translated copies in English of medical documentation received in the adjudication packages (for example X-ray, ECGs, ultrasound images, discharge summaries, pathology reports, and death certificates). The Investigator will provide them as soon as possible, when they receive the request from Novo Nordisk.

The role of the EAC is solely to adjudicate events in a blinded manner. The EACs will have no authorisation to impact on trial conduct, trial protocol and amendments.

The assessments made by the EAC will be included in the CTR as well as assessments made by the Investigator. However, the adjudication made by an EAC, given its independence and in-depth analysis of each event, will be attributed with greater importance of the two. The outcomes of adjudication will be kept in the Global Safety database as well as in the clinical trial database.

### 12.3 Follow-up of adverse events

During and following a subject’s participation in a clinical trial, the Investigator/institution should ensure that adequate medical care is provided to the subject for any adverse events, including clinically significant laboratory values related to the trial. The Investigator/institution should inform the subject when medical care is needed for adverse event(s) of which the Investigator becomes aware.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator’s signature.

Follow-up information (corrections, new or additional information) should be reported within 24 hours of obtaining knowledge of the information for SAEs and MESIs, and if previously non-serious AEs become SAEs by updating the AE form and/or SIF in the eCRF.

All non-serious AEs classified as severe or possibly/probably related to the trial product must be followed until the subject has “recovered” or “recovered with sequelae” and all queries have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (i.e., subject dies from another AE) can be closed with an outcome of “recovering” or “not recovered”. Cases can be closed with an outcome of “recovering” when the subject has completed the post-trial follow-up period and is expected by the Investigator to recover.
All other 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 post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. AEs ongoing at time of death (i.e. subjects dies from another AE) can be closed with an outcome of “recovering” or “not recovered”.

The Investigator must ensure that the worst case severity and seriousness is kept consistent.

The Investigator must record follow-up information on non-serious adverse events by updating the adverse event form in the eCRF. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator’s signature.

Queries or follow-up requests from Novo Nordisk should be responded to within 7 calendar days, unless otherwise specified. This must be done by updating the AE form and/or SIF in the eCRF. If for any reason EDC/eCRF application is unavailable, then the relevant paper forms have to be filled in, marked as follow-up and forwarded by fax or e-mail to Novo Nordisk within the same timelines.

When a MESI of a specific category occurs for the first time in the subject and is selected on the AE form, the predefined follow-up section for that MESI category is automatically activated in the EDC. Each of these sections have follow-up forms related to the reported MESI, and the forms should be considered as a follow-up request from Novo Nordisk, and should therefore also be responded to within 7 calendar days from the date of awareness of the MESI.

For MESIs qualifying for adjudication, the Source Data Collection Tool has to be completed in the eCRF within 7 calendar days.

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 or cancer or AEs ongoing at time of death (i.e the subject dies form another AE) can be closed with the outcome of “recovered” or “not recovered”. Cases can be closed with an outcome of “recovering” when the subject has completed the trial and is expected by the Investigator to recover.

After access to update the AE form and SIF in EDC is removed the Investigator must record any SAE and MESI follow-up information, if required, on the paper CRFs provided at trial closure.

### 12.3.1 Collection and reporting of technical complaints

All technical complaints as defined in section 12.1.1 - occurring from the time of first and until the last usage of trial product - must be collected and reported to Novo Nordisk.

The subject must be asked about technical complaints during each contact (site visit or telephone contact) with the Investigator or trial site staff. This may be done by posing a simple question such as “have you experienced any problems since the last contact?”.

The Investigator must assess whether the technical complaint is related to:
- AE(s), SAE(s) and/or MESI(s)
The AE(s), SAE(s) and MESI(s) related to technical complaint(s) must be reported by the Investigator following the same reporting requirements and timelines as for other AEs, SAEs and MESIs (see section 12.1).

Technical complaints must be reported on the technical complaint form by the Investigator, as described in the following:

- One technical complaint form must be completed for each trial product, non-investigational medicinal product (NIMP) or auxiliary supply. 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 the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- technical complaint assessed as related to a SAE and/or MESI within 24 hours
- all other technical complaints within 5 calendar days

If the eCRF is unavailable, the paper technical complaint form should be completed and faxed to Customer Complaint Center, Novo Nordisk, fax: +45 44 42 13 70, within the same timelines as for eCRF.

12.3.2 Collection, storage and shipment of technical complaint samples

The Investigator must collect the technical complaint sample from the subject. If the technical complaint sample is unobtainable, the Investigator must specify on the technical complaint form why it is unobtainable.

The technical complaint sample and a paper copy of the technical complaint form must be sent to Novo Nordisk within 5 calendar days of receiving the technical complaint sample at trial site by using the following address:

Novo Nordisk, Att.: Customer Complaint Center, Nybrovej 80, 2820 Gentofte, Denmark.

The Investigator must ensure that the technical complaint sample is labelled with the batch number and, if available, the DUN number.

Storage and shipment of the technical complaint sample should be done in accordance with the conditions prescribed for the product (see section 9).

12.4 Pregnancy

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

The Investigator must report any pregnancy reported during the trial to Novo Nordisk except for pregnancies occurring in the screening period. Trial subjects will give consent on enrolment that the Investigator will report any pregnancy during the trial to Novo Nordisk and they will be asked to provide information about the pregnancy, delivery and the health of her infant until one month of age. The Investigator must report
information on pregnancy and follow-up within 14 calendar days of obtaining the information using the pregnancy form part A and the pregnancy form part B respectively. Prior to asking for any data on the female subject’s male partner a ‘male partner consent’ must be obtained. If the pregnancy results in an abnormal outcome, such as congenital anomalies, foetal death, spontaneous abortion, or SAE in the neonate, this should be regarded as an SAE with the same reporting requirements and timelines as for SAEs.

If an SAE occurs in relation to a pregnancy, either to the mother or the newborn, then follow the same reporting requirements and timelines as for SAEs.

Complete the AE form and SIF in the eCRF.

If for any reason the EDC/eCRF application is unavailable, then the relevant paper forms have to be completed and forwarded by fax or email to Novo Nordisk.

(Only applicable to US: 12.4.1 Pregnancies in Partners of Trial Subjects.

In case of an SAE (with a causal relationship evaluated as possible or probable by the Investigator) in the foetus, 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, a “pregnant partner consent” must be completed by the male subject’s partner.)

12.5  Precautions/over-dosage

There is one overdose report for liraglutide. A male subject accidentally administered 17.4 mg of liraglutide instead of the prescribed 0.6 mg. The subject recovered with no intervention and no lasting sequelae was seen. Please refer to liraglutide obesity IB, 3rd edition 2010 or any updates hereof.

When initiating treatment with liraglutide, the subject may in some cases experience loss of fluids/dehydration, eg in cases of vomiting, nausea or diarrhoea. It is important to avoid dehydration by drinking plenty of fluids.

12.6  Safety committee

12.6.1 Internal 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 (all haematology and biochemistry results including calcitonin, amylase and lipase).

The safety committee may recommend unblinding of any data for further analysis. If so, an independent ad hoc group will be established to maintain the blinding.
12.6.2 Calcitonin Monitoring Committee

Monitoring of calcitonin in regular intervals will be implemented in the trial. Algorithm of further clinical and laboratory evaluation, supervised by an independent committee of thyroid experts (Calcitonin Monitoring Committee) will be recommended to be followed in all subjects with clinically relevant abnormal calcitonin values. This algorithm has been developed in collaboration with leading independent experts in thyroid/C-cell disease. In cases where the follow-up action recommended by the CMC, based on the elevated calcitonin levels results in establishing the presence of a thyroid disease, the thyroid disease should be reported as a new MESI. If the thyroid disease is a neoplasm or result in a thyroidectomy, the event will undergo adjudication by the neoplasm EAC.
13 Case report forms

Novo Nordisk will provide a system for electronic data capture (EDC). This system and support services to the system will be supplied by a clinical services vendor Phase Forward. The activities of this vendor will be under the direction and supervision of Novo Nordisk.

13.1 Rules for completing eCRFs

Ensure that all relevant questions are answered and that no empty data blocks exist.

If a test/assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable) indicate this according to the data entry instructions.

The Investigator or Investigator’s authorised staff must ensure that all information derived from source documentation is consistent with the source information. By signing the Case Book sign off electronically, the Investigator confirms that the information is complete and correct.

13.2 Corrections to eCRFs

Corrections to the eCRF data will be made by the Investigator or the Investigator’s authorised staff. An audit trail will be maintained in the EDC application containing as a minimum: 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 of the Investigator’s signature on the Case Book sign off, the form must be signed again by the Investigator.

13.3 eCRF flow

The Investigator must ensure that data is recorded in the eCRFs as soon as possible after the visit, preferably within 3 business days. When data is entered it will be available to Novo Nordisk for data verification activities.

The Investigator will receive the laboratory results directly from the central laboratory. The Investigator must review, sign and date the laboratory report on the day of evaluation. The signed laboratory report is retained by the site as source documentation.

At the end of trial the Investigator must ensure that all remaining data have been entered into the eCRF no later than 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 site after the trial database is released and access to update the trial data on the EDC application is removed. This data will be retained by the site.
When the final clinical trial report 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 source data verification and to monitor drug accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. Factors to be considered in this determination may include objective, purpose, design, complexity, blinding, size, and endpoint for the trial. The intervals between visits should not exceed 12 weeks. The Monitor must visit the site shortly after the first subject has attended Screening visit 1 to ensure that mistakes are caught early. Hereafter the intervals between visits should not exceed 12 weeks However, more frequent monitoring visits are required during peak periods such as recruitment period and finalisation of the trial.

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 evaluation of the clinical trial. In addition, the monitor should be available for discussions by telephone.

The Monitor must ensure that all required eCRF forms for screening failures are completed, (eg screening failure form and that the case book sign off (affirmation statement) is electronically signed by the Investigator).

As a minimum requirement the following data must be source data verifiable in source documentation other than the eCRF:

- Existence of subject (subject identifier; subject number and date of birth)
- Confirmation of participation in the trial (subject identification number [ID], trial ID and signed and dated informed consent form)
- Date of diagnosis of type 2 diabetes
- Visit dates
- Data from:
  - Adverse event form(s)
  - Safety information form(s)
  - Pregnancy form(s)
- Relevant medical history, concomitant illness
- Diabetes treatment including trial product
- Reason for exclusion or withdrawal
- Body weight

For all data recorded the source document must be defined in a source document agreement at each site.
The source data must reflect/document the dose regimen, but not the full drug accountability.

The following data can be recorded directly on the CRFs and will be considered source data:

- PRO questionnaires (IWQoL, DTSQs, BES)
- Mental health questionnaires (PHQ-9, C-SSRS)

For all other data in the eCRFs, it must be possible to verify these against source documents. The monitor will ensure that the eCRFs are completed.

The subjects’ diaries will be collected after each visit and must be kept as source data by the Investigator for verification of the following items:

- The date of first and last dose of administration of liraglutide/liraglutide placebo
- Concomitant medication
- 7-point plasma glucose profiles
- Hypoglycaemic episodes
15 Data management

Data management is the responsibility of Data Management, Novo Nordisk Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk.

The subject and the biological material obtained from the subject will be identified by subject number, trial site and trial identification number. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements.

Appropriate measures such as encryption of data files will be used to assure confidentiality of subject data when it is transmitted over open networks.

Laboratory data will be transferred electronically from the central laboratory performing clinical analyses. The electronic laboratory data will be considered source data. In cases where laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.
16 Computerised systems

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

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

The following analysis sets are defined:

**Full analysis set (FAS)**

All randomised subjects exposed to at least one dose of the trial product and with at least one post-baseline assessment of any efficacy endpoint will be included. Subjects in the FAS will be analysed according to randomised treatment. The requirement of a post-baseline observation is in alignment with the FDA recommendations[27]

**Safety analysis set**

All randomised subjects who have been exposed to at least one dose of trial product. Subjects in the safety analysis set will be analysed “as treated”.

18  Statistical considerations

Biostatistics Novo Nordisk will be responsible for the statistical analysis.

18.1  Sample size calculation

A sample size of 400 subjects randomised to 3.0 mg liraglutide treatment, 200 subjects randomised to 1.8 mg
liraglutide treatment and 200 subjects randomised to placebo was chosen. In order to ensure the blinding of
the subjects, 150 subjects will be randomised to 3.0 mg liraglutide placebo, whereas 50 will be randomised
to 1.8 mg liraglutide placebo. In the statistical analysis the placebo treated subjects will be treated as one
group.

These numbers are considered to provide a reasonable estimation of the safety of liraglutide as a weight-
management product in diabetic subjects. The number of subjects exposed to 3.0 mg liraglutide was chosen
to be larger than the number of subjects exposed to 1.8 mg liraglutide since the safety of the latter dose is
well known from the extensive LEAD programme.

The sample size furthermore provides sufficient power for the primary efficacy endpoints weight change, the
proportion of subjects with a weight loss of at least 5% and the proportion of subjects with a weight loss
larger than 10%. The hypothesis of equality of 3.0 mg liraglutide versus placebo for each of the three
endpoints will be tested in a hierarchical manner in the order in which they are mentioned. If superiority is
demonstrated for liraglutide 3.0 mg compared to placebo for all three endpoints, the hypotheses of equality
between liraglutide 1.8 mg and placebo will be tested in the same hierarchical manner.

The power for the primary endpoint weight change is calculated based on a two sided t-test with a
significance level of 5%. The power with regard to the co-primary dichotomous endpoints is calculated
based on a two-sided chi-square test.

With a sample size of 400 subjects treated with 3.0 mg liraglutide and 200 subjects treated with placebo, the
trial will have 89% power to detect a difference between liraglutide and placebo in the proportion of subjects
with a weight loss greater than 10%, given that the probabilities to achieve this weight loss is 10% for
placebo and 20% for liraglutide. The trial will have 90% power to detect a difference in mean weight change
between liraglutide and placebo, given that the true difference is 1.7 kg and the standard deviation is 5.9 kg.

Similarly, with a sample size of 200 subjects treated with 1.8 mg liraglutide and 200 subjects treated with
placebo, the trial will have 90% power to detect a difference between 1.8 mg liraglutide and placebo in the
proportion of subjects with a weight loss greater than 10%, given that the probabilities to achieve this weight
loss is 10% for placebo and 22% for 1.8 mg liraglutide. Furthermore the trial will have more than 90% power
to detect a difference in mean weight change between 1.8 mg liraglutide and placebo, given that the true
difference is 2 kg and the standard deviation is 5.9 kg.

18.2  Statistical methods

All statistical tests are two-sided at a 5% significance level.
For all efficacy evaluations, only observations on drug (defined as last injection taken the day before or on the day of the visit) will be included in the statistical analyses and summaries. For all weight and glycaemic efficacy endpoints, only observations prior to rescue medication will be included in the statistical analyses and summaries, as rescue medication will confound the subsequent measurement of these parameters. Excluded observations will be listed.

18.2.1 Primary efficacy endpoints

The three co-primary endpoints are defined as:

1. Change from baseline in fasting body weight at 56 weeks
2. The proportion of subjects losing at least 5% of baseline fasting weight (measured at Week 0)
3. The proportion of subjects losing more than 10% of baseline fasting weight (measured at Week 0)

The first primary endpoint is suggested as a primary endpoint in the FDA guidance(28) as well as the EMEA guidance(29). The second primary endpoint is suggested by FDA, whereas EMEA instead focus on the third of the endpoints.

18.2.1.1 Primary analysis of the co-primary endpoints

Description of the applied LOCF approach

In the primary analyses of all three endpoints, the last observation carried forward on treatment will be applied (LOCF). Only fasting weight measurements will be used and only measurements performed after randomization will be carried forward. The follow-up weight measurements at 56 weeks (Visit 16x) after randomisation will not be applied in the primary analyses.

Primary analysis of Change from baseline in fasting Body weight at 56 weeks

The continuous primary endpoint, fasting body weight loss, analysed as change in fasting body weight from Week 0 to Week 56 will be compared between liraglutide and placebo using an ANCOVA (Analysis of Covariance) model with treatment (3.0 mg liraglutide, 1.8 mg liraglutide, placebo), country, Hba1c stratification factor, back ground treatment stratification factor, interaction between stratification factors and gender as fixed effects and with baseline body weight (at Week 0) as a covariate. The analysis will be performed for the FAS. From this model the expected differences in weight change between 3.0 mg liraglutide treatment and placebo, as well as the expected differences in weight change between 1.8 mg liraglutide treatment and placebo will be estimated together with the associated 95% confidence intervals and p-values corresponding to the test of the hypotheses of no difference between treatments.

Primary analysis of the proportion of subjects losing at least 5% of baseline fasting weight (measured at Week 0)

For this categorical primary endpoint, a logistic regression model with treatment (3.0 mg liraglutide, 1.8 mg liraglutide, placebo), country, Hba1c stratification factor, back ground treatment stratification factor, interaction between stratification factors and gender as fixed effects and with baseline fasting body weight (at Week 0) as a covariate, will be used to compare the proportion that after 56 weeks of treatment at least
5% of their baseline fasting bodyweight in the three groups. The analysis will be performed for the FAS using the LOCF approach described above. From this model the odds ratios between the 3.0 mg liraglutide treatment and placebo, as well as the odds ratios between the 1.8 mg liraglutide treatment and placebo will be estimated together with the associated 95% confidence intervals and p-values corresponding to the tests of the hypotheses of no difference between treatments.

### Primary analysis of the proportion of subjects losing more than 10% of baseline fasting weight (measured at Week 0)

This endpoint will be analysed in the same manner as the proportion of subjects losing at least 5% of baseline fasting weight.

### Description of the testing procedure

The tests of equality between 3.0 mg liraglutide and placebo for each of the endpoints are tested in a hierarchical manner in the order in which the endpoints are presented. If superiority of the 3.0 mg liraglutide dose is demonstrated for all three co-primary endpoints, the tests of equality between 1.8 mg liraglutide and placebo will be performed in a similar hierarchical manner.

- 3.0 mg liraglutide will be considered statistically significantly better than placebo with respect to the first co-primary endpoint if the hypothesis of equality between 3.0 mg liraglutide and placebo is rejected and if the estimated effects of treatment are better in the 3.0 mg liraglutide group than in the placebo group for the first co-primary endpoint.

- 3.0 mg liraglutide will only be considered statistically significantly better than placebo with respect to the second co-primary endpoint if it is considered statistically significantly better with respect to the first of the co-primary endpoints, if the hypothesis of equality between 3.0 mg liraglutide and placebo is rejected for the secondary co-primary endpoint, and if the estimated effects of treatment are better in the 3.0 mg liraglutide group than in the placebo group for the second co-primary endpoint.

- 3.0 mg liraglutide will only be considered statistically significantly better than placebo with respect to the third co-primary endpoint if it is considered statistically significantly better with respect to the first and the second of the co-primary endpoints, if the hypothesis of equality between 3.0 mg liraglutide and placebo is rejected for the third co-primary endpoint, and if the estimated effects of treatment are better in the 3.0 mg liraglutide group than in the placebo group for the third co-primary endpoint.

- 1.8 mg liraglutide will only be considered statistically significantly better than placebo with respect to the first of the co-primary endpoints if the 3.0 mg liraglutide is considered statistically significantly better than placebo for all three co-primary endpoints, if the test of equality between the 1.8 mg liraglutide group and placebo is rejected for the first co-primary endpoint and if the estimated effect of treatment with respect to the first endpoint is better in the 1.8 mg liraglutide group than in the placebo group.

- 1.8 mg liraglutide will only be considered statistically significantly better than placebo with respect to the second of the co-primary endpoints if 3.0 mg liraglutide is considered statistically significantly better than placebo for all three co-primary endpoints, if 1.8 mg liraglutide is considered statistically significantly better than placebo for the first co-primary endpoint, if the test of equality between the 1.8 mg liraglutide group and placebo is rejected for the second co-primary endpoint and if the estimated
effect of treatment with respect to the second co-primary endpoint is better in the 1.8 mg liraglutide group than in the placebo group.

- 1.8 mg liraglutide will only be considered statistically significantly better than placebo with respect to the third of the co-primary endpoints if 3.0 mg liraglutide is considered statistically significantly better than placebo for all three co-primary endpoints, if 1.8 mg liraglutide is considered statistically significantly better than placebo for the first and the second co-primary endpoint, if the test of equality between the 1.8 mg liraglutide group and placebo is rejected for the third co-primary endpoint and if the estimated effect of treatment with respect to the third co-primary endpoint is better in the 1.8 mg liraglutide group than in the placebo group.

### 18.2.1.2 Sensitivity analyses of the co-primary endpoints

#### Sensitivity analyses of change from baseline in fasting Body weight at 56 weeks

For supporting evidence, the following sensitivity analyses will be carried out:

- The same analysis as above will be applied to the completers (week 56)
- The same analysis as above, applied to all randomised subjects allowing for baseline carried forward for subjects without a post baseline measurements
- The same analysis as above, applied to the FAS including the fasting and non-fasting weight measurements, off drug weight measurements and the follow-up weight measurements 56 weeks after randomisation (Visit 16x)
- The same analysis as above, applied to the FAS including the fasting and non-fasting weight measurements, off drug weight measurements, and the follow-up weight measurements 56 weeks after randomisation (Visit 16x) and weight measurements following rescue medication
- The same analysis as above, applied to the FAS, but imputing missing observations with the regression method (30). Five sets of imputations and subsequent analyses will be done.
- The following repeated measures analysis (linear mixed effect model) using all longitudinal fasting weight measurements taken prior to glycaemic rescue medication available for the FAS will be applied. The response variable is the change of body weight from baseline, and the model includes visit, treatment, country, HbA1c stratification factor, back ground treatment stratification factor, interaction between stratification factors and gender and the interaction between treatment and visit and baseline body weight and visit as fixed effects and with baseline body weight (at Week 0) as a covariate. Subject will be included as a random factor. The model will be used to compare liraglutide and placebo at Week 56

#### Sensitivity analyses of the proportion of subjects losing at least 5% of baseline fasting weight (measured at Week 0)

For supporting evidence the following sensitivity analyses will be carried out:

- The same analysis as above will be applied to the completers (week 56)
- The same analysis as above, applied to all randomised subjects allowing for baseline carried forward for subjects without a post baseline measurements
• The same analysis as above, applied to the FAS, including the fasting and non-fasting weight measurements, off-drug weight measurements and the follow-up weight measurement 56 weeks after randomisation (Visit 16x)

• The same analysis as above, applied to the FAS including the fasting and non-fasting weight measurements, off-drug weight measurements and the follow-up weight measurements 56 weeks after randomisation (Visit 16x) and weight measurements following rescue medication

• The same analysis as above, applied to the FAS, but regarding subjects without a valid assessment of weight at 56 weeks as non-responders, i.e. as not having lost 5% of their body weight. (For subjects withdrawing prematurely from the trial, their follow-up weights at 52 weeks after randomisation, if available, will be used)

• The same analysis as above, applied to the FAS, but imputing missing observations with the regression method (30). Five sets of imputations and subsequent analyses will be done.

**Sensitivity analyses of the proportion of subjects losing more than 10% of baseline fasting weight (measured at Week 0)**

The sensitivity analyses for this endpoint will be analysed in the same manner as the proportion of subjects losing at least 5% of baseline fasting weight.

**18.2.2 Analysis of secondary efficacy endpoints**

All secondary efficacy endpoints will be based on the FAS.

All endpoints will be summarized descriptively by visit using observed data. At end of treatment (week 56) and follow-up (week 68) summaries will be presented for both observed and LOCF imputed data. Week 56 will only be imputed with observations on treatment (post baseline observations up to end of treatment) and week 68 will only be imputed with observations off treatment (visits in the follow-up period).

Summary statistics for continuous endpoints include number of observations, arithmetic mean, median, standard deviation, minimum and maximum. Summary statistics for categorical endpoints include number of observations, number and percentage of subjects fulfilling the criteria.

Table 18.1 and 18.2 give an overview of the statistical analysis for the secondary endpoints at week 56 and 68

Continuous secondary endpoints will be analysed and presented similarly to the primary analysis of weight change. Baseline values will be included as covariates in the analyses of the corresponding response variables. This analysis is referred to as ANCOVA in table 18.1 and 18.2.

Categorical secondary endpoints will be analysed and presented similarly to the primary analysis of proportion of subjects losing at least 5% of baseline body weight. Continuous baseline values will be included as covariates in the analyses of the corresponding response variables unless otherwise specified. This analysis is referred to as LR in table 18.1 and 18.2.
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Endpoint type</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline (week 0) to week 56 in body weight (kg)</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in HbA1c</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in FPG</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>7-point plasma glucose profile (self-measured)</td>
<td>Continuous</td>
<td>N/A</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in beta cell function (HOMA)</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in insulin resistance (HOMA)</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in fasting glucagon</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in fasting insulin</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in fasting c-peptide</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in pro-insulin to insulin ratio</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Proportion of subjects reaching target HbA1c &lt; 7% at week 56</td>
<td>Categorical</td>
<td>LR</td>
</tr>
<tr>
<td>Proportion of subjects reaching target HbA1c ≤ 6.5% at week 56</td>
<td>Categorical</td>
<td>LR</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in waist circumference</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in systolic blood pressure</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in diastolic blood pressure</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in total cholesterol</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in LDL cholesterol</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in HDL cholesterol</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in vLDL cholesterol</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in triglycerides</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in free fatty acids</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in hsCRP</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in adiponectin</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in fibrinogen</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 PAI-1</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 56 in urinary albumin to creatinine ratio</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Proportion of subjects reaching American Diabetes Association (ADA) treatment targets for LDL cholesterol (&lt; 100 mg/dL) and triglycerides (&lt; 150 mg/dL) at week 56 (yes/ no)</td>
<td>Categorical</td>
<td>LR</td>
</tr>
<tr>
<td>Proportion of subjects who attain ADA treatment targets for blood pressure (&lt; 130/80 mmHg) at week 56</td>
<td>Categorical</td>
<td>LR</td>
</tr>
<tr>
<td>Scores from PRO questionnaire IWQoL-Lite at week 56</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Scores from PRO questionnaire DTSQs at week 56</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Proportion of subjects with change from baseline (week 0) to week 56 in anti-hypertensives (lowering/ increase or no change)</td>
<td>Categorical</td>
<td>LR</td>
</tr>
<tr>
<td>Proportion of subjects with change from baseline (week 0) to week 56 in lipid lowering agents (lowering/ increase or no change)</td>
<td>Categorical</td>
<td>LR</td>
</tr>
<tr>
<td>Proportion of subjects with change from baseline (week 0) to week 56 in oral antidiabetic drugs (lowering/ increase or no change)</td>
<td>Categorical</td>
<td>LR</td>
</tr>
</tbody>
</table>

N/A Not available
Relevant concomitant medication status (present/absent) will be included as covariate.

For assessments in the follow-up period statistical analysis and summaries will be done for subjects in the FAS, who complete the 56 week treatment period and who have a valid assessment in the follow-up period. Statistical analysis models are similar to the main treatment period.

### Table 18.2: Overview of statistical analysis of secondary efficacy endpoints at week 68

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Endpoint type</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline (week 0) to week 68 in fasting body weight (kg and %)</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 68 in waist circumference</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 68 in FPG</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 68 in systolic blood pressure</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 68 in diastolic blood pressure</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 68 in pulse</td>
<td>Continuous</td>
<td>N/A</td>
</tr>
<tr>
<td>Change from baseline (week 0) to week 68 in urinary albumin to creatinine ratio</td>
<td>Continuous</td>
<td>ANCOVA</td>
</tr>
</tbody>
</table>

N/A Not available

### 18.2.3 Analysis of safety endpoints

All conducted analyses will be done with the aim to compare the liraglutide group to the liraglutide placebo group. All analyses and tabulations regarding safety endpoints will be done using the safety analysis set.

#### Physical examination

Physical examinations are recorded at screening and at end of treatment. Physical examination at screening as well as changes in physical examination will be summarised.

#### Hypoglycaemic episodes

Hypoglycaemic episodes follow the same definition as AEs for treatment emergence.

All episodes will be summarized by both the ADA definition and the Novo Nordisk definition. The categorisations are severe, asymptomatic, probable symptomatic, relative, documented symptomatic (ADA definitions) and major, minor, or symptoms only (Novo Nordisk definition). Frequencies of subjects experiencing treatment emergent hypoglycaemic episodes will be summarised by severity and treatment. Hypoglycaemic episodes not defined as treatment emergent will be presented in a listing.
ECG

Summary statistics and the frequencies of shifts from baseline to end of trial will be tabulated for each treatment group.

Adverse events

Adverse events will be coded using the current version of MedDRA. A treatment emergent adverse event (TEAE) is defined as an event that either:
- Occurs before randomisation and increases in severity during the treatment period
- Has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment

Treatment emergent adverse events, TEAEs, are summarised descriptively, whereas non-treatment emergent AE’s are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 years (R). Furthermore, TEAE data are summarized by seriousness, severity, relation to trial drug, MESI, withdrawal due to AEs and outcome.

Summary tables by system organ class and preferred term are made for all TEAEs, serious TEAEs, possible or probably related to trial drug, severe TEAE, treatment emergent MESI, and TEAE occurring in at least 5% of the subjects in any treatment arm. Corresponding tables will be done for TEAEs together with non-TEAEs starting after first drug date (including non-TEAEs in the observational period and MESI’s collected after withdrawal).

Mental health questionnaires and Binge eating scale

Results from the questionnaires will be summarised by treatment and visit.

Pulse

Pulse will be summarised and analysed similar to blood pressure.

Analysis of laboratory safety parameters

Laboratory safety parameters are measured throughout the trials and comprise haematology and biochemistry as defined in the flowchart.

No formal statistical analyses are planned for the laboratory safety parameters.

The distribution of each continuous laboratory parameter will be presented using box plots by treatment and week. Continuous laboratory values will be compared to the relevant references ranges and results will be presented as follows:
• Shift tables for each laboratory parameter will be provided by treatment group. The shift tables will include the number of subjects below, within and above the reference ranges at baseline (Week 0) and after end of treatment.

• For each laboratory parameter the proportion of subjects with laboratory values outside the normal ranges will be tabulated per visit and treatment group.

• For each laboratory parameter individual values outside the reference ranges (abnormal values) will be listed by treatment and subject.

Categorical laboratory parameters will be summarised with shift tables.

**Amylase and lipase**

Tables showing shifts from baseline to highest value in treatment period to UNR, 2UNR or 3UNR will be presented.

Mean plots by visit will be presented. At end of treatment (week 56) and follow-up (week 68) summaries will be presented for both observed and LOCF imputed data. Week 56 will only be imputed with observations in the treatment period (post baseline observations up to week 56) and week 68 will only be imputed with observations off treatment (visits in the follow-up period).

Number and percentage of subjects with amylase and lipase levels ≥UNR, ≥2UNR and ≥3UNR by treatment and visit will be tabulated. At end of treatment (week 56) and follow-up (week 68) summaries will be presented for both observed and LOCF imputed data.

Subjects with values ≥2UNR will be presented with spaghetti plots and listings showing medical history of GI AEs, GI AEs and liver lab parameters.

**Calcitonin**

Number, percentage and incidence of subjects with persistent (all post baseline measurements) and incidental (at least one post baseline measurement) increases in calcitonin for the criteria below will be tabulated for all subjects, males and females.

• From baseline <UNR to ≥UNR
• From baseline <UNR to ≥1.5UNR
• From baseline <UNR to ≥20ng/L
• From baseline <UNR to ≥50ng/L
• From baseline <20ng/L to ≥20ng/L
• From baseline <50ng/L to ≥50ng/L

Number and percentage of subjects with calcitonin levels ≥UNR, ≥1.5UNR, ≥20ng/L and ≥50ng/L by treatment and visit will be tabulated. At end of treatment (week 56) and follow-up (week 68) summaries will be presented for both observed and LOCF imputed data.
The distribution of all calcitonin measurements across treatment groups and time will be shown with histograms and corresponding cumulative plots by gender and total for actual levels. Sum curves will be done for baseline (pooled) and week 56 (LOCF) by treatment. Histograms will be shown for baseline (pooled) and by treatment for week 56 and 68 (both using LOCF).

A summary table showing number and percentage of observations < and ≥ LLOQ, minimum, Q25, median, Q75, maximum and geometric mean will be done by treatment group, gender and week.

Geometric means will be plotted by treatment and visit in order to assess the pattern of the longitudinal changes.

In addition, a scatter plot of baseline vs. maximum post baseline calcitonin measurement will be done by treatment.

Longitudinal changes for subjects with calcitonin ≥ 20ng/L will be evaluated with spaghetti plots. The spaghetti plots will follow the above by treatment group and gender.

Selected listings of subjects with at least one post baseline calcitonin measurement above 20ng/L will be done. The listings will include treatment, age, gender, smoking habits at baseline, risk factor information (use of relevant concomitant medication at time of assessment (proton pump inhibitors and H2 blockers) and medical history of thyroid disorder) and calcitonin measurements.

**Liraglutide antibodies**

Frequencies of subjects with liraglutide antibodies will be tabulated by week and treatment. Frequencies of subjects with liraglutide antibodies with neutralising effect and with cross-reacting liraglutide will be tabulated similarly.

### 18.3 Interim analysis

Not applicable.

### 18.4 Sequential safety analysis/safety monitoring

Sequential safety analysis for medical events of special interest is planned to be monitored by an internal Data Monitoring group. No formal statistical analyses are planned, blinded summary statistics and graphical presentation of data will be the basis of the safety group’s decisions.

### 18.5 Explorative statistical analysis for pharmacogenetics and biomarkers

Not applicable.
18.6 Health economics and/or subject reported outcome

Please refer to Analysis of secondary efficacy endpoints, section 18.2.2

18.7 PK and/or PD modelling

The pharmacokinetics of liraglutide will be evaluated using population PK analysis methods. The analyses will be based on plasma samples taken from all subjects, using a sparse sampling scheme.

A separate modelling plan will be prepared before Database Lock outlining details of the analysis.
19 Ethics

The trial will be conducted in compliance with ICH GCP (25) and applicable regulatory requirements, and in accordance with the Declaration of Helsinki (31).

All subjects participating in the trial will receive instruction in a hypocaloric diet calculated to induce a moderate weight loss during the trial, and all subjects will receive instruction and encouragement on regular physical activity to aid in weight management and improvement of risk factors. A standard panel of safety laboratory evaluations will be performed regularly during the trial (including vital signs, haematology, and biochemistry) and side effects will be monitored closely.

In this trial all subjects will be instructed in symptom recognition and handling of hypoglycaemia as well as regular clinic measurement of fasting plasma glucose as precautionary measures.

The trial drugs 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 participating in the trial. These precautions include thorough information regarding the correct administration of the trial drugs and gradual dose escalation. Furthermore, subjects 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.

Treatment with liraglutide was generally well-tolerated, with high completion rates in groups (75% in liraglutide group, 70% in placebo group). The number of withdrawals due to adverse events was evenly distributed between groups (8.5% in the liraglutide group vs. 8.6% in placebo group). Serious adverse events were relatively uncommon, but were more frequent in liraglutide-treated subjects (4.2%) compared to placebo (2.4%). There were no events of pancreatitis or medullary thyroid cancer, and no treatment-related increases in blood calcitonin levels. Consistent with previous trials with liraglutide, the most commonly reported adverse events were from the gastrointestinal system, with nausea reported by 47% of subjects in the liraglutide group compared to 17% in the placebo groups, and vomiting by 17% vs. 2%, respectively. As in previous trials, the majority of events were reported in the first 6-8 weeks, were mild or moderate in severity and transient in nature. Please refer to liraglutide obesity Investigators Brochure, 3rd Edition, 2010, or any updates hereof. Patients 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.

In order to reduce the level of side effects, liraglutide is gradually escalated up to maximum dose (3.0 or 1.8 mg). If subjects do not tolerate an increase in dose during dose-escalation, the Investigator has the option to individualise the dose escalation with a total delay of up to 7 days. All subjects must be at the target dose of 3.0 mg 35 days after randomisation or 1.8 mg 21 days after randomisation.

All subjects will continue their fixed pre-trial treatment with metformin, sulphonylurea or glitazone as single agent therapy or a combination throughout the trial. Subjects treated with sulphonylureas will however be asked to reduce the dose with 50% to prevent SU-induced hypoglycaemia. Even though this may worsen glycaemic control initially, reinforcement of rescue criteria to reinstate pre-trial dose levels and addition of
rescue background medication should ensure adequate glycaemic control even for subjects on SUs randomised to liraglutide placebo.

Inclusion criteria have been defined in order to ensure that, at enrolment, subjects are eligible for treatment intensification and for trial participation. Furthermore, rescue criteria are defined to ensure that subjects are considered for glycaemic rescue if plasma glucose levels exceed acceptable limits during trial participation.

Liraglutide have shown to be effective in lowering blood glucose levels. It can therefore be expected that subjects receiving liraglutide and enters the trial with insufficiently controlled blood glucose will experience an improved glucose control during the trial.

Another potential benefit of participating in the trial is that the Investigator will obtain an additional knowledge of the subjects’ disease and will therefore be able to provide recommendations for the best treatment to be used following the trial participation.

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 surveillance identified at least 30 cases of pancreatitis with exenatide(14). However, a health services registry-based study found no increased frequency of pancreatitis among exenatide users.(15)

If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory tests have been conducted, and appropriate treatment should be initiated. Subjects diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3x UNR or characteristic findings on CT/MRI) should be withdrawn from the study.

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. Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). 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.

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).

The subjects will have the right to withdraw from the trial at any time, without giving a specific reason. Novo Nordisk will be entitled to keep the data collected until withdrawal of the subject.
19.1 Informed consent form for trial subjects

In seeking and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the ICH GCP[25] and the requirements in the Declaration of Helsinki[31].

Prior to any trial-related activity, the Investigator must give the subject oral and written information about the trial in a form that the subject can read and understand.

A voluntary, signed and personally dated informed consent form will be obtained from the subject prior to any trial-related activity.

The responsibility for seeking informed consent must remain with the Investigator or an adequately medically qualified person delegated by the investigator. The written informed consent must be signed and personally dated by the person who seeks the informed consent.

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

19.2 Data Handling

If the subject withdraws the previously given informed consent the subject’s data will be handled as follows:

- Data collected will be retained by Novo Nordisk and entered into the database
- Safety events will be reported to the department responsible for global product safety, Novo Nordisk/regulatory authorities according to local/national requirements
- If data is used, it will always be in accordance with local law and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) procedures.

19.3 Institutional review boards/independent ethics committee

Prior to commencement of the trial, the protocol, any amendments, subject information/informed consent form, any other written information to be provided to the subject, subject recruitment procedures, if any, IB, information about payments and compensation available to subjects if not mentioned in the subject information, the Investigator’s current CV and/or other documentation evidencing qualifications, and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify (by trial identification number, including version, EudraCT no. where applicable, title and/or date of the document) which documents have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the Investigator must promptly in accordance with local requirements report the following to the IRB/IEC: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial 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 amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate 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.

19.4 Regulatory authorities

Regulatory authorities will receive the Clinical Trial Application (CTA), substantial/non-substantial amendments to the protocol, reports on SAEs, and the Clinical Trial Report (CTR) according to national requirements.
20 Premature termination of the trial/ trial site

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

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the subjects and assure appropriate therapy and follow-up. Furthermore, the Investigator and/or Novo Nordisk should promptly inform the IRB/IEC and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IRB/IEC in case it will have an impact on the planned follow-up of the subjects who have participated in the trial. If so, the actions needed to protect the subjects should be described.
21 Protocol compliance

Deviations from the protocol should be avoided.

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

Protocol deviations must be documented stating the reason, date, the action(s) taken, and the impact for the subjects and/or the trial except for protocol deviations where no corrections are required as described in the trial specific validation checks in the approved Trial Validation Plan (TVP). The Investigator must approve these as outlined in the TVP.

The documentation for the protocol deviations must be kept in the Investigator’s trial file and the Novo Nordisk’s trial master file.

21.1 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk internal Quality Audit System or an inspection from domestic or foreign regulatory authorities. The Investigator and the site staff as well as Novo Nordisk clinical 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 relevant to the conduct of the clinical trial at the site.
22 Critical documents

Before the Investigator starts the trial (i.e. obtains informed consent from the first subject), the following documents must be available to Novo Nordisk:

- Regulatory approval and/or notification as required
- Curricula vitae of Investigator and Sub-Investigator(s) (current, dated and signed and/or supported by an official regulatory document)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any substantial amendment(s), if applicable
- Approval/favourable opinion from IEC/IRB clearly identifying the documents reviewed: the protocol, any substantial amendments, subject information/informed consent form and any other written information to be provided to the subject, subject recruitment procedures
- Copy of IEC/IRB approved subject information/informed consent form/any other written information/advertisement
- List of IEC/IRB members/constitution
- Signed receipt of IB by Investigator
- Other critical documents as required by local regulations
- Financial agreement(s)
  - For US: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest (32)
- FDA financial disclosure form or local equivalent as applicable.
- Signed and dated FDA form 1572 for each US Investigator (listing individual US clinical trial staff if directly involved in the treatment or evaluation of research making a direct and significant contribution to the data).

Protocol NN8022-1922 (US sites):
- Intended for US sites
  - Conducted under the Investigational New Drug Application (IND)
  - All US Investigators will sign FDA Form 1572

Protocol NN8022-1922 (sites outside the US):
- Intended for participating sites outside the US
  - Not conducted under the IND
  - All Investigators outside the US will not sign FDA Form 1572

As documented in writing by protocol signature, all Investigators will fully comply with ICH GCP (25), applicable regulatory requirements, and in accordance with the Declaration of Helsinki (31).

Novo Nordisk will analyse and report data from all sites together.
All staff Novo Nordisk, site, Central Laboratories, CRO etc must conduct the trial in compliance with ICH GCP (25), applicable regulatory requirements, and in accordance with the Declaration of Helsinki (31).

Novo Nordisk will be responsible for the preparation of the protocol, eCRF, supply of trial products and stated equipment, monitoring, data management, statistics, and the CTR as documented by Novo Nordisk procedures and internal specific agreements as well as the current GCP guidelines.

Novo Nordisk will provide a system for EDC. This system and support services to the system will be supplied by a clinical services vendor. The activities of the clinical services vendor will be under the direction and supervision of Novo Nordisk. Furthermore, Novo Nordisk will be responsible for the IV/WRS.

A central laboratory will be responsible for providing all lab supplies for the analysis of all blood samples taken during the trial. All results are received as paper copies at the sites as well as electronic transfer to Novo Nordisk clinical database.

The name of the Central Laboratories will appear in the application to the authorities and in protocol Attachment I.

The Investigator is accountable for the conduct of the trial. 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.

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

In case the Investigator is not able to fulfil the role as Investigator (e.g., retirement), a new Investigator must be appointed in collaboration with Novo Nordisk.

The Investigator will ensure that the last samples are shipped to the central laboratory within 24 hours after the last subject visit at the site.

The Investigator will follow the instructions from Novo Nordisk when processing 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.

Upon request from Novo Nordisk, the Investigator will provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.
24 Reports and publications

The information obtained during the conduct of this trial is considered confidential and can 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.

The signatory Investigator, Professor Melanie Davies, United Kingdom will review and sign the CTR to confirm, to the best of her knowledge, that it accurately describes the conduct and results of the trial.

24.1 Communication and publication

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

Novo Nordisk commits to communicating or 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 by other means.

When the primary results are available, Novo Nordisk plans to discuss the interpretation of these with the principal Investigator, but reserves the right to release results that may impact Novo Nordisk financial expectations (e.g. a press release directly to the public or similar) without prior consultation with the remaining participating Investigators. Novo Nordisk reserves the right not to release data until specified milestones, e.g. a clinical trial report is available. This includes the right not to release interim results from clinical trials, because such results may lead to conclusions that are later shown to be incorrect.

At the end of the trial, one or more manuscripts for publication will be prepared in collaboration between Investigator(s) and Novo Nordisk. Novo Nordisk will not suppress or veto publications; however Novo Nordisk reserves the right to postpone publication and/or communication for a short time to protect intellectual property.

24.1.1 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors’ Uniform Requirements (sometimes referred to as the Vancouver Criteria(33)).

The signatory Investigator will together with Novo Nordisk establish and appoint members to a publication writing group consisting of minimum 3 Investigators that have been involved in the design of the trial or the interpretation of the results and minimum 3 Investigators considered contributing substantially to the acquisition of data. The remaining participating Investigators will be acknowledged as the NN8022-1922 trial group in the author section of publications.
24.1.2 Publication(s)

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

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

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

24.1.3 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 Novo Nordisk’s 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 publication and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

24.2 Investigator access to data and review of results

As owners of the trial database, Novo Nordisk has discretion to determine who will have access to the database. Generally, trial databases are only made available to regulatory authorities.

Individual Investigator(s) will have their own research participants' data and will be provided with the randomisation code after results are available.
25 Retention of clinical trial documentation

Subject notes 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 paperbased 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 after trial completion, Novo Nordisk can refer the Investigator to an independent archiving provider who has a system in place that allows only the Investigator to access the files.

Clinical trial documentation must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Novo Nordisk will maintain Novo Nordisk’s documentation pertaining to the trial as long as the product is on the market plus 15 years. The files from the Investigator site/institution will be retained 20 years after the completion of the trial, or longer if required by national regulations.

For Spain, the following applies: Any record of the participants will be kept confidential, in accordance with Organic Act. 15/1999 of 13 December of Personal Data/Records Protection.
26 Indemnity statement

Novo Nordisk carries product liability for its products and liability 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:

**France**: The French Public Health Code article L.1121-10 (law no 2004-80 6 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004). ‘Novo Nordisk is responsible for identification of the harmful consequences of the biomedical-cal 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 or to the fault of any intervening party, without the Novo Nordisk’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**: Drug law dated August 24, 1976, last amended per fifteenth law for amendment of the drug law dated July 17, 2009

**Spain**: Drug law dated August 24, 1976 last amended per fifteenth law for amendment of the drug law dated July 17, 2009
References


Dore DD, Seeger JD, Chan KA. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Current Medical Research and Opinion 2009 Apr;25(4):1019-27.


ADA. Standard of Medical Care in Diabetes-2010. Diabetes Care 33, supp 1. 1-1-2010.

Ref Type: Generic


Ref Type: Generic

Ref Type: Generic

Ref Type: Generic

Ref Type: Generic


Ref Type: Generic

Ref Type: Generic

2006Available from: URL:

Appendix B

Agreement on the final revised protocol

This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.
Agreement on the final revised protocol

Trial ID: NN8022-1922

The Investigator and Novo Nordisk agree to conduct the trial as outlined in this protocol with reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines. Any modification to the protocol must be agreed upon by both the Investigator and Novo Nordisk and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorised individuals representing Novo Nordisk (including monitoring staff and auditors), to institutional review boards/independent ethics committees (IEC/IRB) and/or to regulatory authorities.

Investigator:

_________________________ ___________________________ __________
Name (printed) Signature Date

Head of medical/clinical research or designee:

_________________________ ___________________________ __________
Name (printed) Signature Date
New York Heart Association (NYHA) Criteria for Functional Capacity
### Criteria for Functional Capacity*

<table>
<thead>
<tr>
<th>Functional Capacity</th>
<th>Objective Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain | A  
No objective evidence of cardiovascular disease. |
| **Class II**        |                      |
| Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain | B  
Objective evidence of minimal cardiovascular disease. |
| **Class III**       |                      |
| Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain | C  
Objective evidence of moderately severe cardiovascular disease. |
| **Class IV**        |                      |
| Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased | D  
Objective evidence of severe cardiovascular disease. |

Appendix D

Instruction for Blood Pressure Measurement

This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.
Instructions for Blood Pressure Measurement

For the purpose of standardisation, blood pressure measurements must be taken according to recent recommendations\(^1,2\):

- The auscultatory method should be used to measure blood pressure
- Caffeine, smoking and physical activity should be avoided at least 30 minutes before measurement
- Before performing a blood pressure reading, the patient should be asked to remove all clothing that covers the location of cuff placement. The sleeve should not be rolled up such that it has a tourniquet effect above the blood pressure cuff
- The same type of sphygmomanometer should be used throughout the trial
- The measurement should be taken in a sitting position, with the legs uncrossed, the back and arm supported
- Subject should be sitting for at least 5 minutes before the first reading is taken
- Location for the measurement should be the upper arm, with the stethoscope at the elbow crease over the brachial artery. The middle of the cuff on the upper arm should be at the level of right atrium (the mid-point of the sternum)
- The same arm should be used for blood pressure measurements at all visits
- The size of the cuff should be selected so that the bladder of the cuff encircles at least 80% of the arm circumference, and the width of the cuff is at least 40% of the arm circumference
- Cuff placement must be preceded with palpation of the brachial artery in the antecubital fossa. The midline of the cuff bladder must be placed over the location of the arterial pulsation. The lower edge of the cuff should be 2-3 cm above the antecubital fossa to allow for stethoscope placement
- The cuff should be inflated to at least 30 mmHg above the point at which the radial pulse disappears. The pressure should then be reduced at 2 to 3 mm/second
- Korotkoff sounds should be used to measure blood pressure: the onset of phase I (appearance of clear tapping sound corresponding to the appearance of palpable pulse) should indicate the
systolic blood pressure, while phase V (the disappearance of sounds) should be used for recording diastolic pressure

- The measurement must be taken with the precision to the nearest 2 mmHg
- Neither the patient nor the observer should talk during the measurement
- Two reliable measurements at intervals of at least 2 minutes should be performed. In case of >5 mmHg difference between the first and the second reading of diastolic blood pressure, one additional reading should be obtained

References:


Appendix E

Extended Flowchart
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Screening</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance period</th>
<th>End of treat</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5a</td>
<td>5b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5a</td>
<td>5b</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Weeks in relation to Visit 2</td>
<td>-2</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Visit Window, days</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
</tbody>
</table>

**SUBJECTS**

- **Informed consent**  
  - X

- **In/exclusion criteria**  
  - X
  - X

- **Randomisation criteria**  
  - X

- **Rescue criteria**  
  - X
  - X
  - X
  - X
  - X
  - X
  - X
  - X

- **Withdrawal criteria**  
  - X
  - X
  - X
  - X
  - X
  - X
  - X
  - X
  - X
  - X

**Demography**

- **Date of birth**  
  - X

- **Sex**  
  - X

- **Race**  
  - X

- **Ethnicity**  
  - X

- **Date of diagnosis of diabetes**  
  - X

- **History of Diabetes complications**  
  - X

- **History of Concomitant Cardiovascular Disease**  
  - X

- **History of Gallbladder Disease**  
  - X

- **History of Psychiatric Disorders**  
  - X

- **Diabetes treatment history**  
  - X

---

1 Only subjects discontinuing the trial prematurely before Visit 16 will be asked to attend Visit 16x 56 weeks after their randomisation date for the assessment of body weight and MESI.
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Screening</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance period</th>
<th>End of treat</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit Window, days</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
<tr>
<td></td>
<td>Current diabetes treatment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose of current diabetes treatment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concomitant illness/Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concomitant medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Smoking habits</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attend visit fasting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>EFFICACY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waist circumference</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>HbA1c</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Fasting plasma glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>7-point plasma profile (self-measured)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Glucose metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasting glucagon</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Fasting insulin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Fasting C-peptide</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Fasting pro-insulin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Urinary Albumin-to-Creatinine ratio</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

2 On a normal representative day of the week (not on a day when they anticipate unusual strenuous exercise), preferably within one week prior to the visit.
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Screening</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance period</th>
<th>End of treat</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5a</td>
<td>5b</td>
</tr>
<tr>
<td>Visit Window, days</td>
<td>±5</td>
<td>Baseline</td>
<td>±3</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
<tr>
<td>Systolic blood pressure, sitting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Diastolic blood pressure, sitting</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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

### Cardiovascular biomarkers
- hsCRP
- Adiponectin
- Fibrinogen
- PAI-1

### PRO questionnaires
- IWQoL-Lite
- DTSQs

### SAFETY
- Physical examination
- Pulse, sitting
- Hypoglycaemic episodes

---

3 Applicable for subjects in France, Germany, Spain, Sweden, United Kingdom and USA
4 The investigator or his delegate must review patient reported outcome(s) for completeness and AEs immediately following administration. For subjects discontinuing the trial prematurely before Visit 16 the questionnaire should be completed at the end of treatment visit (Visit 16).
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Screening</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance period</th>
<th>End of treat</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5a</td>
<td>5b</td>
</tr>
<tr>
<td>Visit Window, days</td>
<td>±5</td>
<td>Baseline</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Eye examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Binge Eating Scale questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Differential count:</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Basophils</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Monocytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urea</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Albumin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bilirubins, total</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ALAT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ASAT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sodium</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visit Number</td>
<td>Screening</td>
<td>Randomisation</td>
<td>Dose escalation period</td>
<td>Maintenance period</td>
<td>End of treatment</td>
<td>Observational follow-up</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>---------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>X</td>
<td>X</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Visit Window, days**

- Baseline ± 3
- 8 ± 5
- 12 ± 5
- 16 ± 5
- 20 ± 5
- 24 ± 5
- 28 ± 5
- 32 ± 5
- 36 ± 5
- 40 ± 5
- 44 ± 5
- 50 ± 5
- 56 ± 5
- 58 ± 5
- 60 ± 5
- 64 ± 5
- 68 ± 5

**Potassium**

- X
- X
- X
- X
- X
- X
- X
- X

**Calcium**

- X
- X
- X
- X
- X
- X
- X
- X

**Amylase**

- X
- X
- X
- X
- X
- X
- X
- X

**Lipase**

- X
- X
- X
- X
- X
- X
- X
- X

**Calcitonin**

- X
- X
- X
- X
- X
- X
- X
- X

**TSH**

- X
- X
- X
- X
- X
- X
- X
- X

**Pregnancy test**

- X
- X

**Blood sample**

- X

**Urine-sticks**

- (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X) (X)

**Liraglutide antibodies**

- X
- X

**Mental health questionnaires**

- C-SSRS
- PHQ-9

**OTHER ASSESSMENTS**

- PK (liraglutide plasma concentration)
- X
- X

**TRIAL MATERIAL**

- Dispense trial card
- X

---

5 For all women of childbearing potential: a serum pregnancy test will be performed at Visit 1, 16 and 20. Furthermore, pregnancy urine tests will be performed at any other clinic visits during the trial if a menstrual period is missed or as required by local law.

6 For subjects discontinuing the trial prematurely before Visit 16 liraglutide antibodies will be measured at the end of treatment visit (Visit 16) while subjects that complete the treatment will have liraglutide antibodies measured at the first follow-up (Visit 17).

7 For subjects discontinuing the trial prematurely before Visit 16 the mental health questionnaires will be completed at the end of treatment visit (Visit 16).

8 The Investigator must assess the PHQ-9 and C-SSRS scores at Visit 1 (screening visit) and Visit 2 (randomisation) to exclude subjects with major depression (PHQ-9 ≥ 15) or any suicidal ideation (of type 4 or type 5). The investigator or his delegate must review the C-SSRS and PHQ-9 questionnaires for completeness and AEs immediately following administration.
<table>
<thead>
<tr>
<th>Visit Number</th>
<th>Screening</th>
<th>Randomisation</th>
<th>Dose escalation period</th>
<th>Maintenance period</th>
<th>End of treat</th>
<th>Observational follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window, days</td>
<td>±5</td>
<td>Baseline</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
<td>±5</td>
</tr>
</tbody>
</table>

### Diary

- Dispense diabetes diary: X X X X X X X X X X X X X X X X X X X X X X
- Transcribe diabetes diary into CRF: X X 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 3-day food diary: X X X X X X X X X X X X X X X X
- Collect 3-day food diary: X X X X X X X X X X X X X X X X X X X X X X
- Diet and physical activity counselling: X° X X° X° X° X° X° X° X° X° X° X° X° X° X° X° X° X° X° X° X° X° X°
- Recording of dietary compliance and physical activity: x X X X X X X X X
- Supply of device(s)/ancillaries
  - Glucose meter: X
  - Pedometer: X
- Dispensing visit: X X X X X X X X X X X X X X X X
- Drug accountability: X X X X X X X X X X X X X X X X
- IV/WRS call: X X X X X X X X X X X X X X X X X X X X X X X X X X X
- End of treatment/End of Trial: X X X

---

9 Diet counselling based on a 3-day food diary
10 At Visit 2 only physical activity will be recorded
11 Subjects discontinuing the trial prematurely before Visit 16 will be asked to attend a last visit at which procedures according to Visit 16 will be performed and the EOT form completed. For subjects discontinuing the trial prematurely after Visit 16 the following will apply: at Visit 17; procedures according to Visit 17 will be performed and the EOT form completed - after Visit 17; procedures according to Visit 20 will be performed and the EOT form completed.
3*(17,21$//</(()7%/$1.
Appendix F

PRO Questionnaires

This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.
Table of contents

| Page |
|------------------|------------------|
| 6785 | Table of contents                                                                 | 2 |
| 6786 | 1 Impact of Weight on Quality of Life (IWQoL-Lite)                                | 3 |
| 6787 | 2 Diabetes Treatment Satisfaction Questionnaire (DTSQs)                          | 6 |
| 6788 | 3 Binge Eating Scale (BES) questionnaire                                         | 7 |
1 Impact of Weight on Quality of Life (IWQoL-Lite)

Please answer the following statements by circling the number that best applies to you in the past week. Be as honest as possible. There are no right or wrong answers.

<table>
<thead>
<tr>
<th>Physical Function</th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because of my weight I have trouble picking up objects.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. Because of my weight I have trouble tying my shoelaces.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Because of my weight I have difficulty getting up from chairs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Because of my weight I have trouble using stairs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Because of my weight I have difficulty putting on or taking off my clothes.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6. Because of my weight I have trouble with mobility (getting around).</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7. Because of my weight I have trouble crossing my legs.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8. I feel short of breath with only mild exertion (e.g. climbing a single flight of stairs).</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>9. I am troubled by painful or stiff joints.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10. My ankles and lower legs are swollen at the end of the day.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>11. I am worried about my health.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
### Self-esteem

|   | 1. Because of my weight I am self-conscious. | 5 | 4 | 3 | 2 | 1 |
|   | 2. Because of my weight my self-esteem is not what it could be. | 5 | 4 | 3 | 2 | 1 |
|   | 3. Because of my weight I feel unsure of myself. | 5 | 4 | 3 | 2 | 1 |
|   | 4. Because of my weight I don’t like myself. | 5 | 4 | 3 | 2 | 1 |
|   | 5. Because of my weight I am afraid of being rejected. | 5 | 4 | 3 | 2 | 1 |
|   | 6. Because of my weight I avoid looking in mirrors or seeing myself in photographs. | 5 | 4 | 3 | 2 | 1 |
|   | 7. Because of my weight I am embarrassed to be seen in public places. | 5 | 4 | 3 | 2 | 1 |

### Sexual Life

|   | 1. Because of my weight I do not enjoy sexual activity. | 5 | 4 | 3 | 2 | 1 |
|   | 2. Because of my weight I have little or no sexual desire. | 5 | 4 | 3 | 2 | 1 |
|   | 3. Because of my weight I have difficulty with sexual performance. | 5 | 4 | 3 | 2 | 1 |
|   | 4. Because of my weight I avoid sexual encounters whenever possible. | 5 | 4 | 3 | 2 | 1 |
### Public Distress

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Because of my weight I experience ridicule, teasing, or unwanted attention.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>Because of my weight I worry about fitting into seats in public places (e.g. theatres, cinemas, restaurants, cars, or aeroplanes).</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3.</td>
<td>Because of my weight I worry about fitting through aisles or turnstiles.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4.</td>
<td>Because of my weight I worry about finding chairs that are strong enough to hold my weight.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5.</td>
<td>Because of my weight I experience discrimination by others.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Work

(Nota: For those not in paid employment, answer with respect to your daily activities.)

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>ALWAYS TRUE</th>
<th>USUALLY TRUE</th>
<th>SOMETIMES TRUE</th>
<th>RARELY TRUE</th>
<th>NEVER TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Because of my weight I have trouble getting things done or carrying out my responsibilities.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>Because of my weight I am less productive than I could be.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3.</td>
<td>Because of my weight I don’t receive appropriate pay rises, promotions or recognition at work.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4.</td>
<td>Because of my weight I am afraid to go for job interviews.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
2 Diabetes Treatment Satisfaction Questionnaire (DTSQs)

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?
   - very satisfied
   - 6 5 4 3 2 1 0 very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?
   - most of the time
   - 6 5 4 3 2 1 0 none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?
   - most of the time
   - 6 5 4 3 2 1 0 none of the time

4. How convenient have you been finding your treatment to be recently?
   - very convenient
   - 6 5 4 3 2 1 0 very inconvenient

5. How flexible have you been finding your treatment to be recently?
   - very flexible
   - 6 5 4 3 2 1 0 very inflexible

6. How satisfied are you with your understanding of your diabetes?
   - very satisfied
   - 6 5 4 3 2 1 0 very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?
   - Yes, I would definitely
     recommend the treatment
   - 6 5 4 3 2 1 0 No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?
   - very satisfied
   - 6 5 4 3 2 1 0 very dissatisfied

Please make sure that you have circled one number on each of the scales.
3  Binge Eating Scale (BES) questionnaire

Instructions: Below are groups of numbered statements. Read all of the statements in each group and check the one that best describes the way you feel about the problems you have controlling your eating behavior.

#1

1. I don’t feel self-conscious about my weight or body size when I’m with others.
2. I feel concerned about how I look to others, but it normally does not make me feel disappointed with myself.
3. I do get self-conscious about my appearance and weight which makes me feel disappointed in myself.
4. I feel very self-conscious about my weight and frequently, I feel intense shame and disgust for myself. I try to avoid social contacts because of my self-consciousness.

#2

1. I don’t have any difficulty eating slowly in the proper manner.
2. Although I seem to “gobble down” foods, I don’t end up feeling stuffed because of eating too much.
3. At times, I tend to eat quickly and then, I feel uncomfortably full afterwards.
4. I have the habit of bolting down my food, without really chewing it. When this happens I usually feel uncomfortably stuffed because I’ve eaten too much.

#3

1. I feel capable to control my eating urges when I want to.
2. I feel like I have failed to control my eating more than the average person.
3. I feel utterly helpless when it comes to feeling in control of my eating urges.
4. Because I feel so helpless about controlling my eating I have become very desperate about trying to get in control.
#4
1. I don’t have the habit of eating when I’m bored.
2. I sometimes eat when I’m bored, but often I’m able to “get busy” and get my mind off food.
3. I have a regular habit of eating when I’m bored, but occasionally, I can use some other activity to get my mind off eating.
4. I have a strong habit of eating when I’m bored. Nothing seems to help me break the habit.

#5
1. I’m usually physically hungry when I eat something.
2. Occasionally, I eat something on impulse even though I really am not hungry.
3. I have the regular habit of eating foods that I might not really enjoy, to satisfy a hungry feeling even though physically, I don’t need the food.
4. Even though I’m not physically hungry, I get a hungry feeling in my mouth that only seems to be satisfied when I eat a food, like a sandwich, that fills my mouth. Sometimes, when I eat the food to satisfy my mouth hunger, I then spit the food out so I won’t gain weight.

#6
1. I don’t feel any guilt or self-hate after I overeat.
2. After I overeat, occasionally I feel guilt or self-hate.
3. Almost all the time I experience strong guilt or self hate after I overeat.

#7
1. I don’t loose total control of my eating when dieting even after periods when I overeat.
2. Sometimes when I eat a “forbidden food” on a diet, I feel like I “blew it” and eat even more.
3. Frequently, I have the habit of saying to myself, “I’ve blown it now, why not go all the way” when I overeat on a diet. When that happens I eat even more.
4. I have a regular habit of starting strict diets for myself, but I break the diets by going on an eating binge. My life seems to be either a “feast” or “famine.”

#8
1. I rarely eat so much food that I feel uncomfortable stuffed afterwards.
2. Usually about once a month, I eat such a quantity of food; I end up feeling very stuffed.
3. I have regular periods during the month when I eat large amounts of food, either at mealtime or at snacks.
4. I eat so much food that I regularly feel quite uncomfortable after eating and sometimes at bit nauseous.
1. My level of calorie intake does not go up very high or go down very low on a regular basis.
2. Sometimes after I overeat, I will try to reduce my caloric intake to almost nothing to compensate for the excess calories I’ve eaten.
3. I have a regular habit of overeating during the night. It seems that my routine is not to be hungry but overeat in the evening.
4. In my adult years, I have had week long periods when I overeat. It seems I live a life of either “feast” or “famine.”

1. I usually am able to stop eating when I want to. I know when “enough is enough.”
2. Every so often, I experience a compulsion to eat which I can’t seem to control.
3. Frequently, I experience strong urges to eat which I seem unable to control, but at other times I can control my eating urges.
4. I feel incapable of controlling urges to eat. I have to fear of not being able to stop eating voluntarily.

1. I don’t have any problem stopping eating when I feel full.
2. I usually can stop eating when I feel full but occasionally overeat leaving me feeling uncomfortably stuffed.
3. I have a problem stopping eating once I start and usually I feel uncomfortable stuffed after I eat a meal.
4. Because I have a problem not being able to stop eating when I want, I sometimes have to induce vomiting to relieve my stuffed feeling.

1. I seem to eat just as much when I’m with others (family, social gatherings) as when I’m by myself.
2. Sometimes, when I’m other persons, I don’t eat as much as I want to eat because I’m self-conscious about my eating.
3. Frequently, I eat only a small amount of food when others are present, because I’m very embarrassed about my eating.
4. I feel so ashamed about overeating that I pick times to overeat when I know no on will see me. I feel like a “closet eater.”
#13
1. I eat three meals a day with only an occasional between meal snack.
2. I eat 3 meals a day, but I also normally snack between meals.
3. When I am snacking heavily, I get in the habit of skipping regular meals.
4. There are regular periods when I seem to be continually eating, with no planned meals.

#14
1. I don’t think much about trying to control unwanted eating urges.
2. At least some of the time, I feel my thoughts are pre-occupied with trying to control my eating urges.
3. I feel that frequently I spend much time thinking about how much I ate or about trying not to eat more.
4. It seems to me that most of my waking hours are pre-occupied with thoughts about eating or not eating. I feel like I’m constantly struggling not to eat.

#15
1. I don’t think about food a great deal.
2. I have strong cravings for food but they last only for brief periods of time.
3. I have days when I can’t seem to think about anything else but food.
4. Most of my days seem to be pre-occupied with thoughts about food. I feel like I live to eat.

#16
1. I usually know whether or not I’m physically hungry. I take the right portion of food to satisfy me.
2. Occasionally, I feel uncertain about knowing whether or nor I’m physically hungry. At these times, its hard to know how much food I should take to satisfy me.
3. Even though I might know how many calories I should eat, I don’t have any idea what is a “normal” amount of food for me.
Appendix G

Mental Health Questionnaires
## Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of contents</td>
<td>2</td>
</tr>
<tr>
<td>1 Colombia Suicide Severity Rating Scale (C-SSRS), Baseline</td>
<td>3</td>
</tr>
<tr>
<td>2 Colombia Suicide Severity Rating Scale (C-SSRS), Since last visit</td>
<td>7</td>
</tr>
<tr>
<td>3 Patient Health Questionnaire-9 (PHQ-9)</td>
<td>11</td>
</tr>
</tbody>
</table>
1 Colombia Suicide Severity Rating Scale (C-SSRS), Baseline

<table>
<thead>
<tr>
<th>SUICIDAL IDEATION</th>
<th>Lifetime – Time He / She Felt Most Suicidal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Wish to be Dead</strong></td>
<td>Yes  No</td>
</tr>
<tr>
<td>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish</td>
<td></td>
</tr>
<tr>
<td>to fall asleep and not wake up.</td>
<td></td>
</tr>
<tr>
<td>Have you wished you were dead or wished you could go to sleep and not wake up?</td>
<td>[ ] [ ]</td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
</tr>
<tr>
<td>Frequency of Ideation: ___</td>
<td></td>
</tr>
</tbody>
</table>

| **2. Non-Specific Active Suicidal Thoughts**                                     | Yes  No                                    |
| General non-specific thoughts of wanting to end one’s life / commit suicide “I |                                            |
| have thought about killing myself” without thoughts of ways to kill oneself /  |                                            |
| associated methods, intent, or plan during the assessment period.               |                                            |
| Have you actually had any thoughts of killing yourself?                          | [ ] [ ]                                    |
| If yes, describe:                                                                |                                            |
| Frequency of Ideation: ___                                                        |                                            |

| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**| Yes  No                                    |
| Subject endorses thoughts of suicide and has thought of at least one method     |                                            |
| during the assessment period. This is different than a specific plan with and   |                                            |
| place or method details worked out (e.g. thought of method to kill self but    |                                            |
| not a specific plan). Includes person who would say “I thought about taking    |                                            |
| an overdose but I never made a specific plan as to when, where or how I would |                                            |
| actually do it, …… and I would never go through with it”.                      |                                            |
| Have you been thinking about how you might do this?                             |                                            |
| If yes, describe:                                                                |                                            |
| Frequency of Ideation: ___                                                        |                                            |

| **4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan**  | Yes  No                                    |
| Active suicidal thoughts of killing oneself and subject reports having some     |                                            |
| intent to act on such thoughts, as opposed to “I have the thoughts but I      |                                            |
| definitely will not do anything about them”.                                   |                                            |
| Have you had these thoughts and had some intention of acting on them?          |                                            |
| If yes, describe:                                                               |                                            |
| Frequency of Ideation: ___                                                        |                                            |

<p>| <strong>5. Active Suicidal Ideation with Specific Plan and Intent</strong>                    | Yes  No                                    |
| Thoughts of killing oneself with details of plan fully or partially worked out |                                            |
| and subject has some intent to carry it out.                                   |                                            |
| Have you started to work out or worked out the details of how to kill yourself?|                                            |
| Do you intend to carry out this plan?                                          |                                            |
| If yes, describe:                                                               |                                            |
| Frequency of Ideation: ___                                                        |                                            |</p>
<table>
<thead>
<tr>
<th>Intensity of Ideation</th>
<th>Description of Ideation</th>
<th>Lifetime - Time He / She Felt Most Suicidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>Most Common</td>
</tr>
<tr>
<td>Most Common Ideation</td>
<td></td>
<td>Most Severe</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he / she was feeling the most suicidal. Only rate most common if most severe and most common are different.

### Frequency

**How many times have you had these thoughts?**

1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

### Duration

**When you have the thoughts how long do they last?**

1. Fleeting - few seconds or minutes
2. Less than 1 hour / some of the time
3. 1-4 hours / a lot of time
4. 4-8 hours / most of day
5. More than 8 hours / persistent or continuous

### Controllability

**Could / can you stop thinking about killing yourself or wanting to die if you want to?**

1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
6. Does not attempt to control thoughts

### Deterrents

**Are there things - anyone or anything (eg. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?**

1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
5. Deterrents definitely did not stop you
6. Does not apply; wish to die only

### Reasons for Ideation

**What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?**

1. Completely to get attention, revenge or a reaction from others.
2. Mostly to get attention, revenge or a reaction from others.
3. Equally to get attention, revenge or a reaction from others and to end / stop the pain.
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
### SUICIDAL BEHAVIOR

(No multiple answers. If answer is No, answer Yes)

**Actual Attempt:**
A potentially self-injurious act committed with at least some wish to die, as a result of that act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent / desire to die associated with the act, then it can be considered an actual suicide attempt. **There does not have to be any injury or harm, just the potential for injury or harm.** If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Intending Intent: Even if an individual denies intent / wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor / story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

**Have you made a suicide attempt?**

<table>
<thead>
<tr>
<th>Question</th>
<th>Total # of attempts</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What did you do?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you ... as a way to end your life?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you want to die (even a little) when you ...?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were you trying to end your life when you ...?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Or did you think it was possible you could have died from ...?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe: 

**Has subject engaged in Non-Suicidal Self-Injurious Behavior?**

Yes | No
---|---

**Interrupted Attempt:**
When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that actual attempt would have occurred).

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an act rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

**Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?**

If yes, describe:

**Aborted Attempt:**
When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him / herself, instead of being stopped by something else.

**Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?**

If yes, describe:

**Preparatory Acts or Behavior:**
Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note).

**Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?**

If yes, describe:

**Suicidal Behavior:**
Suicidal behavior was present during the assessment period.

**Completed Suicide:**

Yes | No
---|---
**Answer for Actual Attempts Only**

<table>
<thead>
<tr>
<th>Actual Lethality / Medical Damage:</th>
<th>Most Recent Attempt Date:</th>
<th>Worst / Most Lethal Attempt Date:</th>
<th>Initial / First Attempt Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. No physical damage or very minor physical damage (e.g. surface scratches)</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
<tr>
<td>1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
</tbody>
</table>

**Potential Lethality: Only Answer if Actual Lethality=0**

Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).

- 0 = Behavior not likely to result in injury
- 1 = Behavior likely to result in injury but not likely to cause death
- 2 = Behavior likely to result in death despite available medical care
## Colombia Suicide Severity Rating Scale (C-SSRS), Since last visit

### Suicidal Ideation

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5.

<table>
<thead>
<tr>
<th>Question</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wish to be Dead</td>
<td>Yes  No</td>
</tr>
<tr>
<td>Subject endorses thoughts about a wish to be dead or not alive anymore,</td>
<td></td>
</tr>
<tr>
<td>or wish to fall asleep and not wake up.</td>
<td></td>
</tr>
<tr>
<td>Have you wished you were dead or wished you could go to sleep and not</td>
<td></td>
</tr>
<tr>
<td>wake up? Frequency of Ideation: $$___$$</td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
</tr>
<tr>
<td>2. Non-Specific Active Suicidal Thoughts</td>
<td>Yes  No</td>
</tr>
<tr>
<td>General non-specific thoughts of wanting to end one’s life / commit</td>
<td></td>
</tr>
<tr>
<td>suicide “I’ve thought about killing myself” without thoughts of ways to</td>
<td></td>
</tr>
<tr>
<td>kill oneself / associated methods, intent, or plan during the</td>
<td></td>
</tr>
<tr>
<td>assessment period.</td>
<td></td>
</tr>
<tr>
<td>Have you actually had any thoughts of killing yourself?</td>
<td></td>
</tr>
<tr>
<td>Frequency of Ideation: $$___$$</td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
</tr>
<tr>
<td>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent</td>
<td>Yes  No</td>
</tr>
<tr>
<td>to Act</td>
<td></td>
</tr>
<tr>
<td>Subject endorses thoughts of suicide and has thought of at least one</td>
<td></td>
</tr>
<tr>
<td>method during the assessment period. This is different than a specific</td>
<td></td>
</tr>
<tr>
<td>plan with time, place or method details worked out (e.g. thought of</td>
<td></td>
</tr>
<tr>
<td>method to kill self but not a specific plan). Includes person who would</td>
<td></td>
</tr>
<tr>
<td>say, “I thought about taking an overdose but I never made a specific</td>
<td></td>
</tr>
<tr>
<td>plan as to when, where or how I would actually do it….and I would</td>
<td></td>
</tr>
<tr>
<td>never go through with it”.</td>
<td></td>
</tr>
<tr>
<td>Have you been thinking about how you might do this?</td>
<td></td>
</tr>
<tr>
<td>Frequency of Ideation: $$___$$</td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
</tr>
<tr>
<td>4. Active Suicidal Ideation with Some Intent to Act, Without Specific</td>
<td>Yes  No</td>
</tr>
<tr>
<td>Plan</td>
<td></td>
</tr>
<tr>
<td>Active suicidal thoughts of killing oneself and subject reports having</td>
<td></td>
</tr>
<tr>
<td>some intent to act on such thoughts, as opposed to “I have the</td>
<td></td>
</tr>
<tr>
<td>thoughts but I definitely will not do anything about them”.</td>
<td></td>
</tr>
<tr>
<td>Have you had these thoughts and had some intention of acting on them?</td>
<td></td>
</tr>
<tr>
<td>Frequency of Ideation: $$___$$</td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
</tr>
<tr>
<td>5. Active Suicidal Ideation with Specific Plan and Intent</td>
<td>Yes  No</td>
</tr>
<tr>
<td>Thoughts of killing oneself with details of plan fully or partially</td>
<td></td>
</tr>
<tr>
<td>worked out and subject has some intent to carry it out.</td>
<td></td>
</tr>
<tr>
<td>Have you started to work out or worked out the details of how to kill</td>
<td></td>
</tr>
<tr>
<td>yourself? Do you intend to carry out this plan?</td>
<td></td>
</tr>
<tr>
<td>Frequency of Ideation: $$___$$</td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
</tr>
</tbody>
</table>
### INTENSITY OF IDEATION

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Description of ideation</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Most Common</td>
</tr>
</tbody>
</table>

#### Most Common ideation:

#### Most Severe ideation:

The following features should be rated with respect to both most common and most severe types of ideation experienced since last visit. Only rate most common if most severe and most common are different.

#### Frequency

**How many times have you had these thoughts?**

1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

#### Duration

**When you have the thoughts how long do they last?**

1. Feeling - few seconds or minutes
2. Less than 1 hour / some of the time
3. 1-4 hours / a lot of time
4. 4-8 hours / most of day
5. More than 8 hours / persistent or continuous

#### Controllability

**Could / can you stop thinking about killing yourself or wanting to die if you want to?**

1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
6. Does not attempt to control thoughts

#### Deterrents

**Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?**

1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
5. Deterrents definitely did not stop you
6. Does not apply. Wish to die only

#### Reasons for ideation

**What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?**

1. Completely to get attention, revenge or a reaction from others.
2. Mostly to get attention, revenge or a reaction from others.
3. Equally to get attention, revenge or a reaction from others and to end / stop the pain. 
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
**SUICIDAL BEHAVIOR**
(Check all that apply; so long as these are separate events; must ask about all types)

<table>
<thead>
<tr>
<th>Actual Attempt:</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent / desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun in mouth but gun is broken, no injury results, this is considered an attempt.</td>
<td>Yes</td>
</tr>
<tr>
<td>Inferring intent: Even if an individual denies intent / wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor / story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Have you done anything to harm yourself?**

**Have you done anything dangerous where you could have died?**

- **What did you do?**
  - **Did you use a method to end your life?**
  - **Did you want to die (even a little) when you _____?**
  - **Were you trying to end your life when you ____?**
  - **Or did you think it was possible you could have died from ____?**

**Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?** (Self-Injurious Behavior without suicidal intent)

If yes, describe.

**Has subject engaged in Non-Suicidal Self-Injurious Behavior?**

**Interrupted Attempt:**
When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred).

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has rope around neck but has not yet started to hang - is stopped from doing so.

**Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?**

If yes, describe.

**Aborted Attempt:**
When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him / herself instead of being stopped by something else.

**Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?**

If yes, describe.

**Preparatory Acts or Behavior:**
Acts or preparations towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note).

**Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?**

If yes, describe.

**Suicidal Behavior:**
Suicidal behavior was present during the assessment period.

**Completed Suicide:**

No
## Answer for Actual Attempts Only

<table>
<thead>
<tr>
<th>Actual Lethality / Medical Damage:</th>
<th>Most Recent Attempt Date:</th>
<th>Worst / Most Lethal Attempt Date:</th>
<th>Initial / First Attempt Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. No physical damage or very minor physical damage (e.g., surface scratches).</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
</tr>
<tr>
<td>1. Minor physical damage (e.g., lethargic speech, first degree burns, mild bleeding, sprains).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Potential Lethality: Only Answer if Actual Lethality=0

Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire, no medical damage; laying on train tracks with oncoming train but pulled away before run over).

- 0 = Behavior not likely to result in injury
- 1 = Behavior likely to result in injury but not likely to cause death
- 2 = Behavior likely to result in death despite available medical care
3 Patient Health Questionnaire-9 (PHQ-9)

**Patient Health Questionnaire-9**

Only the patient (subject) should enter information onto this questionnaire.

<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by any of the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Scoring for use by study personnel only**

\[ \text{Score} = 0 + \text{Box 1} + \text{Box 2} + \text{Box 3} \]

\[ \text{Total Score: } \frac{\text{Score}}{9} \]

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>[]</td>
<td>[]</td>
<td>[]</td>
<td>[]</td>
</tr>
</tbody>
</table>

Copyright © 2005 Pfizer, Inc. All rights reserved. Reproduced with permission.
Medical Events of Special Interest (MESI)
<table>
<thead>
<tr>
<th>MESIs</th>
<th>Definitions</th>
<th>Event Adjudication Committee (EAC)</th>
<th>Calcitonin Monitoring Committee (CMC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication errors concerning trial products</td>
<td>The following should be reported:</td>
<td>No adjudication</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• administration of wrong drug or use of wrong device</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• wrong route of administration, such as intramuscular instead of subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• administration of a high dose with the intention to cause harm, eg suicide attempt</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• administration of an accidental overdose, i.e. dose which may lead to significant health consequences, as judged by the Investigator, irrespective of whether the SAE criteria are fulfilled or not</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected transmission of an infectious agent via a trial product</td>
<td>Events which may be mediated by transmission of an infectious agent via a trial product (as judged by the Investigator)</td>
<td>No adjudication</td>
<td>N/A</td>
</tr>
<tr>
<td>MESIs</td>
<td>Definitions</td>
<td>Event Adjudication Committee (EAC)</td>
<td>Calcitonin Monitoring Committee (CMC)</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td>--------------------------------------</td>
</tr>
</tbody>
</table>
| **Death**                                                          | All types of death must be reported:  
  - Cardiovascular death, includes  
    - Sudden cardiac death  
    - Death due to acute myocardial infarction  
    - Death due to heart failure or cardiogenic shock  
    - Death due to stroke  
    - Death due to other cardiovascular causes  
  - Non-cardiovascular death (any death not covered by cardiac death or vascular death)  
  - Undetermined cause of death  | All events will be adjudicated | N/A                               |
| **Acute coronary syndrome**                                         | All types of myocardial infarction must be reported:  
  - Acute MI  
    - Spontaneous MI  
    - Percutaneous coronary intervention (PCI) related MI  
    - Coronary artery bypass graft surgery (CABG) related MI  
  - Silent or Prior MI (with or without symptoms)  
  - Re-infarction  
  All events with new onset or worsening unstable angina requiring hospitalisation must be reported. The EAC charter provides further details and definitions relevant to adjudication. | All events will be adjudicated | N/A                               |
| **Cerebrovascular event**                                          | Stroke is defined as the rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral haemorrhage with no apparent non- | All events will be adjudicated | N/A                               |
### MESIs Definitions

<table>
<thead>
<tr>
<th>Event Adjudication Committee (EAC)</th>
<th>Calcitonin Monitoring Committee (CMC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>vase</strong>cular cause (eg, trauma, tumor, or infection).</td>
<td></td>
</tr>
<tr>
<td>TIA is defined as a transient (&lt;24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction</td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td><strong>All heart failure requiring hospitalisation defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay will be adjudicated</strong></td>
</tr>
<tr>
<td>Clinical manifestations of new episode or worsening of existing heart failure.</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Stent thrombosis</strong></td>
<td><strong>To be adjudication</strong></td>
</tr>
</tbody>
</table>
| Following should be reported:  
  - Definite Stent Thrombosis  
  - Probable Stent Thrombosis  
  - Possible Stent Thrombosis | |
| **Revascularisation procedure** | **Only coronary will be adjudicated** |
| A coronary revascularisation procedure is defined as either CABG or a PCI (eg, angioplasty, coronary stenting).  
  A peripheral revascularisation procedure is defined as vascular surgery or percutaneous intervention. | N/A |
<p>| <strong>Hospitalisation for Cardiac Arrhythmia</strong> | <strong>No adjudication</strong> |
| Specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de | N/A |</p>
<table>
<thead>
<tr>
<th>MESIs</th>
<th>Definitions</th>
<th>Event Adjudication Committee (EAC)</th>
<th>Calcitonin Monitoring Committee (CMC)</th>
</tr>
</thead>
</table>
| pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement | Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis:  
  - severe acute upper abdominal pain  
  - elevated blood levels of pancreatic enzymes (lipase, amylase) 3xUNR  
  - characteristic imaging finding (ultrasound, computerised axial tomography (CT), magnetic resonance imaging (MRI))  
  Chronic pancreatitis will be defined by characteristic imaging finding (ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings | To be adjudicated | N/A |
| Pancreatitis or acute, severe and persistent abdominal pain leading to a suspicion of pancreatitis | Gallbladder disease including biliary colic, symptomatic cholelithiasis, cholecystitis. | No adjudication | |
| Elevated lipase or amylase ≥ 3xUNR        | No Adjudication                                                             |                                   |                                       |
| Neoplasm                                  | All types of neoplasms must be reported including:  
  - Malign neoplasm  
  - In situ neoplasm  
  - Benign neoplasm  
  - Neoplasms of uncertain or unknown behaviour | To be adjudicated | N/A |
<p>| Thyroid disease                           | All disorders of thyroid gland must | Only thyroid | Can be |</p>
<table>
<thead>
<tr>
<th>MESIs</th>
<th>Definitions</th>
<th>Event Adjudication Committee (EAC)</th>
<th>Calcitonin Monitoring Committee (CMC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MESIs</td>
<td>Definitions</td>
<td>Event Adjudication Committee (EAC)</td>
<td>Calcitonin Monitoring Committee (CMC)</td>
</tr>
<tr>
<td></td>
<td>be reported.</td>
<td>disorders requiring thyroidectomy will be adjudicated</td>
<td>identified by the CMC or by the Investigator</td>
</tr>
<tr>
<td>Any confirmed episode of calcitonin value ≥ 20 ng/L, if not already reported as an ongoing MESI</td>
<td>All confirmed episodes of values ≥ 20 ng/L.</td>
<td>No adjudication</td>
<td>All calcitonin values ≥ 10 ng/L will be evaluated by the CMC</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Acute renal failure, insufficiency or clinically significant paraclinical abnormalities indicating a decrease in renal function must be reported</td>
<td>No adjudication</td>
<td>N/A</td>
</tr>
<tr>
<td>Severe hypoglycaemic event</td>
<td>An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions</td>
<td>No adjudication</td>
<td>N/A</td>
</tr>
<tr>
<td>Immunogenicity event (allergic reactions including allergic reactions at injection sites, and immune-complex disease)</td>
<td>All events suspected to involve an immune reaction to trial product must be reported. Events to be reported can be defined according to the below: A) Immediate hypersensitivity reactions Typically occurring within minutes after administration of the antigen. Clinical symptoms include (but are not limited to): • Urticaria (pruritic wheals with surrounding erythema, involving superficial layers of the skin). This includes local allergic reactions at</td>
<td>No adjudication</td>
<td>N/A</td>
</tr>
<tr>
<td>MESIs</td>
<td>Definitions</td>
<td>Event Adjudication Committee (EAC)</td>
<td>Calcitonin Monitoring Committee (CMC)</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>injection site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Angioedema (Swelling of the affected area of the skin, involving deep layers of the skin and the subcutis; painful rather than pruritic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Allergic rhinitis (with symptoms like sneezing, itching, nasal congestion, itchy and watery eyes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Exacerbation of pre-existing or de novo development of allergic asthma (acute bronchoconstriction with symptoms like chest tightness, shortness of breath, wheezing and cough)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Systemic anaphylaxis (typically presented as generalised skin lesions/pruritus, hypotension, upper/lower respiratory tract swelling/constriction, shock)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B) Delayed Hypersensitivity Reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typically occurring 48 to 72 hours after exposure to the antigen and manifested by various types of skin rashes with or without pruritus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MESIs</td>
<td>Definitions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| C) De novo development or exacerbation of pre-existing immune complex disease. Most frequent clinical syndromes include: | • Lupus erythematosus  
• Vasculitis syndromes  
• Non-viral hepatitis  
• Pneumonitis  
• Arthritis  
• Glomerulonephritis  

D) Anti-liraglutide antibody formation: | • Detected based on laboratory assessment of antibody titres undertaken due to suspected immunological reaction to trial product  
• Detected based on suspicion of neutralising effect of antibodies, i.e. in case of unexplained rapid deterioration of glycaemic control |

<table>
<thead>
<tr>
<th>Adverse events leading to withdrawal</th>
<th>If not any of the mentioned MESIs No adjudication</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Disorders</td>
<td>All Mental and Behavioural Disorders included in ICD-10 or DSM-IV classification systems, included those diagnosed by C-SSRS or PHQ-9 score must be reported</td>
<td>No adjudication</td>
</tr>
</tbody>
</table>
Calcitonin Monitoring Committee - Screening of Calcitonin (CT) Levels
# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of contents</td>
<td>2</td>
</tr>
<tr>
<td>1 Background</td>
<td>3</td>
</tr>
<tr>
<td>2 Procedure</td>
<td>4</td>
</tr>
<tr>
<td>3 Evaluation and follow-up</td>
<td>5</td>
</tr>
<tr>
<td>3.1 CT ≥ 100 ng/l</td>
<td>5</td>
</tr>
<tr>
<td>3.2 CT ≥ 50 ng/l and &lt; 100 ng/l</td>
<td>5</td>
</tr>
<tr>
<td>3.3 CT ≥ 20 ng/l and &lt; 50 ng/l</td>
<td>5</td>
</tr>
<tr>
<td>3.4 CT ≥ 10 ng/l and &lt; 20 ng/l</td>
<td>6</td>
</tr>
<tr>
<td>4 References</td>
<td>7</td>
</tr>
</tbody>
</table>
1 Background

The approach that follows was developed in collaboration with two leading clinical thyroid experts: and represents a synthesis of the medical literature and extensive personal experience.

All previous calcitonin screening studies in the literature have been performed in patients with thyroid nodular disease. The nodular status of the subjects in the current trial will mostly be unknown. Nevertheless, for the purpose of follow-up, it will be assumed that the same calcitonin cut-offs will apply. Up to 50% of subjects in the age group to be studied in the current trial will have clinical or subclinical thyroid nodules; the majority of which will be clinically apparent. Subjects with a known personal or family history of medullar thyroid cancer (MTC) or multiple endocrine neoplasia type 2 (MEN 2) and subjects with a screening calcitonin of 2: 50ng/l will be excluded from the trial.
2 Procedure

A blood sample will be drawn at trial visits 1, 2, 4, 7, 10, 13, 16, 17 and 20 for measurement of calcitonin.

Monitoring of calcitonin at regular intervals will be implemented in the trial and performed by an independent Calcitonin Monitoring Committee (CMC) of thyroid experts. The CMC will be blinded to trial treatment. The CMC may require additional information from the site, require more frequent calcitonin measurements or will provide Investigators with recommendations as to individual follow-up (i.e. laboratory tests and/or other relevant diagnostic procedures) in subjects with elevated calcitonin levels.

All calcitonin values 10 ng/l will be flagged on the laboratory reports from the central laboratory and will be submitted to the CMC, together with relevant supplementary data, i.e. subject's demographics, diabetes history, concomitant medical history, concomitant medications, smoking status, results of other laboratory tests conducted as part of trial procedures as well as events reported during the trial.

For subjects with a calcitonin value 20 ng/l (from Visit 2 and onwards) a repeat measurement of calcitonin must be done preferably within four weeks, and the event "elevated calcitonin" should be reported as a MESI.

In cases where the follow-up action recommended by the CMC, based on the elevated calcitonin levels, results in establishing the presence of a thyroid disease, the thyroid disease should be reported as a new MESI.
### 3 Evaluation and follow-up

The summary for a rationale for the use of specific calcitonin (CT) values to trigger medical evaluation and overview of the algorithm to be followed by the CMC is provided below:

#### 3.1 CT 100 ng/l

These values were found in 0.15% of the population published by Costante et al., and in one subject (on active comparator) in the liraglutide development program. For a baseline (pre-randomisation) or post-randomisation value of 2:100 ng/l, the subject should be assumed to have significant C-cell disease and a high likelihood of having medullary carcinoma of the thyroid. Diagnostic evaluation should consist of thyroid ultrasound, fine needle aspiration of any nodules >1 cm and potentially surgery with neck dissection. Family history of MTC or MEN2 should be evoked and a rearranged during transfection (RET) proto-oncogene analysis should be undertaken.

#### 3.2 CT 50 ng/l and < 100 ng/l

These values were found in 0.18% of the population published by Costante et alJ. If baseline values are in this range subjects should have a repeat measurement of calcitonin to be reviewed by the CMC for recommendation of diagnostic evaluation which will likely include ultrasound examination. If there is no contraindication, subjects should undergo a pentagastrin stimulation test (EU and Europe) [NB: pentagastrin is contraindicated in subjects with known coronary artery disease].

If subjects develop a calcitonin value within this specified range post-randomisation, specific medical evaluation will be indicated by the CMC including a thyroid ultrasound and a pentagastrin stimulation test if available and if not contraindicated. Those subjects with positive pentagastrin stimulation tests will be considered to undergo surgery. In the US where pentagastrin is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information informing the need for surgery. Further, all individual subject data will be reviewed by the CMC that will make diagnostic and therapeutic recommendations to the Investigator of that subject.

#### 3.3 CT 20 ng/l and <50 ng/l

These values will be found in up to 1% of subjects. At this level of calcitonin based on data from Costante et alJ, the predictive value of the level itself for clinically significant C-cell disease begins to fall. However, up to 25% of these subjects have a positive pentagastrin stimulation test. The likelihood of harboring a medullary carcinoma >1 cm with calcitonin in this range is extremely low.
Subjects with calcitonin levels in this range at baseline should have the measurement repeated for confirmation. This cohort will provide valuable insights into any potential effect that liraglutide may have on calcitonin levels in subjects with values above the normal range at baseline.

If the repeat value is \( \geq 50 \text{ ng/l} \) or if any subsequent value measured during the trial exceeds \( 50 \text{ ng/l} \) then the subject moves into the evaluation category listed above for values \( 50 \text{ ng/l} \).

The decision to proceed or not to proceed with surgery in subjects without cytological confirmation of disease should be made by the attending physician in consultation with subject, based on recommendation from the CMC.

3.4 CT 2: 10 ng/l and < 20 ng/l

These values may be found in ~2.5 to 4% of the trial population. Costante et alii had 216 patients in this category. 11126 had a subsequent basal (unstimulated) CT of \( 33 \text{ ng/l} \), and had C-cell hyperplasia at surgery, a lesion of unknown clinical significance. Two other studies used a cutoff of CT > 10 ng/l to screen for C cell disease, but they do not provide sufficient information on patients with basal CT > 10 ng/l and < 20 ng/l to allow conclusions.

In cases of calcitonin values of 10 ng/l and <20 ng/l the Investigator should evaluate confounding factors and repeat calcitonin at next protocol scheduled calcitonin visit.

Specific history should be elicited to identify these confounders. Confounders: i.e. drugs (H2 blockers, Proton Pump Inhibitors (PPIs)), other causes of hypergastrinemia (e.g. pernicious anemia), smoking, autoimmune thyroiditis, presence of heterophilic antibodies should be factored into the interpretation of the values on a case-by-case basis. If drugs can be discontinued safely, basal calcitonin can be repeated after a washout period. Gastrin levels return to the normal range by \(-10 \text{ days after stopping PPIs}\).\(^2\)
4 References


