



## **Liraglutide 3.0 mg for Weight Management**

**NDA 206-321**

**Briefing Document**

**Endocrinologic and Metabolic Drug Advisory Committee**

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## List of Abbreviations and Definitions

|         |  |
|---------|--|
| ADA     | American Diabetes Association                        |
| ADME    | Absorption, distribution, metabolism and elimination |
| AE      | Adverse event  |
| AGRP    | agouti-related protein                               |
| AHI     | apnea-hypopnea index                                 |
| ALT     | alanine aminotransferase                             |
| ANCOVA  | analysis of covariance                               |
| ANOVA   | analysis of variance                                 |
| ARC     | arcuate nucleus                                      |
| AST     | aspartate aminotransferase                           |
| AUC     | area under the curve                                 |
| BMI     | body mass index                                      |
| BOCF    | baseline observation carried forward                 |
| BP      | blood pressure                                       |
| Bpm     | beats per minute                                     |
| CART    | cocaine- and amphetamine-regulated transcript        |
| CI      | confidence interval                                  |
| CIS     | carcinoma <i>in situ</i>                             |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration    |
| CL/F    | Plasma clearance                                     |
| Cmax    | maximum concentration                                |
| CPAP    | continuous positive airway pressure                  |
| CrCL    | creatinine clearance                                 |
| CRO     | contract research organization                       |
| C-SSRS  | Columbia Suicide Severity Rating Scale               |
| CT      | computerized axial tomography                        |
| CV      | cardiovascular                                       |
| CVD     | cardiovascular disease                               |
| DCIS    | ductal carcinoma <i>in situ</i>                      |
| DEXA    | dual energy x-ray absorptiometry                     |
| DPP-4   | dipeptidyl peptidase-4                               |
| DTSQs   | Diabetes Treatment Satisfaction Questionnaire        |
| E       | number of events                                     |
| EAC     | Event Adjudication Committee                         |
| ECG     | Electrocardiogram                                    |
| eCRF    | electronic case report form                          |
| EMA     | European Medicines Agency                            |
| EMDAC   | Endocrinologic and Metabolic Drug Advisory Committee |
| EOSS    | Edmonton Obesity Staging System                      |
| ESS     | Epworth Sleepiness Scale                             |



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|                     |   |
|---------------------|---|
| ETD                 | estimated treatment difference  |
| FAS                 | full analysis set   |
| FDA                 | Food and Drug Administration  |
| FOSQ                | Functional Outcomes of Sleep Questionnaire                                  |
| FPG                 | fasting plasma glucose  |
| GD                  | gestational day   |
| GLP-1               | glucagon-like peptide-1   |
| HbA <sub>1c</sub>   | glycosylated hemoglobin   |
| HDL                 | high-density lipoprotein  |
| HLGT                | High Level Group Terms  |
| HLTs                | High Level Terms  |
| HOMA                | Homeostasis Model Assessment  |
| HOMA-B              | HOMA of beta-cell function  |
| HOMA-IR             | HOMA of insulin resistance  |
| HR                  | heart rate  |
| hsCRP               | high-sensitivity C-reactive protein   |
| ICH                 | International Conference on Harmonization                                   |
| IGF-1               | insulin-like growth factor-1  |
| IWQoL-Lite          | Impact of Weight on Quality of Life-Lite questionnaire                      |
| LDL                 | low-density lipoprotein   |
| LEADER <sup>®</sup> | Liraglutide effect and action in diabetes: evaluation of CV outcome results |
| LOCF                | last observation carried forward  |
| MACE                | Major Adverse Cardiovascular Events   |
| MedDRA              | Medical Dictionary for Regulatory Activities                                |
| MEN 1               | multiple endocrine neoplasia type 1   |
| MEN 2               | multiple endocrine neoplasia type 2   |
| MESI                | medical events of special interest  |
| MI                  | myocardial infarction   |
| MRCP                | Magnetic Resonance Cholangiopancreatography                                 |
| MRI                 | magnetic resonance imaging  |
| MTC                 | medullary thyroid carcinoma   |
| N                   | number of patients  |
| NDA                 | New Drug Application  |
| NEP                 | neutral endopeptidase   |
| NOAEL               | no-observed-adverse-effect level  |
| NPY                 | neuropeptide Y  |
| NAACCR              | North American Association of Central Cancer Registries                     |
| OADs                | oral anti-diabetic drugs  |
| OGTT                | oral glucose tolerance test   |
| OSA                 | obstructive sleep apnea   |
| PAI-1               | plasminogen activator inhibitor-1   |
| PCOS                | polycystic ovary syndrome   |

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|             |   |
|-------------|---|
| PHQ-9       | Patient Health Questionnaire 9                        |
| PI          | prescribing information                               |
| PMR         | Post Marketing Requirements                           |
| POMC        | proopiomelanocortin                                   |
| PSG         | polysomnography                                       |
| PT          | preferred term  |
| PVN         | paraventricular nucleus                               |
| PYE         | patient years of exposure                             |
| PYR         | patient years at risk                                 |
| QTc         | corrected QT interval                                 |
| R           | event rate per 100 patient exposure years             |
| REMS        | Risk Evaluation and Mitigation Strategy               |
| RR          | relative risk   |
| s.c.        | subcutaneous  |
| SAEs        | serious adverse events                                |
| SD          | standard deviation                                    |
| SF-36       | 36-item Short-Form health status survey               |
| SMQs        | Standard MedDRA Queries                               |
| SOC         | system organ class                                    |
| SU          | sulfonylurea  |
| T2DM        | type 2 diabetes mellitus                              |
| TEAE        | Treatment-emergent adverse event                      |
| TRIM-Weight | Treatment Related Impact Measure-Weight questionnaire |
| TVDT        | tumor volume doubling times                           |
| ULN         | upper limit of the normal range                       |
| VAS         | visual analog scale                                   |
| VLDL        | very low-density lipoprotein                          |
| Vz/F        | volume of distribution                                |
| WC          | waist circumference                                   |
| WG          | weight gain   |
| WL          | weight loss   |

## 1 Executive Summary

Novo Nordisk is seeking approval for liraglutide 3.0 mg, a glucagon-like peptide 1 (GLP-1) receptor agonist for once daily subcutaneous (s.c.) administration, for chronic weight management as an adjunct to a reduced calorie diet and increased physical activity in adults with an initial body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup> (obese) or  $\geq 27$  kg/m<sup>2</sup> (overweight) with at least one weight-related co-morbidity.

Liraglutide is a GLP-1 analog with 97% amino acid homology to native GLP-1,<sup>1</sup> a post-prandially released gut hormone with numerous benefits on glucose metabolism and appetite regulation. Originally described as an incretin hormone, GLP-1 lowers blood glucose in a glucose-dependent manner by stimulation of insulin secretion and inhibition of glucagon secretion through activation of GLP-1 receptors in the pancreas.<sup>2-4</sup> GLP-1 also delays gastric emptying and consequently nutrient absorption after a meal.<sup>3,5,6</sup> GLP-1 has been implicated as a physiological regulator of appetite and food intake, which signals satiety through specific activation of GLP-1 receptors in appetite centers of the brain.<sup>7-12</sup> Thus in humans, weight loss with liraglutide is primarily mediated via appetite regulation (increased fullness and satiety and decreased hunger and prospective food consumption), leading to reduced caloric intake.<sup>13</sup> As a GLP-1 receptor agonist, liraglutide belongs to a different pharmacological class than the other weight management products currently available, with a different mechanism of action.<sup>14</sup> Liraglutide has a unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycemic control and other weight-related co-morbidities.

Liraglutide was approved in the U.S. in 2010 at doses up to 1.8 mg and is currently marketed for the treatment of type 2 diabetes mellitus (T2DM) worldwide under the brandname Victoza®.<sup>15</sup> Since the approval of Victoza®, the number of patient years of exposure (PYE) to liraglutide is estimated to be greater than 3.3 million.

### Need for effective and safe pharmacotherapy to treat obesity

Obesity is common, serious and costly. In the U.S. alone, more than one-third of adults and 17% of youth are obese.<sup>16</sup> Obesity is a multifactorial, chronic disease that is associated with major co-morbidities, including hypertension, hyperglycemia, type 2 diabetes mellitus, dyslipidemia, certain types of cancer, obstructive sleep apnea and atherosclerosis,<sup>17-20</sup> as well as with reduced life expectancy.<sup>21,22</sup> Individuals with obesity also suffer physical symptoms (e.g., joint pain, urinary incontinence), functional limitations (e.g., impaired mobility), and psycho-social problems (e.g., body image disorders and depression).<sup>23-27</sup> In 2010, the conditions of overweight and obesity were estimated to cause 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life-years (DALYs) worldwide.<sup>28</sup>

Even a moderate weight loss of 5–10% has been shown to have significant health benefits in terms of improving weight-related co-morbidities, physical symptoms and quality of life.<sup>29-32</sup> Lifestyle intervention, in the form of dietary and behavioral changes and exercise, is the first line of treatment

for obesity. While initially effective for many patients, this approach alone tends not to be sustainable and many patients regain weight after weight loss.<sup>17,33,34</sup> At the other extreme of the therapeutic continuum, surgical treatments offer an effective alternative for some people with severe obesity; however, these are unavailable or unsuitable for many obese individuals and are often associated with risks and complications.<sup>17,35</sup> The use of surgical intervention to treat obesity indicates the overall seriousness of the disease and its co-morbidities, and provides an additional rationale for the development of treatments that can effectively manage obesity earlier in its course. Pharmacotherapy has the potential to fill the therapeutic gap and may serve as a valuable adjunct to lifestyle intervention in achieving and sustaining clinically relevant weight loss. Despite two recently approved pharmacologic therapies for weight management, lorcaserin and phentermine/topiramate in the U.S. in 2012, the range of weight management medications currently available is limited and unlikely to meet the needs of all individuals who can benefit from weight loss.<sup>36</sup> There is a need for new and diverse treatment options.

### **Non-clinical pharmacology and toxicology**

The non-clinical safety studies conducted to support approval of liraglutide at doses up to 1.8 mg for the use in T2DM (Victoza<sup>®</sup>) are also considered supportive for the review of liraglutide 3.0 mg for weight management. The non-clinical safety pharmacology program raised no safety concerns for humans. Liraglutide is neither genotoxic nor mutagenic, and there were no increases in overall benign and malignant tumor burden in two-year carcinogenicity studies in mice and rats. The only treatment-induced neoplasms associated with lifetime liraglutide administration in rodent carcinogenicity studies were C-cell tumors of the thyroid. The risk to humans for liraglutide-induced C-cell tumors is considered to be low, based on species differences in the number of C-cells and GLP-1 receptor expression and action in the thyroid. Animal studies with liraglutide did not indicate a risk for development of pancreatitis or proliferative pancreatic lesions, including pancreatic cancer. A numerical increase in the incidence of cholecystitis was observed in male and female mice after lifetime treatment with liraglutide. There was no dose dependency, and the finding only attained statistical significance and exceeded the historical control range in the low dose females. No gallbladder histopathology was observed in toxicity studies in mice and monkeys. No abortions were observed in embryo-fetal studies in rats and rabbits. Few fetal abnormalities were observed with no specific organs affected. These were likely related to reduced maternal food intake.

### **Clinical pharmacology**

#### ***Pharmacokinetics and dose***

The pharmacokinetic characteristics of liraglutide 3.0 mg were consistent with those previously established for liraglutide at doses up to 1.8 mg (Victoza<sup>®</sup>), and exposure increased proportionally to dose. A relatively slow absorption ( $T_{\max}$  8-12 hours) and  $t_{1/2}$  of approximately 13 hours, coupled with the high plasma protein binding capability and decreased susceptibility to degradation, make liraglutide suitable for once-daily administration, at any time of the day. Liraglutide is fully degraded in the body with no single organ as a major route of elimination, and no active metabolites

of liraglutide have been identified. As with Victoza<sup>®</sup>, no dose adjustment is required for co-administered drugs, based on pharmacokinetic drug-drug-interaction trials with liraglutide. Likewise, no dose adjustment is required for any sub-population, based on demographic characteristics, or for renal or hepatic impairment.

A clear exposure-response relationship for mean and categorical weight loss was observed for the entire exposure range, including exposures associated with the 3.0 mg dose. Liraglutide doses of 3.0 mg were required for exposures that led to a clinically relevant weight loss in all studied sub-populations.

### ***Pharmacodynamics***

Weight loss with liraglutide 3.0 mg in overweight and obese patients is primarily mediated by a decrease in appetite, as evidenced by increased patient ratings of satiety and fullness and decreased ratings of hunger and prospective food consumption following a 5-hour standardized mixed meal, and subsequent reduction in caloric intake. The glucose-dependent glycemic effects of liraglutide 3.0 mg involve the reduction of fasting and postprandial glucose levels, decreased secretion of postprandial glucagon and improvements in the insulin secretion profile based on a mixed meal test. Gastric emptying with liraglutide 3.0 mg was equivalent to liraglutide 1.8 mg and placebo, as assessed by the acetaminophen method over 5 hours following a mixed meal test. Similar to findings with doses up to 1.8 mg, liraglutide 3.0 mg delayed gastric emptying during the first hour of the meal, which likely contributed to the observed improvement in postprandial glycemia.

### **Overview of global clinical development program**

The clinical development program for liraglutide 3.0 mg in weight management included six trials that enrolled close to 6,000 obese or overweight patients with at least one weight-related co-morbidity ([Table 1-1](#)). Of these, more than 3,300 patients were exposed to liraglutide 3.0 mg in phase 2 and 3 trials. A single-blind two-year pre-planned extension of the largest phase 3 trial (1839) is currently ongoing and due to complete in 2015.

All trials were randomized, double-blind, controlled (placebo and/or active comparator) and included participants generally representative of the intended target population. The six trials included one phase 1 clinical pharmacology trial (trial 3630) which evaluated the pharmacokinetic properties of liraglutide 3.0 mg, as well as its effects on gastric emptying, appetite, energy intake and energy expenditure, one phase 2 liraglutide dose-finding trial (trial 1807) which identified the 3.0 mg as the optimal dose for further evaluation in the phase 3a program and four phase 3a trials (1839, 1923, 1922, and 3970). Three of the phase 3 trials were of 56 weeks duration and one was a 32-week trial. One phase 3 trial was conducted in patients with T2DM, while another was conducted in patients with obstructive sleep apnea (OSA). In the phase 2 and 3 trials, participants received lifestyle intervention in the form of an energy-restricted diet (approximately 500 kcal/day energy deficit based on individual requirements) and exercise counseling (recommended minimum physical activity of 150 minutes/week).

**Table 1–1 Global clinical development program for weight management**

| Liraglutide 3.0 mg weight management program<br>Liraglutide 3.0 mg 3,384 patients; Placebo 1,941 patients                                     |   |      |  |  |
|---|---|------|--|--|
|   | Overview  | N    | BMI (kg/m <sup>2</sup> )               | Duration   |
| <b>Phase 1</b>  | Clinical pharmacology   |      |  |  |
| <b>Trial 3630</b>   | Obese<br>Liraglutide 3.0 mg, 1.8 mg, placebo                                    | 49   | 30 - 40                                | 5 weeks  |
| <b>Phase 2</b>  | Dose-finding  |      |  |  |
| <b>Trial 1807</b>   | Obese<br>Liraglutide 1.2, 1.8, 2.4 and 3.0 mg,<br>placebo, orlistat             | 564  | 30 - 40                                | 20 weeks plus 84-week<br>extension (and interim analysis<br>at 52 weeks)   |
| <b>Phase 3</b>  |   |      |  |  |
| <b>Trial 1839</b>   | Overweight/obese<br>With or without pre-diabetes<br>Liraglutide 3.0 mg, placebo | 3731 | ≥ 27 with<br>co-morbidities<br>or ≥ 30 | 56 weeks plus 12-week re-<br>randomized treatment period*<br>(patients with pre-diabetes at<br>enrollment continued in a 2-<br>year extension) |
| <b>Trial 1923</b>   | Overweight/obese<br>Weight maintenance<br>Liraglutide 3.0 mg, placebo           | 422  | ≥ 27 with<br>co-morbidities<br>or ≥ 30 | 56 weeks plus 12-week off-<br>treatment observational period   |
| <b>Trial 1922</b>   | Overweight/obese<br>Type 2 diabetes<br>Liraglutide 3.0 mg, 1.8 mg, placebo      | 846  | ≥ 27                                   | 56 weeks plus 12-week off-<br>treatment observational period   |
| <b>Trial 3970</b>   | Obese<br>Obstructive sleep apnea<br>Liraglutide 3.0 mg, placebo                 | 359  | ≥ 30                                   | 32 weeks   |
| Lifestyle modification in the form of a 500 kcal/day deficit diet and<br>increased physical activity was included in all phase 2 and 3 trials |   |      |  |  |

\*Re-randomized period was for patients without pre-diabetes

N: number of randomized patients.

As of the New Drug Application (NDA) submission cut-off date (02 July 2013), 3,384 patients were exposed to liraglutide 3.0 mg that accounted for 2,974 patient years of exposure (PYE) with liraglutide 3.0 mg across the five phase 2 and 3 weight management trials. According to the 120-Day Safety Update (cut-off date: 11 November 2013) based on the extension of trial 1839, 1,087 patients were exposed to liraglutide 3.0 mg that accounted for an additional 1,115 patient years of exposure.

### Clinical efficacy

Efficacy was evaluated according to the benchmarks set forth in the current FDA guidance on the development of products for weight management,<sup>37</sup> which states that a product can be considered effective if either of the following occurs after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant

- The proportion of patients who lose at least 5% of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

The primary endpoints of the phase 3 trials are shown in [Table 1–2](#). Treatment with liraglutide 3.0 mg, as adjunct to diet and exercise, resulted in significantly greater weight loss than diet and exercise alone in overweight and obese patients with at least one weight-related co-morbidity, including patients with T2DM and OSA ([Table 1–3](#)). Liraglutide 3.0 mg met the pre-specified mean and categorical weight-loss endpoints in each of the phase 2 and 3 individual trials. In each trial, more than 35% of patients in the group assigned to liraglutide 3.0 mg achieved the 5% weight loss benchmark set forth in the FDA guidance (the proportion across the trials was 46 to 78%), and the proportion achieving the benchmark was more than twice the proportion that did so in the group assigned to placebo (i.e., diet and exercise alone) (which ranged from 13.5 to 30% across trials) ([Table 1–3](#)). Among all the demographic sub-populations evaluated (defined according to sex, age, race/ethnicity, BMI category and glycemic status), liraglutide 3.0 mg had greater efficacy for mean and categorical weight loss than diet and exercise alone, and all met the FDA categorical benchmark. In trials with a treatment duration of at least 56 weeks, mean weight loss was generally maintained as long as patients remained on treatment with liraglutide 3.0 mg, and for up to 2 years in completers of the 2-year extension of the dose-ranging trial.

**Table 1–2 Pre-specified co-primary endpoints in the phase 3 trials**

| <b>Trial</b> | <b>1<sup>st</sup> Co-primary endpoint</b>   | <b>2<sup>nd</sup> Co-primary endpoint</b>   | <b>3<sup>rd</sup> Co-primary endpoint</b>                                     |
|--------------|---|---|---|
| 1839         | Change in body weight from baseline (% and kg)  | Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight   | Proportion of patients achieving $>10\%$ reduction of baseline body weight    |
| 1923         | Change in body weight from baseline (after low calorie diet run-in period) (% and kg) | Proportion of patients that maintained the $\geq 5\%$ reduction in initial body weight achieved during the low calorie diet run-in period | Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight |
| 1922         | Change in body weight from baseline (% and kg)  | Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight   | Proportion of patients achieving $>10\%$ reduction of baseline body weight    |
| 3970         | Change from baseline in AHI   |   |   |

Hierarchical testing of co-primary endpoints was applied in trials 1839, 1923 and 1922. Baseline=randomization.

AHI: apnea-hypopnea index

**Table 1–3 Body weight-related parameters – change from baseline to end of treatment**

| Trial | Benchmarks Included in FDA Guidance |      |               |                      |                              |      |               |                      |                               |      |            |
|-------|-------------------------------------|------|---------------|----------------------|------------------------------|------|---------------|----------------------|-------------------------------|------|------------|
|       | Body weight loss (%)                |      |               |                      | ≥5% weight loss (% patients) |      |               |                      | >10% weight loss (% patients) |      |            |
|       | Lira<br>3.0 mg                      | Pbo  | Lira -<br>pbo | Met FDA<br>benchmark | Lira<br>3.0 mg               | Pbo  | Lira /<br>pbo | Met FDA<br>benchmark | Lira<br>3.0 mg                | Pbo  | Lira / pbo |
| 1839  | -8.0                                | -2.6 | -5.4*         | Yes                  | 63.5                         | 26.6 | 4.8*          | Yes                  | 32.8                          | 10.1 | 4.3*       |
| 1923  | -6.3                                | -0.2 | -6.1*         | Yes                  | 50.7                         | 21.3 | 3.8*          | Yes                  | 27.4                          | 6.8  | 5.1*       |
| 1922  | -5.9                                | -2.0 | -4.0*         | No                   | 49.8                         | 13.5 | 6.4*          | Yes                  | 22.9                          | 4.2  | 6.8*       |
| 3970  | -5.7                                | -1.6 | -4.2*         | No                   | 46.4                         | 18.1 | 3.9*          | Yes                  | 22.4                          | 1.5  | 19.0*      |
| 1807  | -9.2                                | -3.1 | -6.1*         | Yes                  | 78.1                         | 29.7 | 8.5*          | Yes                  | 35.9                          | 9.7  | 5.2*       |

\*p&lt;0.0001.

Data are for the full analysis set with the last observation carried forward. Mean changes are analyzed by ANCOVA and categorical changes by logistic regression. End of treatment is 56 weeks for trials 1839, 1923 and 1922, 32 weeks for trial 3970 and 52 weeks for trial 1807. Lira: liraglutide. Pbo: placebo.

In line with the current FDA guidance,<sup>37</sup> pre-specified secondary endpoints were chosen to investigate the effect of liraglutide on these abnormalities associated with overweight and obesity and to confirm the clinical relevance of the weight loss achieved ([Table 5–6](#)). As expected and consistent with its pharmacology, liraglutide 3.0 mg compared with placebo resulted in statistically significant and clinically meaningful improvements in glycemic control in patients with T2DM (trial 1922), in terms of reductions in glycosylated hemoglobin (HbA<sub>1c</sub>), fasting and postprandial glycemia, greater numbers of patients achieving HbA<sub>1c</sub> targets, and reduced use of concomitant oral antidiabetic (OAD) medications ([Table 1–4](#)). Trial 1922 further showed that the glycemic effects of liraglutide were dose-dependent, with statistically significantly greater reductions in HbA<sub>1c</sub> and fasting plasma glucose (FPG) as well as more patients achieving a target HbA<sub>1c</sub>≤6.5% with liraglutide 3.0 mg than 1.8 mg, consistent with the greater weight loss observed at the higher dose. Importantly, the added glycemic benefit was not accompanied by increased risk of hypoglycemia (see below), consistent with the glucose-dependent mechanism of action of liraglutide.<sup>2–4</sup> Similar, though lesser, improvements were seen in patients without T2DM in the other trials.



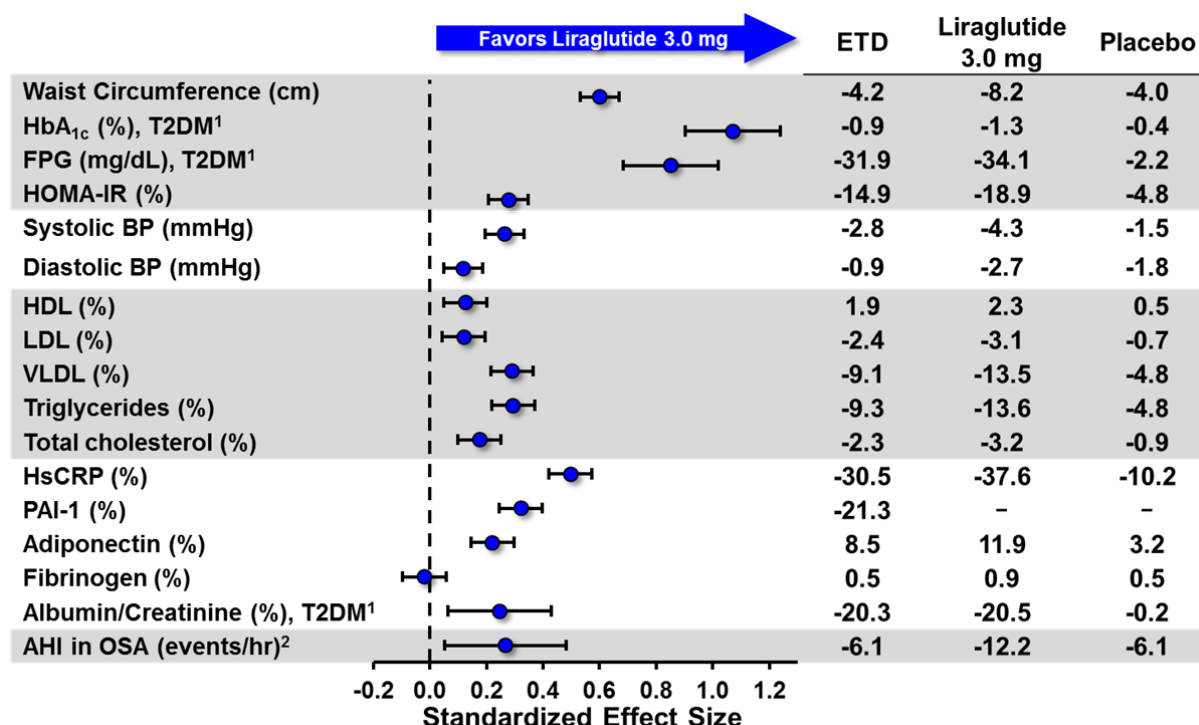
**Table 1–4 Change from baseline to week 56 in glycemic parameters: Trial 1922 in patients with T2DM**

|  | Liraglutide 3.0 mg, N=412 / Placebo, N=211 |
|--|--|
| HbA <sub>1c</sub> (%-points)                           |  |
| Baseline (mean)  | 7.9/7.9                                    |
| Change from baseline mean estimates                    | -1.32 / -0.38                              |
| Treatment difference [95% CI]; p-value                 | -0.93 [-1.08; -0.79]; p<0.0001             |
| HbA <sub>1c</sub> <7.0% at end-of -trial (% patients)  | 72%/23%                                    |
| HbA <sub>1c</sub> ≤6.5% at end-of -trial (% patients)  | 57%/12%                                    |
| Fasting plasma glucose (FPG) (mg/dL)                   |  |
| Baseline (mean)  | 158.4/155.5                                |
| Change from baseline mean estimates                    | -34.10 / -2.18                             |
| Treatment difference [95% CI]; p-value                 | -31.92 [-38.18; -25.65]; p<0.0001          |
| Postprandial glucose increment (mg/dL)                 |  |
| Baseline (mean)  | 41.4 / 43.9                                |
| Change from baseline mean estimates                    | -15.3 / -5.4                               |
| Treatment difference [95% CI]; p-value                 | -9.9 [-15.2; -4.6]; p=0.0003               |
| Use of concomitant oral antidiabetic (OAD) medications |  |
| Baseline (% of patients)                               | 88.8 / 90.5                                |
| Decrease in OAD use (% of patients)                    | 12.4 / 2.5                                 |
| Increase in OAD use (% of patients)                    | 5.1 / 23.2                                 |

Data are estimated means (ANCOVA) and treatment differences for the full analysis set with the last observation carried forward.

In patients with pre-diabetes at screening in trial 1839 (61.2%), a greater proportion of those treated with liraglutide 3.0 mg compared with placebo no longer had pre-diabetes after 56 weeks (71% vs. 37%, respectively), and fewer of those without pre-diabetes at screening in the liraglutide group compared with the placebo group had developed pre-diabetes (7% vs. 20%, respectively). Few patients developed T2DM during trial 1839, whether they were treated with liraglutide 3.0 mg (4 patients, 0.2%) or placebo (14 patients, 1.1%), also reflecting the effectiveness of the lifestyle intervention program. Nevertheless, the likelihood of developing T2DM during the 56-week trial was 86% lower in the liraglutide group than in the placebo group (odds ratio 0.12 [95% confidence interval (CI) 0.04; 0.39], p=0.0003). Patients with pre-diabetes at enrolment are being followed up for an additional 2 years in the pre-planned, ongoing extension, with new onset of T2DM as its primary endpoint.

Consistent with the greater overall weight loss with liraglutide as compared with placebo, treatment with liraglutide 3.0 mg was also associated with favorable effects on comorbid conditions such as OSA, hypertension, dyslipidemia and insulin resistance, as well as cardiovascular (CV) risk markers such as waist circumference, high-sensitivity C-reactive protein (hsCRP), plasminogen activator inhibitor-1 (PAI-1) and adiponectin, all of which are expected to improve with weight loss.<sup>37</sup> Standardized effects sizes across multiple secondary efficacy endpoints are presented in [Figure 1–1](#).



<sup>1</sup>Trial 1922; <sup>2</sup>Trial 3970.

Data are standardized effect sizes with estimated means shown at the right, together with the estimated treatment difference (ETD) for liraglutide 3.0 mg vs. placebo. For lipids, cardiovascular biomarkers and HOMA-IR, data at the right are % relative changes from baseline and % relative treatment differences (ANCOVA on a log scale).

PAI-1 was analyzed using different methods at baseline and week 56, therefore changes from baseline to week 56 cannot be calculated

AHI: apnea-hypopnea index. BP: blood pressure. ANCOVA: analysis of covariance. FPG: fasting plasma glucose.

HDL: high-density lipoprotein cholesterol. HsCRP: high sensitivity C-reactive protein. HOMA-IR: a measure of insulin resistance (Homeostasis Model Assessment). LDL: low-density lipoprotein cholesterol. PAI-1: plasminogen activator inhibitor-1. SBP: systolic blood pressure. VLDL: very low density lipoprotein cholesterol.

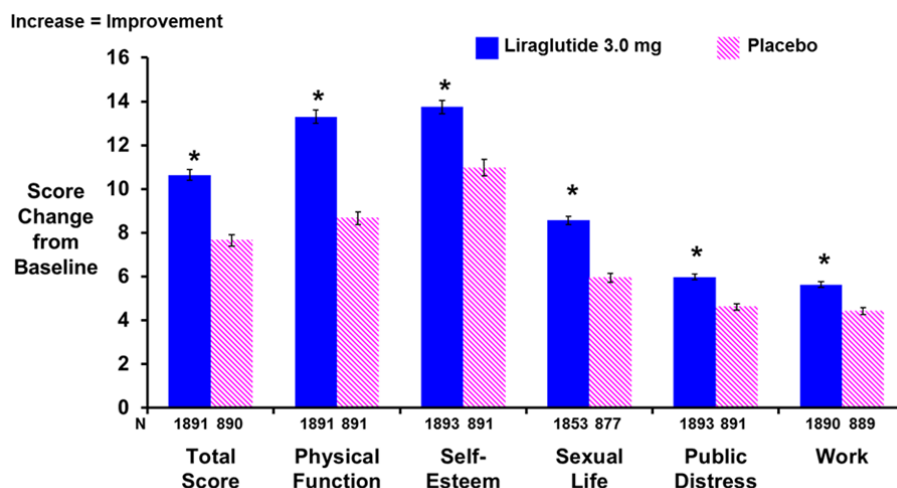
### Figure 1–1 Effects of liraglutide 3.0 mg on cardio-metabolic risk markers

Estimates of change from baseline for liraglutide 3.0 mg and placebo are given to the right-hand side of the figure. Unless indicated, results are shown for trial 1839, the largest of the phase 3 trials. Consistent results were seen across the 5 trials where parameters were measured. Generally, more weight loss led to greater improvements.

Obese individuals often have lower self-esteem and poorer quality of life than normal-weight individuals.<sup>38</sup> Moreover, obesity can adversely affect physical function and mental health.<sup>39,27</sup>

Obese individuals often suffer from physical symptoms, such as joint pain, and psycho-social problems.<sup>23-26</sup> Therefore, multiple and diverse questionnaires were used to assess patient perspectives in the weight management program. Liraglutide 3.0 mg was associated with clinically meaningful improvements in quality of life, with statistically significant increases in the Impact of

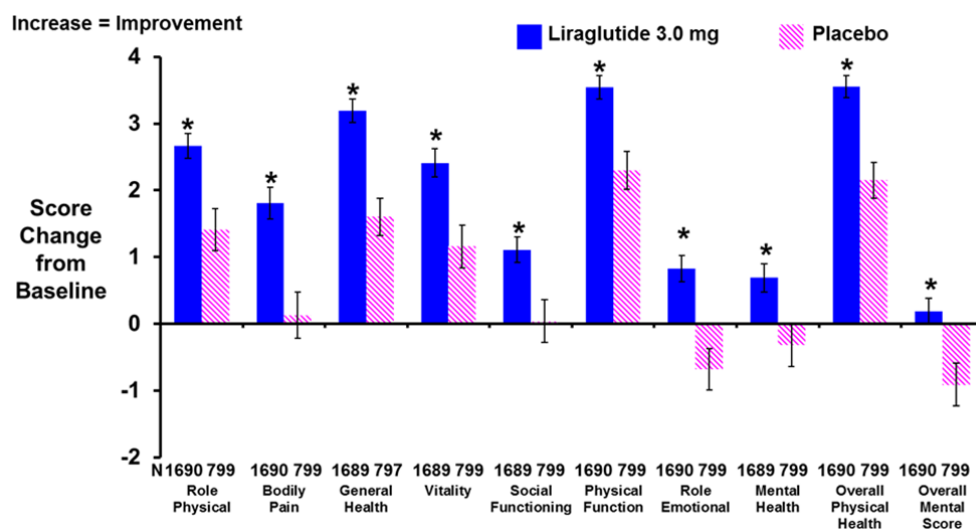
Weight on Quality of Life-Lite (IWQoL-Lite) total scores in 1839 in which the questionnaire was used, as well a greater likelihood of experiencing clinically relevant changes ([Figure 1-2](#)).



\* $p < 0.001$ . Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. N: number of patients.

**Figure 1-2 Improvements in IWQoL-Lite health-related quality of life: Trial 1839**

Significant increases in overall physical and mental health domains of the Short Form-36 (SF-36) questionnaire were also observed in trial 1839, as was a greater likelihood of experiencing a clinically meaningful change in physical function ([Figure 1-3](#)).



\* $p < 0.001$ . Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. Overall physical and mental health scores (SF-36) are shown at the right. N: number of patients.

**Figure 1-3 Improvements in SF-36 health-related quality of life: Trial 1839**

Improvements in physical function occurred consistently across the different trial populations, including patients with T2DM and OSA, and may be translated into benefits for the individual in terms of improved mobility, greater ease in dressing and undressing, having less painful or stiff joints and having fewer health worries.<sup>40,41</sup> Generally, greater weight loss led to greater improvements.

### **Clinical safety**

The safety profile of liraglutide 3.0 mg in the weight management trials was generally similar to that of liraglutide at lower doses in patients with T2DM; the only type of adverse event (AE) in the weight management pool that was found to be dose-dependent was gastrointestinal disorders.

More patients on liraglutide 3.0 mg than on placebo reported AEs (91.6% vs. 83.6%). The majority of AEs were mild in severity. Consistent with the pharmacodynamic effects of a GLP-1 receptor agonist, the most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders (e.g., nausea, diarrhea, constipation and vomiting), particularly at the start of treatment. Most gastrointestinal AEs were transient, of mild or moderate severity and usually resolved while patients continued to take liraglutide. The proportion and rate of patients reporting serious AEs (SAEs) was low overall, but was higher in the liraglutide 3.0 mg group [6.3%, 9.3 events per 100 PYE] than in the placebo group [4.6%, 7.1 events per 100 PYE]. All specific types of SAEs (at preferred term level) were reported by <1% of patients and no dose-response with respect to SAE incidence was seen with liraglutide 3.0 mg compared to the lower liraglutide doses (trials 1807 and 1922). Overall, 6 deaths occurred in the weight management program: 3 deaths in the liraglutide group and 3 deaths in the placebo group. The overall proportion of patients withdrawing from the trial due to AEs was higher with liraglutide 3.0 mg (9.8%) than with placebo (4.3%); the difference in the AE-related withdrawal rate between liraglutide and placebo was only seen in the initial 8 weeks of treatment. As expected with a GLP-1 receptor agonist, the higher proportion of AE withdrawals with liraglutide was mainly attributable to the greater number of withdrawals related to gastrointestinal disorders in this group.

Adverse events considered by Novo Nordisk to be of special interest included those in the categories of gallbladder, pancreatitis, cardiovascular, neoplasms, thyroid, hypoglycemia, pregnancy and neuropsychiatric function, based on previous experience during development of Victoza<sup>®</sup>, or safety issues identified during development or post-marketing of other anti-obesity agents. Selected events (cardiovascular, pancreatitis, neoplasms and thyroid disease requiring thyroidectomy) were subject to blinded assessment by an external event adjudication committee (EAC). Furthermore, an external group of Central Electrocardiogram (ECG) readers evaluated all scheduled ECGs from trials 1839, 1922, and 3970 for signs of ischemia, rhythm/conduction disorders and any other abnormalities not present at baseline and/or at the prior scheduled ECG. In addition, all confirmed cases of elevated calcitonin concentration ( $\geq 20$  ng/L) were subject to ongoing blinded review by an independent, external group of thyroid experts (Calcitonin Monitoring Committee).

Gallbladder-related AEs (mainly ‘cholelithiasis’ and ‘cholecystitis’) were observed at a higher frequency with liraglutide 3.0 mg [2.3% of patients, 3.1 per 100 PYE] versus placebo [0.9% of patients, 1.2 per 100 PYE]. Approximately 70% of patients reporting events of gallbladder-related adverse events (53/79 liraglutide 3.0 mg-treated patients and 12/17 placebo-treated patients) underwent a cholecystectomy, mostly as elective surgery. Events occurred throughout the trials, with no apparent time-course pattern with either treatment. As expected, events occurred more frequently in female patients and patients who experienced greater weight loss, both of which are associated with higher risk of gallstone formation,<sup>42-48</sup> and which may explain why such an imbalance is not observed with use of liraglutide at lower doses in patients with T2DM (Victoza®). The rate of gallbladder-related SAEs diminished over time based on reports in the ongoing extension of trial 1839, where presumably no further substantial weight loss is observed. The observed imbalance in these events in the weight management population is due in part to the increased weight loss achieved with liraglutide. However, a weight-loss independent drug-class-related effect cannot be excluded. Accordingly, the risk will be managed through proposed labeling and post-marketing surveillance.

Externally adjudicated (EAC-confirmed) events of acute pancreatitis occurred at a higher rate with liraglutide 3.0 mg [0.4% of patients, 0.3 events per 100 PYR] compared to placebo [<0.1% of patients, <0.1 events per 100 PYR]. Incidence rates were comparable with background rates in the obese general population and similar to the low rate found with liraglutide doses up to 1.8 mg in the diabetes development programs. There was no uniform mode of presentation, neither in time to onset, symptoms nor weight loss prior to onset. The positive predictive value of elevated pancreatic enzymes was very low (<1% for lipase values  $\geq 3$  the upper limit of the normal range [ULN], no amylase values  $\geq 3$  ULN). While there was no clear relationship between the occurrence of cholelithiasis and pancreatitis, approximately half of the pancreatitis cases in liraglutide-treated patients had gallstone-induced pancreatitis, indicated by gallstones on imaging and/or the presence of ALT levels 3 or more times the upper limit of normal range at admission to hospital. This criterion has been shown to have greater than 95% positive predictive value for acute gallstone disease.<sup>49</sup> Pancreatitis events were generally uncomplicated, none were necrotizing or hemorrhagic. All patients recovered. Even though a final conclusion regarding a causal relationship has not been established, a causal relationship is possible. Pancreatitis is considered an identified risk for all GLP-1 receptor agonists and will be included in the proposed labeling for liraglutide 3.0 mg and addressed in the REMS. Close monitoring of these events will be carried out in the post-marketing setting and by routine pharmacovigilance.

No signals or notable imbalances between liraglutide 3.0 mg and placebo were noted in the adjudicated CV AEs across the 5 weight management trials (CV deaths, non-fatal acute myocardial infarction, non-fatal stroke, unstable angina pectoris requiring hospitalization, transient ischemic attack, heart failure requiring hospitalization), consistent with the pharmacology of a GLP-1 receptor agonist and the non-clinical and clinical data observed with liraglutide. Events were infrequent and generally less frequent with liraglutide as compared to placebo. An increase in resting heart rate has previously been reported with liraglutide at doses up to 1.8 mg,<sup>15</sup> as well as

other GLP-1 receptor agonists,<sup>50,51</sup> and this finding was replicated in the weight management program (end-of-treatment estimated treatment difference of 2.5 beats/min). The increase peaked around week 6 and gradually declined thereafter, and was reversible upon treatment cessation. The clinical significance of the increase in resting heart rate remains to be determined. Based on available data from the weight management and diabetes development programs with liraglutide, there was no evidence of a dose-response in the therapeutic dose range of 1.2 mg to 3.0 mg; this observation was further supported by the absence of an exposure-response relationship with respect to resting heart rate, based on liraglutide plasma concentration obtained through population pharmacokinetic sampling. The mechanism underlying the increase in resting heart rate is not currently understood but does not appear to involve increased activation of the sympathetic nervous system. The presence of GLP-1 receptors on the sino-atrial node suggests a direct chronotropic effect of liraglutide treatment.<sup>52</sup> In the weight management trials, the resting heart rate increase was accompanied by decreases in both systolic and diastolic blood pressure and improvements in other cardio-metabolic risk factors, and was not associated with an increased risk of a Major Adverse Cardiovascular Event (MACE) (relative risk <1.0 for liraglutide 3.0 mg vs. placebo based on pre-specified analysis) or other clinically significant adverse CV outcomes. An ongoing long-term cardiovascular outcomes trial (CVOT) in patients with T2DM at high CV risk, LEADER<sup>®</sup> (liraglutide 1.8 mg vs. placebo), will provide robust data on the CV-risk profile of liraglutide.<sup>53</sup>

There was no increased risk of EAC-confirmed neoplasms identified in the weight management program, based on all treatment-emergent and non-treatment-emergent events reported up to and including the 120-Day safety update (estimated odds ratio (OR) [95% CI] for total liraglutide vs. placebo of 1.00 [0.56; 1.85], 0.96 [0.57; 1.68], and 1.31 [0.72; 2.49], for malignant, malignant and pre-malignant combined, and benign neoplasms, respectively. All events occurring in individuals currently or previously treated with liraglutide were conservatively counted in the liraglutide group. The overall incidence of adjudicated malignant neoplasms was low and similar between liraglutide 3.0 mg and placebo [0.88 events per 100 PYR and 0.96 events per 100 PYR, respectively]. Breast cancer and breast carcinoma *in situ* (pre-malignant) occurred more frequently in women treated with liraglutide 3.0 mg as compared with placebo (liraglutide 3.0 mg: 11 women with 12 malignant events [0.46% of female patients, 0.36 events per 100 PYR] and 3 pre-malignant events [0.13% of female patients, 0.09 events per 100 PYR]; placebo: 2 patients with 2 malignant events [0.15% of female patients, 0.12 events per 100 PYR] and 1 pre-malignant event [0.08% of female patients, 0.06 events per 100 PYR]). Relative to exposure (total PYR), the majority of the events occurred within the first 12 months of treatment ([Figure 6–24](#)), which does not indicate increased incidence with longer-term exposure. Events were typically stage 2 and 3, hormone-receptor positive cancers, as is to be expected from a population of obese women. The average tumor volume doubling times is about 190 days for breast cancer, with 241 days being the most recent estimate in estrogen-receptor positive breast cancers,<sup>54</sup> making it likely that these cancers were present before exposure to the drug. Mammography was not done as part of the clinical development program, and mammographic history was not generally collected. Liraglutide-treated women with events generally experienced greater than the average weight loss for the liraglutide-treated cohort, which could have led to higher mammogram uptake/accuracy and resulted in an earlier diagnosis.<sup>55–57</sup>

There has been no signal during development or post-marketing use with Victoza<sup>®</sup>, or with any other GLP-1 receptor agonist. Non-clinical studies do not support a role for liraglutide as an initiator or promoter of breast cancer, breast carcinomas do not express GLP-1 receptors,<sup>58</sup> and the only available literature relevant to GLP-1 and breast cancer is suggestive of tumor inhibition.<sup>59</sup> Nevertheless, the presence of an unconfirmed signal requires further specific follow-up in the post-marketing period.

There were no events of exocrine pancreas cancer in either treatment group. The overall incidence of thyroid cancers was low in both liraglutide 3.0 mg and placebo groups. Four out of the five thyroid cancers were of non C-cell origin; the single event of medullary thyroid carcinoma occurred in the placebo group.

More patients treated with liraglutide 3.0 mg than with placebo reported benign colorectal neoplasms, mainly colon adenomas diagnosed by routine colonoscopy in males aged above 50 years. Based on all events reported up to and including the 120-Day safety update, 17 liraglutide 3.0 mg treated patients had 17 events [0.52%, 0.38 events per 100 PYR], compared to 4 placebo-treated patients with 4 events [0.22%, 0.17 events per 100 PYR]. Most had relevant medical history. Information about baseline status as well as colonoscopy history during the clinical trial program was not collected, and it is therefore not known whether the frequency differed between treatments. Two patients with liraglutide 3.0 mg [0.06%, 0.04 events per 100 PYR] and 1 with placebo [0.05%, 0.04 events per 100 PYR] had EAC-confirmed malignant colorectal neoplasms. The latter was a neuroendocrine carcinoid tumor reported during the 120-Day Safety Update. Due to the low number of events no firm conclusions can be made on the difference between frequencies with liraglutide 3.0 mg and placebo. No signals were seen in non-clinical studies, nor during clinical development or post-marketing for Victoza<sup>®</sup> or any other GLP-1 receptor agonist. Colorectal carcinomas do not express GLP-1 receptors, and in the normal colon, only myenteric plexus cells express the receptors.<sup>58</sup> The effect of GLP-1 receptor activation in the myenteric nerve plexus is to regulate gastric motility.<sup>52</sup>

The neoplasm risk is addressed by several post-marketing commitments for Victoza<sup>®</sup> and by routine pharmacovigilance.

In weight management trials with liraglutide 3.0 mg, the risk of hypoglycemia was low in patients without T2DM, and the events were mostly biochemical hypoglycemia without accompanying symptoms recorded at oral glucose tolerance test (OGTT) or FPG testing visits. None required third party assistance. In patients with T2DM taking sulfonylurea (SU) as background medication, the risk of hypoglycemia with liraglutide 3.0 mg was similar to 1.8 mg but higher than placebo, and comparable to the rates observed in the Victoza<sup>®</sup> trials,<sup>15</sup> indicating no increased risk associated with a higher liraglutide dose and greater weight loss. Most patients with hypoglycemia experienced a single episode of hypoglycemia, and only one liraglutide-treated patient without T2DM withdrew from a trial because of hypoglycemia. Five events of severe hypoglycemia occurred in 3 T2DM patients treated with liraglutide 3.0 mg (rate based on T2DM patients: 13 event per 1000 PYE);

none were reported with placebo. All severe episodes occurred in patients concomitantly treated with SUs, which are known to increase the risk of hypoglycemia in patients co-treated with a GLP-1 receptor agonist.<sup>60</sup> The observed increase in the risk of hypoglycemia (by 3–4 times) with concomitant SU usage highlights the importance of dose adjustment for anti-diabetic treatment in obese patients with T2DM undergoing weight management therapy.

While the overall proportion of patients who became pregnant and the proportion of pregnancies resulting in healthy babies were similar for liraglutide and placebo in the weight management pool, the incidence of spontaneous abortions was higher with liraglutide (liraglutide: 25.6% of pregnant patients, placebo: 10.0% of pregnant patients), based on all events up to and including the 120-Day Safety Update. The incidence was within the range observed in obese women (25–37%).<sup>61–63</sup> There is no clear explanation for the difference in the incidence of spontaneous abortions between liraglutide- and placebo-treated women. Weight loss is not recommended for pregnant women or for those attempting to become pregnant. Liraglutide 3.0 mg therefore should not be used in such circumstances. Pregnancy is addressed in the product labeling informing prescribers that liraglutide 3.0 mg should not be used during pregnancy or by women who intend to become pregnant.

There was no imbalance in the overall prevalence of psychiatric disorder events between liraglutide 3.0 mg and placebo in the weight management pool (15.4 vs. 15.3 events per 100 PYE, respectively), and also no signal for depression or suicidality with liraglutide 3.0 mg, based on the assessment with validated mental health questionnaires.

### **Benefit/risk profile and risk management**

Liraglutide 3.0 mg significantly increases the likelihood that a patient achieves and sustains a clinically meaningful weight loss. Importantly, the weight loss promoted improvements in multiple weight-related co-morbidities. In all 5 phase 2 and 3 trials in the weight management clinical development program, liraglutide 3.0 mg as an adjunct to a reduced calorie diet along with increased physical activity induced a mean weight loss from baseline of >5% that was superior to placebo (i.e., diet and exercise alone). In each trial, the proportion of patients in the liraglutide 3.0 mg group achieving at least 5% weight loss at the end of the trial was greater than 35%, and more than double that in the placebo group, supporting that liraglutide is efficacious in producing clinically meaningful weight loss according to current recommendations.<sup>37</sup> Weight loss was consistently seen across all studied sub-populations, with the FDA categorical benchmark met in each.<sup>37</sup> Weight loss with liraglutide 3.0 mg was maintained over the 56-week treatment period in phase 3 trials while on treatment and was sustained for up to 2 years in the phase 2 trial. Weight loss with liraglutide 3.0 mg was accompanied by consistent positive effects on multiple secondary efficacy parameters, including waist circumference and total body fat, insulin resistance, fasting and postprandial glycemic control, prevalence of pre-diabetes and incidence of progression to T2DM, blood pressure, lipids and CV biomarkers, and patient-reported quality of life.

Treatment with liraglutide 3.0 mg, as adjunct to a reduced-calorie diet and increased physical activity, was generally well-tolerated, with a side-effect profile that was overall consistent with that



of Victoza<sup>®</sup>. Importantly, treatment was not associated with any of the side effects typically associated with centrally-acting obesity medications (cardiovascular or neuropsychiatric).<sup>11,64,65</sup> There was no indication of a dose or exposure response for safety/tolerability parameters, except for gastrointestinal side effects, which generally occurred early in treatment, were of mild or moderate severity and resolved without sequelae. Adverse effects were mostly predictable based on the known effects of GLP-1 receptor agonists, infrequent in the case of serious adverse drug reactions, easily diagnosed and monitored, and were reversible upon treatment discontinuation. The risks identified for liraglutide 3.0 mg and described above can be appropriately managed through product labeling and post-marketing monitoring. Based on the limited number of events reported, imbalances observed with regards to breast cancer and spontaneous abortions with liraglutide 3.0 mg are evaluated to be inconclusive. Novo Nordisk is committed to investigate these imbalances further in the LEADER<sup>®</sup> trial and via post-marketing monitoring.

It is important to note that the target population for liraglutide 3.0 mg is already at serious risk from obesity and its associated major co-morbidities. The overall efficacy and safety results from the weight management program demonstrated that the benefit-risk balance is in favor of liraglutide 3.0 mg, as adjunct to a reduced-calorie diet and increased physical activity, within the investigated population of overweight and obese individuals.

## 2 Introduction

### 2.1 Development of liraglutide for weight management

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analog classified as a ‘GLP-1 receptor agonist’, with 97% amino acid homology to human GLP-1.<sup>1</sup> GLP-1 was first identified as a potent glucose-lowering incretin hormone, released from L-cells in the gut in response to a meal. Through activation of GLP-1 receptors in the pancreas, it stimulates insulin secretion and inhibits glucagon secretion, both in a glucose-dependent manner.<sup>2-4</sup> Such glucose-dependent action is particularly attractive because, when the plasma glucose concentration is in the normal fasting range, GLP-1 no longer stimulates insulin secretion that results in hypoglycemia. In addition, GLP-1 inhibits gastric secretion and motility, which delays and protracts carbohydrate absorption after meal ingestion.<sup>3,5,6</sup> GLP-1’s role as a physiological regulator of appetite and food intake has been the focus of much research.<sup>7,8</sup> It is understood to modulate feeding behavior through signaling in central nervous system appetite centers.<sup>9-12</sup>

Liraglutide was filed with the Food and Drug Administration (FDA) for approval as a therapy for type 2 diabetes mellitus (T2DM) in May 2008. An EMDAC meeting was held in April 2009 to discuss the safety and efficacy of liraglutide, thereafter liraglutide was approved as Victoza<sup>®</sup> by the FDA in 2010 for the treatment of T2DM at doses up to 1.8 mg once daily. Since the approval of Victoza<sup>®</sup>, the number of patient years of exposure (PYE) to liraglutide is estimated to be greater than 3.3 million.

The clinical data with liraglutide in type 2 diabetes suggested that further weight loss may be achieved with a higher dose than 1.8 mg. A dose-finding trial in obese patients without diabetes showed a dose-dependent weight loss with doses up to 3.0 mg and therefore liraglutide 3.0 mg was evaluated further in a clinical development program as a pharmacological agent for weight loss and weight management.

The clinical development program for liraglutide 3.0 mg in weight management includes one clinical pharmacology trial (trial 3630), one dose-finding phase 2 trial (trial 1807) and four phase 3a trials (trials 1839, 1922, 3970 and 1923). All trials are complete and involved close to 6,000 obese patients, or overweight patients with at least one weight-related co-morbidity such as dysglycemia (pre-diabetes and T2DM), hypertension, dyslipidemia or obstructive sleep apnea (OSA). Of these, more than 3,300 were exposed to liraglutide 3.0 mg in phase 2 and 3 trials. A single-blind two-year extension of the largest phase 3 trial (1839) is currently ongoing and scheduled to complete in 2015. The trials were all randomized, double-blinded and placebo-controlled. The clinical development program is further described in Section [5.2](#).

The NDA for liraglutide 3.0 mg had a cut-off date of 02 July 2013 and was filed with the FDA on 20 December 2013. Additional safety data relevant to liraglutide 3.0 mg as a weight management agent was filed with the FDA in the 120-Day Safety Update that had a cut-off date of 11 November 2013. The update pertains primarily to patients in the ongoing extension of trial 1839, which

included 1,584 individuals with pre-diabetes who were exposed to liraglutide (N=1,087) or placebo (N=497) for 56 weeks during the main treatment period and an additional year by the time of the safety cut-off ([6.1.1](#)).

## 2.2 Proposed indication

Liraglutide 3.0 mg is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

- 30 kg/m<sup>2</sup> or greater (obese) or
- 27 kg/m<sup>2</sup> or greater (overweight) in the presence of at least one weight-related co-morbidity such as hypertension, dysglycemia (pre-diabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea

Liraglutide 3.0 mg, consistent with the labeling for Victoza<sup>®</sup> (liraglutide up to 1.8 mg for the treatment of type 2 diabetes mellitus), will be contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia type 2 (MEN 2). Women should not lose weight when pregnant or when attempting to become pregnant. Liraglutide 3.0 mg therefore should not be used in such circumstances. Pregnancy will be addressed in the product labeling; informing prescribers that liraglutide 3.0 mg should not be used during pregnancy or by women who intend to become pregnant.

## 2.3 Need for effective and safe pharmacotherapy to treat obesity

Obesity is one of the most significant public health challenges globally. Its impact is considerable in the Western world and it is now also an emerging epidemic in developing countries.<sup>66</sup> Overweight and obesity are commonly classified using the body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters. More than one-third of adults in the U.S. are obese (BMI  $\geq 30$  kg/m<sup>2</sup>); in countries across Europe 10-30% are classified as obese and 30–70% are overweight (BMI of  $\geq 25$  kg/m<sup>2</sup>).<sup>16,67</sup> The American Medical Association as well as a number of leading institutions such as the National Institutes of Health (1998), The Obesity Society (2008) and the American Association for Clinical Endocrinology (2012) now classify obesity as a disease, calling for dedicated efforts in prevention, diagnosis and treatment for this chronic condition.<sup>68</sup>

Obesity is a complex chronic disease associated with many serious health consequences, and decreased life expectancy by 5–10 years, which makes reducing its high prevalence a public health priority.<sup>17,22</sup> It is associated with major co-morbidities such as hypertension, hyperglycemia, dyslipidemia, certain types of cancer, obstructive sleep apnea (OSA) and atherosclerosis.<sup>18,21</sup> The global obesity epidemic largely explains the 3-fold increase in the rates of T2DM in recent years<sup>19</sup>, with obesity-related pre-diabetes increasing the risk of developing T2DM 5- to 6-fold.<sup>20</sup> Moreover, OSA independently can contribute to T2DM, hypertension and other cardiovascular (CV) morbidities, sleepiness, impaired cognitive function and depression.<sup>69,70</sup> Obesity and overweight are also independent risk factors for myocardial infarction and ischemic heart disease,<sup>71</sup> the leading

cause of death worldwide.<sup>72</sup> Obesity adversely affects physical and mental health and reduces quality of life.<sup>27</sup> Obese individuals often suffer from physical symptoms, such as joint pain, and psycho-social problems.<sup>23-26</sup> In aggregate, the individual and societal impact of the obesity epidemic is substantial, affecting the individuals themselves, their employers and healthcare systems.<sup>36</sup>

Although not all people with obesity develop health problems, the risk of obesity-related complications and co-morbidities increases with increasing BMI. Importantly, even a moderate weight loss of 5–10% has been shown to have significant health benefits in terms of improving glycemic control, reducing progression to T2DM, improving OSA severity and related symptoms and other weight-related co-morbidities, as mentioned above, as well as improving physical symptoms and quality of life.<sup>29-32</sup> Furthermore, the American College of Physicians recommends that overweight and obese patients diagnosed with OSA should be encouraged to lose weight, as weight loss has been shown to improve OSA symptoms and patient-reported outcomes.<sup>73,74</sup>

Lifestyle intervention in the form of dietary and behavioral changes is the first line of treatment for obesity. While initially effective for many patients, this approach alone tends not to be sustainable and many patients have weight regain after weight loss. Scientific evidence suggests that weight gain and obesity lead to hormonal, metabolic and neurochemical adaptations that affect the regulation of energy balance, promoting maintenance of the increased weight and making weight loss difficult.<sup>17,33</sup> Moreover, during weight loss the body compensates by reducing metabolism and increasing the production of hormones that stimulate appetite.<sup>33,34</sup> These compensatory effects tend to elicit weight regain, and explain why sustained weight loss is difficult to achieve and why many people struggle to maintain their weight loss by lifestyle intervention alone.

Obesity surgery resides at the other extreme of the treatment continuum. Surgical treatments offer an effective alternative for some people with severe obesity; however, these are unavailable or unsuitable for many obese individuals and are associated with risks and complications related to the problems inherent in operating on obese individuals.<sup>17</sup> Major and minor complications occurred in 3.3% and 27% of patients, respectively, in one study.<sup>35</sup> Indeed, the use of surgery to treat severe obesity and its co-morbidities point to the medical seriousness of obesity and provide additional rationale for the development of treatments that can effectively manage obesity earlier in its course.

Pharmacotherapy has the potential to fill the therapeutic gap, and may serve as a valuable adjunct to lifestyle intervention in achieving and sustaining clinically relevant weight loss; it may also have the potential to moderate the metabolic responses that favor weight regain.<sup>17</sup>

Despite two recently approved pharmacologic therapies for weight management, lorcaserin and phentermine/topiramate in the U.S. in 2012, the range of weight management medications currently available is limited and unlikely to meet the needs of all individuals who can benefit from weight loss.<sup>36</sup>

There is a need for new and diverse treatment options that can assist obese individuals in reducing their weight and thereby improving their health. Liraglutide is in a different pharmacological class

to the other weight management products currently available, with a different mechanism of action and well-documented safety profile. Liraglutide 3.0 mg for weight management will therefore effectively supplement the existing weight-lowering strategies and treatments available making it possible for more individuals to lose weight and maintain that weight loss.

## **2.4 Rationale for liraglutide as a weight management agent**

Liraglutide has a unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycemic control, blood pressure and other weight-related co-morbidities. Indeed, the direct effects of liraglutide to improve dysglycemia, in addition to its ability to promote weight loss, may make it particularly advantageous for obese individuals with impaired glucose tolerance or overt T2DM.

The well-characterized effects of liraglutide in the body are mediated via specific activation of the GLP-1 receptors. In animal studies, peripheral administration of liraglutide leads to decreased food intake and weight loss.<sup>75-78</sup> Animal studies have demonstrated that liraglutide can access brain regions that are critical to the regulation of energy intake. These regions contain specific neurons involved in appetite regulation and express GLP-1 receptors. Thus, liraglutide has the potential to directly modulate neuronal activity in centers key to energy homeostasis. The studies describing the mechanism of action of liraglutide to promote weight loss were recently accepted for publication.<sup>14</sup>

In humans, weight loss with liraglutide is primarily mediated by its effects on appetite with no increase in energy expenditure.<sup>13</sup> Liraglutide treatment affects the four main components of appetite regulation (fullness, satiety, hunger and prospective food consumption [how much a person thinks he/she can eat]), leading to reduced caloric intake. Liraglutide-induced weight loss is primarily due to reduction in fat mass rather than lean body mass.

## **2.5 Dosage and Administration**

Liraglutide 3.0 mg is taken once daily at any time of day, independent of meals and is injected subcutaneously, via an easy to use, state of the art pen device, in the abdomen, thigh or upper arm.

The most commonly reported adverse drug reactions for liraglutide are associated with gastrointestinal symptoms. To reduce the likelihood of these gastrointestinal symptoms, all patients should start on a dose of 0.6 mg for one week. The dose should then be escalated (1.2 mg, 1.8 mg, 2.4 mg), in weekly increments of 0.6 mg, until the patient reaches the maintenance dose of 3.0 mg. If patients do not tolerate an increased dose during dose escalation, the dose escalation can be delayed by up to 7 days.

### 3 Non-clinical Safety Pharmacology and Toxicology

#### Summary

- The non-clinical pharmacology program conducted to support the approval of liraglutide 1.8 mg (Victoza®) for treatment of type 2 diabetes mellitus is supportive for the liraglutide 3.0 mg for weight management program.
- Safety pharmacology studies assessing the effect of liraglutide on vital organ systems raised no safety concerns for humans.
- No gallbladder abnormalities were observed in non-human primates. Few sporadic incidences of cholecystitis were observed in mice dosed with liraglutide for two years in a non-dose dependent manner.
- Lifelong dosing with liraglutide did not cause an increased overall tumor burden in mice or rats nor did it lead to increases in any specific tumor types except for the C-cells described below.
- No signal for pancreatitis or pancreatic cancer was observed in any of the non-clinical studies.
- Liraglutide dose-dependently induced proliferative changes and neoplasia in C-cells (parafollicular cells) of the thyroid during rodent 2-year carcinogenicity studies. The rodent C-cell findings are considered a class effect caused by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive.
- No abortions were observed in embryo-fetal studies in rats and rabbits. Few fetal abnormalities were observed with no specific organs affected. These were likely related to reduced maternal food intake.

#### 3.1 Overview of the non-clinical development program

The non-clinical safety studies conducted to support approval of liraglutide 1.8 mg for treatment of T2DM are also considered supportive for the liraglutide 3.0 mg for weight management NDA. Systemic exposure in *in vivo* safety pharmacology and general toxicology studies exceeded human exposure at the 3.0 mg dose.

The non-clinical program was designed in accordance with guidance given by the International Conference on Harmonization (ICH) for new chemical entities to support chronic clinical use in humans.<sup>79</sup>

#### 3.2 Safety pharmacology/effect on vital organ systems

The organ-specific non-clinical safety pharmacology program assessing the effect of liraglutide on cardiovascular and respiratory function, kidney function, and the autonomic and central nervous systems in pharmacologically responsive animals (mouse, rat, rabbit, guinea-pig and cynomolgus monkey) raised no safety concerns for humans.

A small increase in heart rate (6%) was observed in the rabbit isolated Langendorff heart preparation after perfusion with liraglutide.

### 3.3 Non-clinical pharmacokinetics and absorption, distribution, metabolism and excretion

There was no gender difference or time-dependency in the pharmacokinetic parameters and dose proportionality was demonstrated in the species used in the safety pharmacology and toxicology studies.

Liraglutide is highly bound to albumin (98%) in all species resulting in a volume of distribution close to the plasma volume. No special target organ was identified in tissue distribution studies where the highest concentrations were observed in well-perfused organs. Using fluorescence labeled liraglutide, it was demonstrated that liraglutide binds to specific GLP-1 receptors in brain areas in the hypothalamus.

The metabolism and excretion pattern was highly similar across species, including humans. Liraglutide was fully degraded in the body with no single organ as a major route of elimination. The metabolism/catabolism of liraglutide, which consists of a peptide moiety with a fatty acid attached via a glutamate spacer, results in amino acids and a fatty acid, and subsequently CO<sub>2</sub> and H<sub>2</sub>O when fully metabolized. Metabolism occurs via sequential cleavage of N- and C-terminal peptide fragments and amino acids involving the peptidases dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP), also responsible for the metabolism of native GLP-1. No active metabolites have been identified. *In vitro*, binding to albumin was demonstrated to control the metabolic rate of liraglutide but changes from 1-5% albumin, considered to cover clinical variations, result in only minimal changes in metabolic rate due to the very high excess of albumin to liraglutide.

No clinically relevant induction or inhibition in cytochrome P450 activity was observed in agreement with the protein-based nature of liraglutide.

### 3.4 Toxicology findings

The majority of findings in the short-, medium- and long-term toxicity studies were attributed to dose-dependent primary pharmacology via GLP-1 receptor mediated effects, i.e., decrease in food consumption and a decrease in body weight gain.

#### 3.4.1 Pancreatic findings

The pancreas was examined macro- and microscopically in all toxicology studies in mice, rats and cynomolgus monkeys. The maximal exposure levels were approximately 36- (mice), 8- (rats), and 57-fold (cynomolgus monkey) more than in humans, based on dosing with liraglutide 3.0 mg. In a 52-week study with liraglutide, a dose-related increase in absolute pancreas weight was observed in female monkeys only.<sup>80</sup> Such dose-related increase was not found in studies of 4, 13, or 87 weeks' duration. There were no findings related to drug suggestive of inflammation or any other toxicology in the pancreas in any of the studies, including the 104-week carcinogenicity studies, an 87-week study in cynomolgus monkeys, and a 3-month study in diabetic rats.<sup>80-82</sup>

### 3.4.2 Gallbladder findings

No abnormal gallbladder necropsy and histological findings were noted in the repeat-dose toxicity studies in mice and monkeys of up to 13 weeks and 52 weeks duration, respectively. In the 2-year mouse carcinogenicity study, more animals in the dosed groups had distended/dilated or enlarged gallbladders than in the vehicle control group. There was an increase in the incidence rate of cholecystitis (4 of 60 mice), which was statistically significant ( $p < 0.05$ ) only in the low dose group of females. This rate was above the historical control range of 0-3.3% in female mice at the test laboratory. The incidence of cholecystitis in the high dose male group was also above the historical control of 3.4% in this sex at the test laboratory. Relation to treatment was uncertain as there was no apparent dose relationship for these findings ([Table 3-1](#)).

**Table 3-1 Incidences of cholecystitis and cholelithiasis in 104-week mouse carcinogenicity study**

| Sex     | Group (mg/kg/day)               | Dose Group (mg/kg/day) |          |         |         |         | Historical control range |
|---------|---------------------------------|------------------------|----------|---------|---------|---------|--------------------------|
|         |                                 | 0                      | 0.03     | 0.2     | 1.0     | 3.0     |                          |
|         | Exposure multiples animal:human | -                      | 0.2      | 1.7     | 14      | 40      |                          |
| Males   | Number examined                 | 72                     | 59       | 58      | 65      | 68      |                          |
|         | Cholelithiasis, n (%)           | 0                      | 0        | 0       | 0       | 0       | 0 – 1.7 %                |
|         | Cholecystitis, n (%)            | 0                      | 2 (3.4)  | 2 (3.4) | 1 (1.5) | 3 (4.4) | 0 – 3.4 %                |
| Females | Number examined                 | 71                     | 60       | 61      | 58      | 71      |                          |
|         | Cholelithiasis, n (%)           | 0                      | 0        | 0       | 1.7     | 1.4     | 0 – 6.8 %                |
|         | Cholecystitis, n (%)            | 0                      | 4 (6.6*) | 1 (1.6) | 2 (3.4) | 0 (0)   | 0 – 3.3 %                |

\* $p < 0.05$  vs control. Historical control range is the incidences of findings recorded at test laboratory where study was conducted.

### 3.4.3 Carcinogenicity

Liraglutide was tested in a full range of genotoxic tests consisting of Ames test, human peripheral blood lymphocyte chromosome aberration test, and *in vivo* micronucleus test in the rat. All tests were negative.

Two-year carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. No treatment-related effects on the overall benign and malignant tumor incidence rates were noted.

Dorsal skin sarcomas at the injection site were significantly increased in male mice at the highest dose of 3 mg/kg/day. The percentages of male mice with dorsal skin sarcomas in controls and high dose animals were 2.5% and 20%, respectively. The tumors were located in the area of the micro-chip implant and the injection site area. Repeated subcutaneous injections of non-genotoxic compounds and solutions, as well as implantation of solid material such as micro-chips in the



subcutis, are known to cause development of skin sarcomas in rodents.<sup>83</sup> The no-observed-adverse-effect level (NOAEL) for skin sarcomas was 1.0 mg/kg.

Liraglutide dose-dependently induced proliferative changes and tumors in C-cells (parafollicular cells) of the thyroid during the mouse and rat 2-year carcinogenicity studies. Low grade proliferative C-cell changes were also identified in repeated dose toxicity studies. Based on published literature and a wide range of dedicated non-clinical *in vitro* and *in vivo* studies, the mode-of-action behind the C-cell findings can be summarized in the following sequential key events: 1) circulating liraglutide binds to and activates GLP-1 receptors on C-cells, resulting in calcitonin release; 2) persistent stimulation of GLP-1 receptors on the C-cells is followed by C-cell hyperplasia; 3) long-term, C-cell hyperplasia may lead to C-cell neoplasia in rodents. Calcitonin was demonstrated to be an important biomarker for C-cell activity and mass. The experimental findings supporting the mode-of-action demonstrated substantial species differences between rodents and primates, including man, in C-cell reactivity to GLP-1 receptor agonists are published in following key references.<sup>84-86</sup> Humans have far fewer C-cells than rodents; few humans have GLP-1 receptors on their C-cells and no GLP-1 receptor activation of C-cells in terms of calcitonin release has been found in humans treated with any GLP-1 receptor agonist.<sup>58,84,86-88</sup> The rodent C-cell findings are considered a class effect caused by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. Thus, the relevance of these findings to humans is uncertain but considered to be low.

#### 3.4.4 Reproductive toxicology in rats

The reproductive toxicity of liraglutide was investigated in standard studies covering fertility, embryo-fetal development and pre- and postnatal development in rats and embryo-fetal development in rabbits.

No effects on male fertility were observed. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day (12-fold human exposure). Reduced maternal body weight gain and food consumption were observed at the 1.0 mg/kg/day dose.

In the combined fertility and embryo-fetal development study in rats, no abortions in terms of total litter loss were noted, but a slight increase in early embryonic deaths was observed in the high dose group. Liraglutide did not increase the incidence of fetal abnormalities ([Table 3–2](#)).

In the pre- and post-natal development study in rats, pharmacological effects on food consumption and body weight were observed at all dose levels in the F0 (parent) generation. The body weight effect persisted into the pre-weaning period in the F1 generation (offspring) at all dose levels and during the post-weaning period in the 1.0 mg/kg dose group. Group mean litter weight was reduced in the high dose F2 (second) generation, probably due to a lower body weight of the F1 animals at this dose level.

**Table 3–2 Summary of findings in the combined fertility and embryo-fetal development study in rats**

| Liraglutide Dose (mg/kg/day)         | 0                     | 0.1      | 0.25     | 1.0      |
|--------------------------------------|-----------------------|----------|----------|----------|
| Exposure multiples <sup>a</sup>      | –                     | 0.9      | 3.6      | 12.4     |
| Animals mated (N)                    | 24                    | 24       | 24       | 24       |
| Total corpora lutea graviditatis (n) | 391                   | 394      | 346      | 375      |
| Number of implants (n)               | 376                   | 369      | 345      | 365      |
| Total live implants [n (%)]          | 356 (95)              | 343 (93) | 332 (96) | 333 (91) |
| Early embryonic deaths [n (%)]       | 16 (4)                | 19 (5)   | 11 (3)   | 31 (8)   |
| Number of spontaneous abortions      | 0                     | 0        | 0        | 0        |
| Major malformations                  | Fetuses (litters)     |          |          |          |
| Major abnormality                    | 2 (2)                 | 4 (2)    | 3 (3)    | 2 (2)    |
| Total number examined                | 355 <sup>b</sup> (24) | 343 (24) | 332 (23) | 333 (24) |
| Visceral morphology findings         | Fetuses (litters)     |          |          |          |
| Minor visceral abnormality/variant   | 89 (23)               | 62 (21)  | 62 (20)  | 42 (21)  |
| Total examined viscera               | 356 (24)              | 343 (24) | 332 (23) | 333 (24) |
| Skeletal findings                    | Fetuses (litters)     |          |          |          |
| Minor abnormality/variant            | 5 (5)                 | 6(5)     | 5(5)     | 10 (7)   |
| Any with incomplete ossification     | 87 (23)               | 59 (18)  | 57 (19)  | 56 (20)  |
| Total examined skeletally            | 177 (24)              | 170 (24) | 166 (23) | 166 (24) |

a: exposure multiples are based on liraglutide 3.0 mg dose; b: One fetus lost in processing

### 3.4.5 Reproductive toxicology in rabbits

Pregnant female rabbits were dosed from gestational day 6 to 19. Maternal food intake was markedly reduced in all dose groups, to 7-28% of that of the control group, starting immediately after initiation of dosing. No food intake was noted in a few female dams during the days following initiation of treatment. The food intake slowly increased over the dosing period but did not reach that of controls.

The sum of incidences of major malformations increased dose dependently, but no specific organ was affected in a dose-dependent manner (Table 3–3). A dose dependent increased incidence of fetuses with supernumerary ribs was observed. An increased incidence of jugals fused to the maxilla just exceeding the historical control range was noted in the high dose animals. These findings were considered related to the maternal stress and the significant decrease in food consumption at the beginning of the dosing period.<sup>89,90</sup>

**Table 3–3 Overview of rabbit embryo-fetal findings**

| <b>Dose level (mg/kg)</b>                                  | <b>0</b>          | <b>0.01</b> | <b>0.025</b> | <b>0.05</b> |
|--|-------------------|-------------|--------------|-------------|
| <b>Exposure rabbit:human</b>                               | <b>-</b>          | <b>0.2</b>  | <b>0.3</b>   | <b>0.5</b>  |
| <b>Animals mated (N)</b>                                   | <b>20</b>         | <b>20</b>   | <b>20</b>    | <b>20</b>   |
| Maternal body weight on GD9 (kg)                           | 3.95              | 3.79        | 3.83         | 3.77        |
| Food intake in GD9 (g)                                     | 135               | 34          | 38           | 30          |
| Number of spontaneous abortions                            | 0                 | 0           | 0            | 0           |
| Major malformations  | Fetuses (litters) |             |              |             |
| Major abnormality  | 3 (3)             | 6 (6)       | 7 (6)        | 11 (6)      |
| Total number examined                                      | 138 (17)          | 161 (20)    | 122 (17)     | 144 (19)    |
| Visceral morphology findings                               | Fetuses (litters) |             |              |             |
| Minor visceral abnormality/variant                         | 8 (6)             | 12 (12)     | 12 (9)       | 11 (9)      |
| Total examined viscera                                     | 138 (17)          | 161 (20)    | 122 (17)     | 144 (19)    |
| Skeletal findings  | Fetuses (litters) |             |              |             |
| Connected/fused jugal(s) to maxilla                        | 3 (3)             | 9 (6)       | 6 (4)        | 15 (8)      |
| Supernumerary rib(s) on 13 <sup>th</sup> thoracic vertebra | 29 (11)           | 52 (16)     | 59 (16)      | 61 (16)     |
| Number with skeletal abnormality                           | 37 (13)           | 46 (17)     | 22 (12)      | 57 (17)     |

## 4 Clinical Pharmacology

### Summary

- Pharmacokinetic properties of liraglutide 3.0 mg were consistent with those previously established for liraglutide at doses up to 1.8 mg (Victoza®).
- No dose adjustment is required for any sub-population, defined according to demographic characteristics, or mild or moderate renal and hepatic impairment.
- No dose adjustment is required for co-administered drugs, based on pharmacokinetic drug-drug interaction trials with liraglutide.
- Liraglutide doses of 3.0 mg were required for exposures that led to a clinically relevant weight loss in all studied sub-populations.
- Liraglutide 3.0 mg was associated with a modest delay in gastric emptying in the first hour after a mixed meal.
- Weight loss with liraglutide is mediated by decreased appetite and subsequent reduction in energy (caloric) intake, not by increased energy expenditure.
- Weight loss was accompanied by improvements in fasting and postprandial glycemia.

### 4.1 Introduction

The clinical pharmacology evaluation of liraglutide 3.0 mg in weight management is based on data from one clinical pharmacology trial (trial 3630), one phase 2 trial (dose-finding trial 1807) and two phase 3 trials (trial 1839, the largest in the program, and trial 1922, which included patients with T2DM). The clinical pharmacology properties of liraglutide at doses up to 1.8 mg were extensively characterized during the clinical development of Victoza®.<sup>15</sup> As described in the sections below, the findings are considered applicable to liraglutide 3.0 mg for weight management based on linear pharmacokinetics in the full dose range (relevant for pharmacokinetic assessment for hepatic and renal impairment), no further delay of gastric emptying (relevant for drug-drug interaction program), and considerable overlap between liraglutide exposures in healthy individuals dosed with 1.8 mg in the QTc trial and those in obese individuals dosed with 3.0 mg. A brief summary of relevant findings from the Victoza® clinical pharmacology program is provided in Section [4.2](#).

Trial 3630 was a randomized, placebo-controlled, double-blind, incomplete crossover trial conducted in 49 obese, but otherwise healthy, individuals with a BMI between 30 and 40 kg/m<sup>2</sup>. Each participant received 2 of 3 treatments (hence ‘incomplete’ crossover): liraglutide 3.0 mg, liraglutide 1.8 mg or corresponding placebo, and each treatment period was of 5 weeks duration. Treatment was initiated with 0.6 mg and the dose was escalated in weekly intervals of 0.6 mg until the target liraglutide/placebo dose was achieved. The trial was designed to evaluate the pharmacokinetic and pharmacodynamic properties (gastric emptying, appetite sensations, energy intake and expenditure, postprandial glycemic excursions) of liraglutide in the target obese population. The primary objective was to confirm equivalence in gastric emptying between liraglutide 3.0 mg and 1.8 mg to enable bridging to the drug-drug interaction program conducted for

Victoza<sup>®</sup>.<sup>13,15</sup> Assessments were made after 5 weeks of treatment (at pharmacokinetic steady state with liraglutide 3.0 mg and including the dose escalation period).

Trials 1839 and 1922 contribute with data for the population pharmacokinetic analyses and, together with data from trial 1807, also for the exposure-response analyses. Trial design information for these trials is presented in Sections [5.3](#) and [5.4.1](#), and body weight results are presented in Sections [5.3.2](#) and [5.4.6](#).

## 4.2 Relevant findings from the Victoza<sup>®</sup> clinical pharmacology program

### 4.2.1 Absorption, distribution, metabolism and excretion and pharmacokinetic properties of Victoza<sup>®</sup>

Liraglutide is administered by subcutaneous injection in the abdomen, thigh or upper arm, and injection sites can be changed without dose adjustment. The absorption of liraglutide is slow, reaching maximum concentration 8–12 hours after administration, and exposure increases proportionally with dose. The *in vitro* plasma protein binding capability is > 98%.<sup>15</sup> Liraglutide is metabolized by dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP) enzymes, as described in Section [3.3](#). No active metabolites have been identified. Liraglutide is fully degraded in the body with no single organ as a major route of elimination. The relatively slow absorption and  $t_{1/2}$  of approximately 13 hours make liraglutide suitable for once-daily administration, at any time of the day.<sup>15</sup>

Pharmacokinetic studies and population pharmacokinetic analysis showed that exposure increases with decreasing body weight and is higher for women than for men. The same pharmacokinetic observations were found with liraglutide 3.0 mg in the weight management program (Section [4.3](#)). No differences in liraglutide pharmacokinetics were found between elderly and younger individuals or between individuals of different race or ethnicity.

In accordance with the non-specific route of elimination, renal or hepatic impairment did not result in elevated liraglutide exposure, in terms of area under the curve (AUC) measurements. Compared to healthy individuals, liraglutide AUC<sub>(0-∞)</sub> in mild (creatinine clearance (CrCL) 50–80 mL/min), moderate (30–50 mL/min) and severe (<30 mL/min) renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively, with no apparent increase with increasing severity of impairment. Accordingly, a regression analysis supported that renal function (in terms of CrCL) had no statistically significant effect on AUC. No relevant change of liraglutide clearance in patients with mild or moderate renal impairment was found with liraglutide 3.0 mg in the weight management program, based on population pharmacokinetic analysis (Section [4.3.1](#)). Individuals with mild to moderate (Child Pugh score 5–9) hepatic impairment had reduced liraglutide exposures (by 11 and 14%) compared with individuals with normal hepatic function, and those with severe impairment (score >9) had 42% lower exposures. Dose adjustment is not required for these populations.<sup>15</sup> There is, however, limited therapeutic experience with liraglutide in people with renal or hepatic impairment.

#### 4.2.2 Drug-drug interaction

Liraglutide has low potential for drug-drug interactions related to cytochrome P450 and plasma protein binding. The focus of the drug-drug interaction studies has therefore been on the observed delay in gastric emptying, which may influence the absorption of concomitantly administered oral compounds. The drug-drug interaction program for Victoza<sup>®</sup> investigated the influence of liraglutide on the absorption of the compounds acetaminophen, atorvastatin, griseofulvin, digoxin, lisinopril, and an oral combination contraceptive [ethinyl estradiol and levonorgestrel]. Liraglutide 1.8 mg did not affect absorption of the investigated compounds to any clinically relevant degree and dose adjustment is therefore not required.<sup>15</sup> In obese individuals in trial 3630, equivalence was observed between liraglutide 3.0 mg and 1.8 mg in gastric emptying, as assessed using the acetaminophen absorption method.<sup>91</sup> The acetaminophen AUC<sub>0-5h</sub> ratio [90% CI] for the comparison of liraglutide 3.0 mg and 1.8 mg was 1.03 [0.90–1.15], which was within the pre-specified limits for equivalence [0.80–1.25].<sup>13</sup> Therefore, it is anticipated that liraglutide 3.0 mg will likewise not affect the absorption of concomitant oral compounds in the target overweight or obese population.

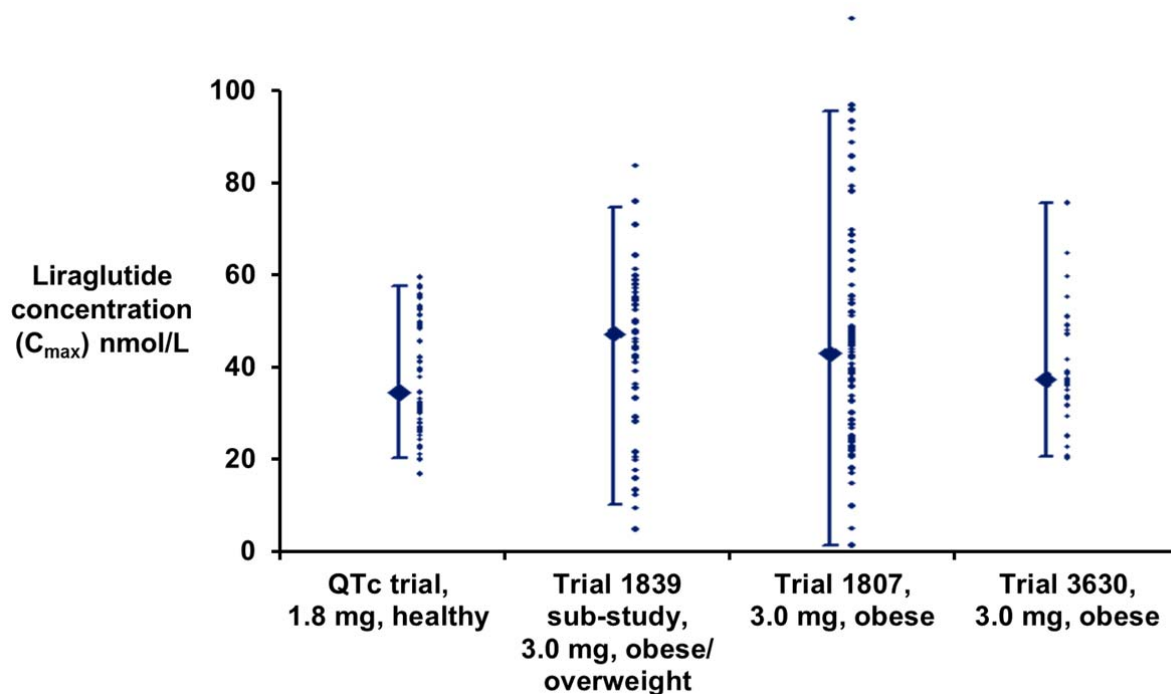
#### 4.2.3 Pharmacodynamic properties of Victoza<sup>®</sup>

Liraglutide improves glycemic control by lowering fasting and postprandial glucose. These effects are primarily mediated through stimulation of insulin secretion and inhibition of glucagon secretion, both in a glucose-dependent manner, i.e. only when plasma glucose levels are above normal.<sup>15</sup> Liraglutide also causes a minor delay in gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation. Liraglutide reduces body weight through mechanisms involving decreased hunger and lowered energy intake. Information about the pharmacodynamic effects of liraglutide 3.0 mg in obese individuals is included in Section [4.5](#).

#### 4.2.4 Cardiac repolarization (QTc study)

The effect of liraglutide on cardiac repolarization was investigated in a thorough QTc trial, conducted in healthy individuals as part of the Victoza<sup>®</sup> program. Liraglutide exposures obtained with 1.8 mg did not produce QTc prolongation,<sup>15</sup> consistent with *in vitro* electrophysiology and animal studies (Section [3.2](#)).

Following consultation with the FDA, the study results are considered relevant to the use of liraglutide 3.0 mg for weight management for the following three reasons; 1) there was no adverse exposure-response relationship in the studied exposure range, i.e., no indication of QT prolongation with increasing exposure; 2) a substantial overlap was noted between the maximum liraglutide exposures (in terms of C<sub>max</sub>) observed in overweight and obese patients treated with liraglutide 3.0 mg and those observed in the healthy individuals treated with liraglutide 1.8 mg in the QTc study, which was as expected based on the established effect of body weight on plasma liraglutide exposure ([Figure 4-1](#)); and 3) because liraglutide elimination is not organ specific, conditions such as renal or hepatic impairment are not expected to further increase plasma liraglutide exposure.



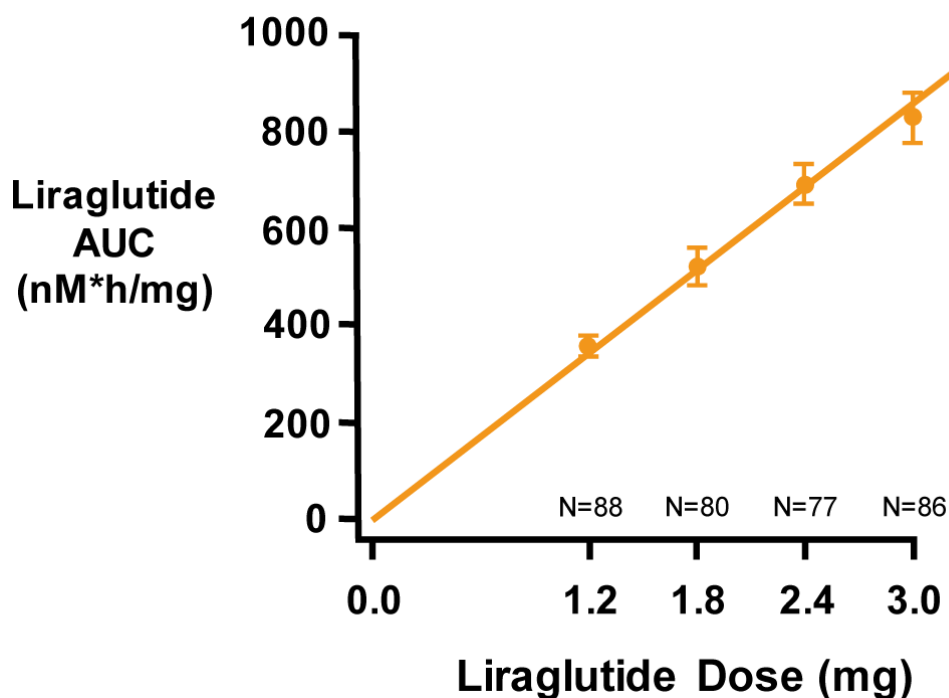
Data are individual  $C_{max}$  values with medians and 95% range. Number of participants: 51 (QTc trial), 50 (trial 1839), 86 (trial 1807) and 29 (trial 3630).

**Figure 4–1**  $C_{max}$  values from the Victoza<sup>®</sup> QTc trial and weight management trials 1839, 1807 and 3630

### 4.3 Pharmacokinetic properties of liraglutide 3.0 mg for weight management

The pharmacokinetic properties of liraglutide 3.0 mg in obese individuals were consistent with those previously observed at doses up to 1.8 mg in patients with T2DM, in the Victoza<sup>®</sup> program. In trial 3630, the time to maximum concentration was approximately 11 hours and the half-life was 13 hours. The volume of distribution ( $V_z/F$ ) observed for an obese individual weighing approximately 100 kg was slightly larger (20–25 L) than that observed across trials in the Victoza<sup>®</sup> program (11–17 L). Based on the population pharmacokinetic model, plasma clearance ( $CL/F$ ) values for liraglutide 3.0 mg for obese individuals ranged between 0.9 and 1.4 L/h, and were consistent with those obtained in the Victoza<sup>®</sup> program (1.2 L/h).<sup>15</sup> Dose proportionality up to and including 3.0 mg was supported by the model-derived AUCs by dose from the phase 2 dose-finding trial, 1807 ([Figure 4–2](#)).





Data are means and 95% CI. AUC: area under the curve. N: number of patients.

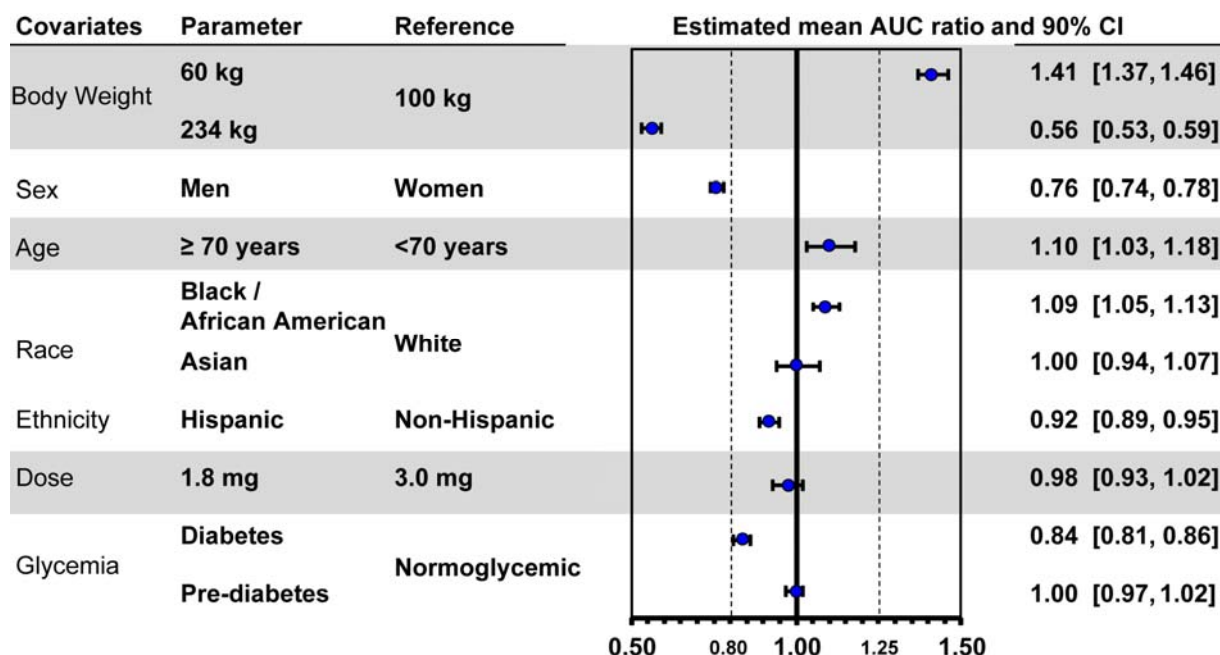
**Figure 4-2 Model-derived relation between liraglutide AUC and dose in obese individuals: Trial 1807**

#### 4.3.1 Effect of intrinsic factors and other covariates on liraglutide exposure

For the population pharmacokinetic analyses, liraglutide exposure (in terms of model-derived liraglutide AUC) was derived from plasma concentrations in samples taken at weeks 2, 12 and 28 in the phase 3 trials 1839 and 1922, supplemented by data from 50 patients in trial 1839 who each had 5 samples drawn at week 16, at the approximate time of  $C_{max}$ . The population pharmacokinetic analyses showed that age, race, ethnicity and glycemic status did not have a relevant impact on liraglutide exposure (Figure 4-3), since the 90% CIs of the estimated AUC ratio were within the limits for equivalence (0.80–1.25). Likewise, in a *post hoc* analysis, neither baseline renal function (normal, mild [N=1264] and moderate [N=150] renal impairment), nor injection site (abdomen, thigh, upper arm) had a relevant effect on liraglutide clearance. Similar to previous experience, exposure was influenced by body weight and sex.<sup>15</sup> Men had 24% lower exposure than women of a comparable body weight, corresponding to a 32% higher exposure in women compared to men. Moreover, as expected, exposures were inversely related to body weight; a person with a body weight of 60 kg (the lowest observed body weight in trials 1839 and 1922) had 41% higher exposure than one who weighed 100 kg. These results are in accordance with the observations made in the Victoza<sup>®</sup> program.<sup>15</sup>



An evaluation of body weight loss in sub-populations, defined according to sex and baseline body weight, in relation to liraglutide exposure levels is provided in the subsequent sections.

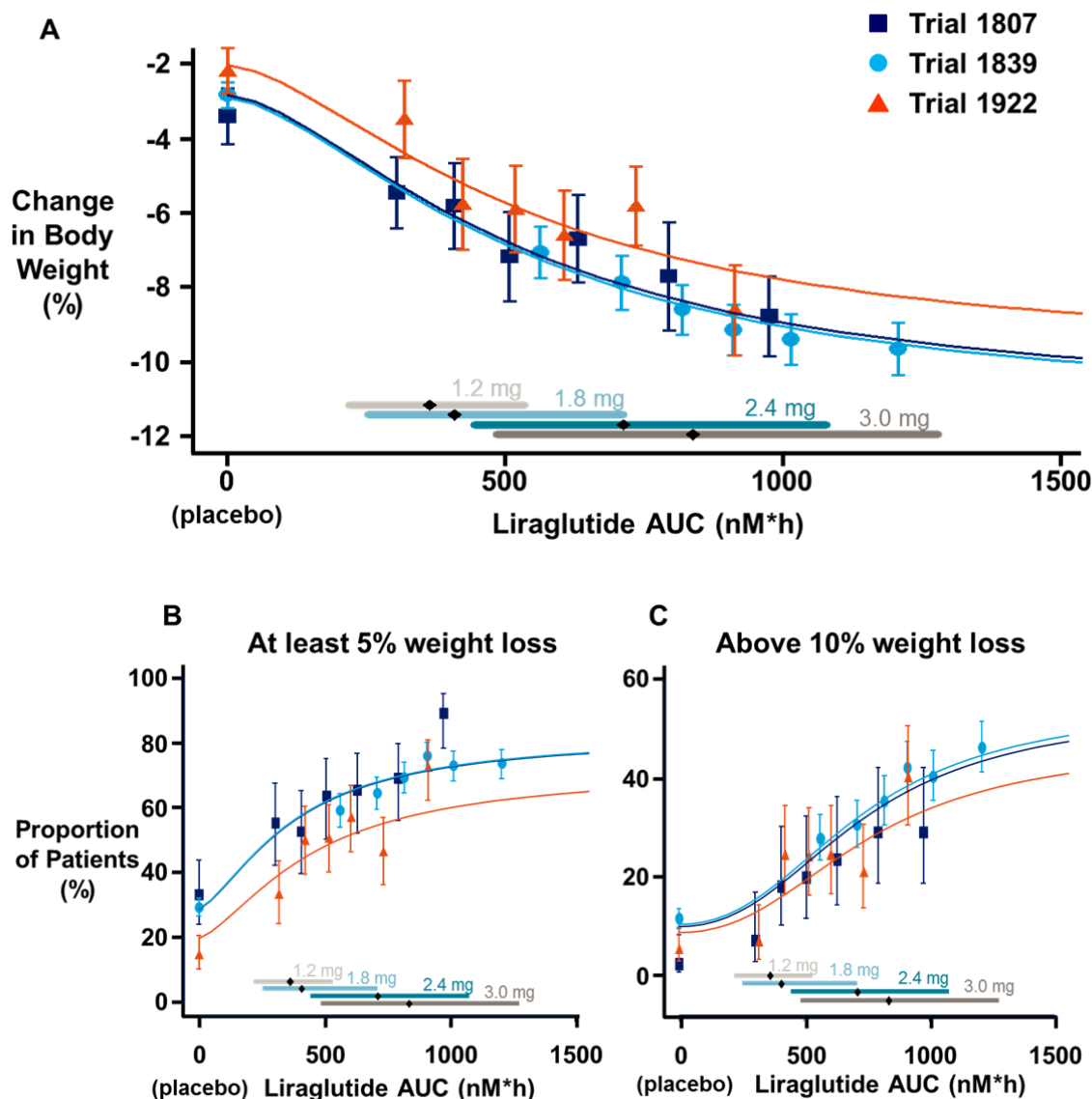


The values to the right (together with the symbols) show geometric mean exposures (AUC ratio) and 90% CI. Exposures are dose-normalized ( $AUC_{0-24h}/dose$ ) and relative to the reference. Dotted lines indicate the bioequivalence limits (0.8–1.25). 60 kg and 234 kg are the lowest and highest observed body weights in trials 1839 and 1922. AUC: area under the curve. CI: confidence interval.

**Figure 4–3 Covariate analysis expressed as steady-state dose-normalized exposure ( $AUC_{0-24 h}/dose$ ) relative to reference: Trials 1839 and 1922**

#### 4.4 Relationship between liraglutide exposure and body weight loss

Exposure response was analyzed by relating body weight loss to exposure, in terms of model-derived liraglutide AUC. There was a clear exposure-response relationship for both mean and categorical weight loss ([Figure 4–4](#)). Body weight loss increased with increasing liraglutide exposure over the entire investigated exposure range, with possible plateauing only at the highest exposures achieved with the 3.0 mg dose ([Figure 4–4A](#)), clearly favoring liraglutide 3.0 mg over any of the lower liraglutide doses investigated.



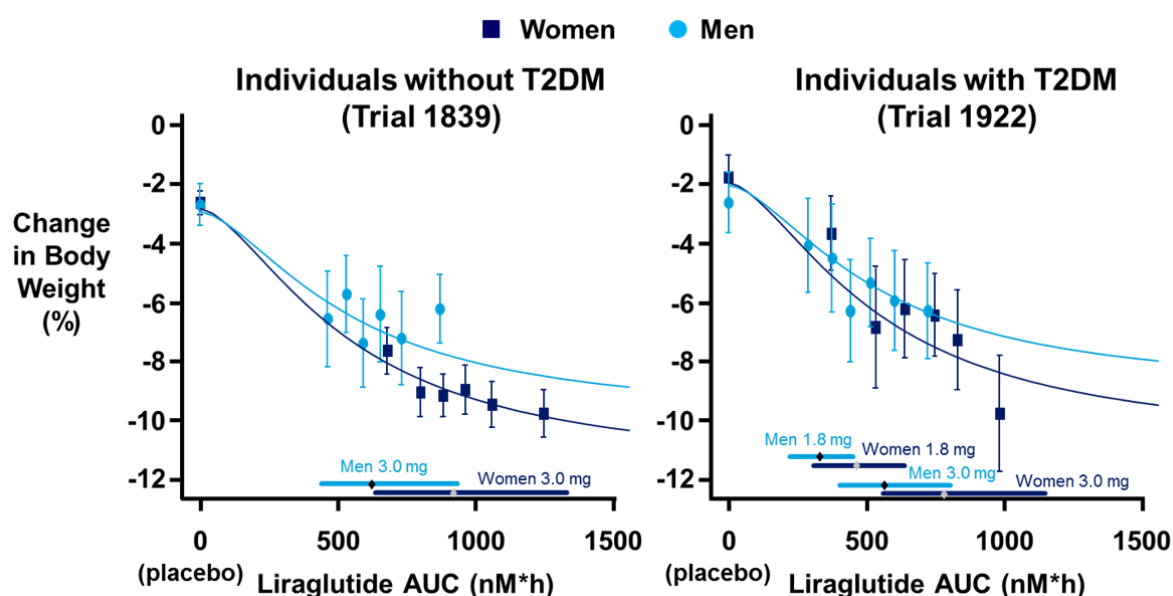
Data are mean observed response values with 95% CI vs. exposure (in 6 quantiles of AUC) by trial. Placebo is indicated on the figure as AUC=0. Curves represent covariate-adjusted model-based exposure-response estimates for each trial population. Horizontal lines with diamonds represent median and 90% exposure ranges for each dose level.

AUC: area under the curve. CI: confidence interval.

**Figure 4-4 Mean (A) and categorical (B and C) weight loss from baseline versus liraglutide exposure (AUC) at steady state: Trials 1807, 1839 and 1922**

There was a clear exposure-response relationship in both men and women, both in individuals without T2DM ([Figure 4-5](#), left panel) and in those with T2DM ([Figure 4-5](#), right panel). Women exhibited more weight loss than did men at comparable exposures. As shown in the right panel of [Figure 4-5](#), liraglutide 1.8 mg was associated with the quantiles representing the lowest exposure

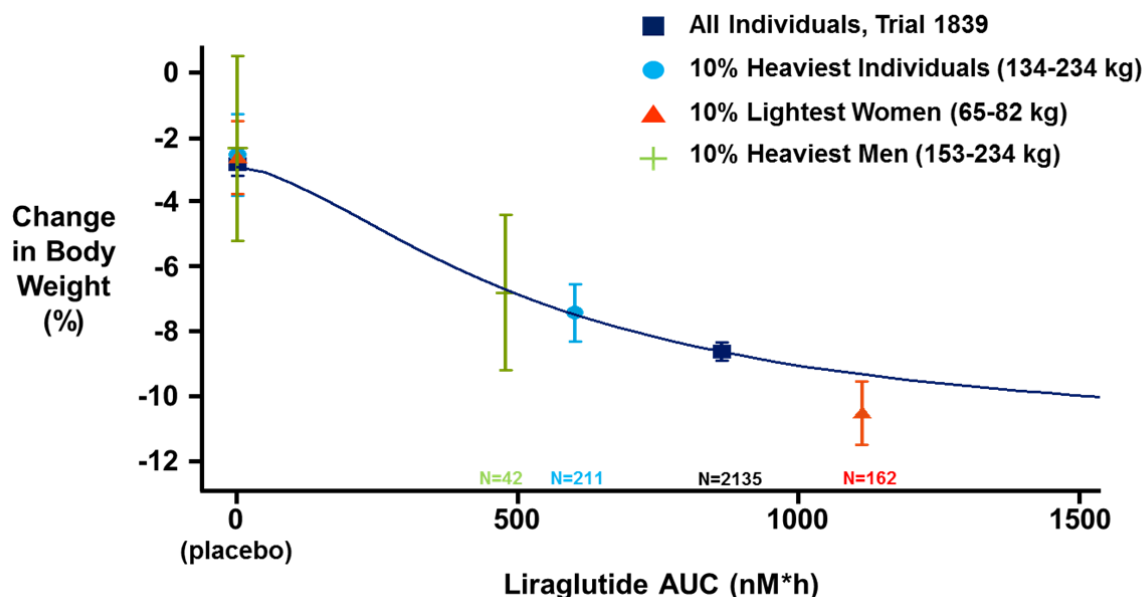
levels in both sexes. In men, the two lowest exposure quantiles associated with liraglutide 1.8 mg resulted in weight loss that could not be distinguished from placebo. This is in contrast to the exposure quantiles associated with liraglutide 3.0 mg, all of which provided weight loss clearly separated from placebo in both men and women, again supporting the use of liraglutide 3.0 mg over lower doses.



Data are mean observed response values with 95% CI versus exposure (6 AUC quantiles) for each sex. Placebo is indicated on the figure as AUC=0. Curves represent covariate-adjusted model-based exposure-response estimates for each sex. AUC: area under the curve. CI: confidence interval. T2DM: type 2 diabetes mellitus.

**Figure 4–5 Body weight change from baseline versus liraglutide exposure (AUC) at steady state for each sex: Trials 1839 (left) and 1922 (right)**

To further evaluate the clinical impact of plasma exposure extremes, weight loss in men and women was analyzed separately in sub-populations with high and low baseline body weights in trial 1839, in which all received liraglutide 3.0 mg. In both groups, the 10% of men with the highest baseline body weight and the 10% of women with the lowest baseline body weight achieved a weight loss that was greater than that achieved with placebo ([Figure 4–6](#)). As expected, the women with the lowest body weight experienced the greatest weight loss (~10.5% absolute reduction from baseline, ~8% placebo-adjusted), compared to the men with the highest body weight (~7% absolute reduction, ~4.5% placebo-adjusted weight loss).



Data are mean observed response values with 95% CI versus mean exposure for each sub-population. Placebo is indicated on the figure as AUC=0. The curve represents the estimated exposure-response relationship. AUC: area under the curve. CI: confidence interval. N: number of patients.

**Figure 4-6 Body weight change from baseline for liraglutide 3.0 mg in sub-populations of sex and body weight, compared to all patients: Trial 1839**

In summary, the exposure-response analyses support that liraglutide 3.0 mg is the *only* dose which provides adequate exposure to obtain a clinically relevant weight loss in *all* populations, including at the extremes of the exposure range (i.e., as obtained in the heaviest men and the lightest women). Importantly, the safety profile of liraglutide 3.0 mg in the women who had the lowest baseline body weights was not appreciably different from those with higher baseline body weights (as described in Section 6.2.4), further supporting a positive benefit to risk ratio of liraglutide 3.0 mg in all populations, including at exposure extremes.

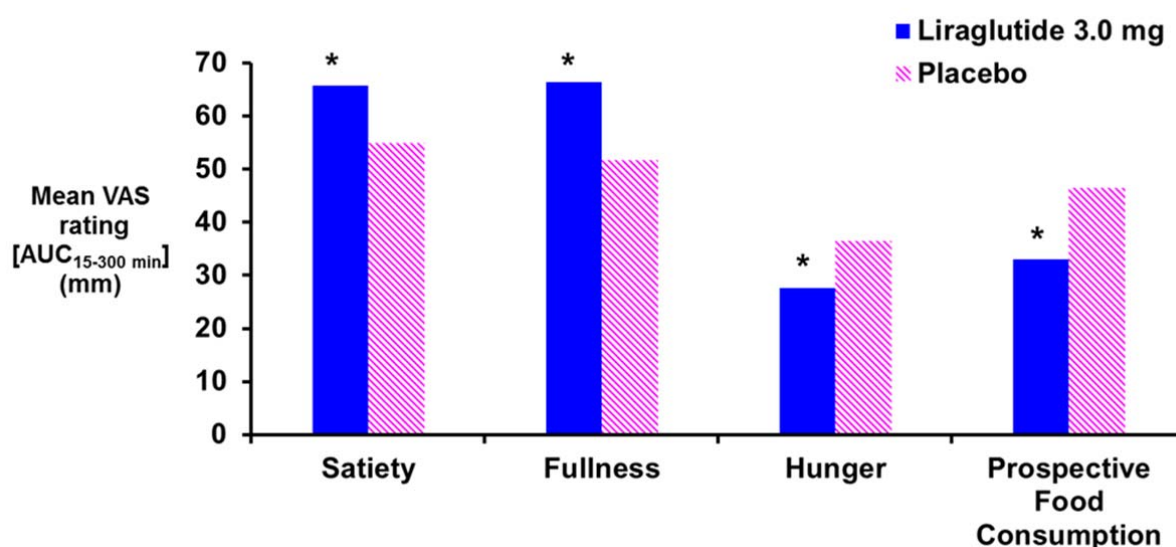
#### 4.5 Pharmacodynamic properties of liraglutide 3.0 mg for weight management

The pharmacodynamic properties of liraglutide 3.0 mg in obese individuals, including the mechanisms for weight loss, were evaluated after sub-acute administration in trial 3630, at the end of the 5-week treatment period (which included a dose escalation period of up to 4 weeks).<sup>13</sup> Acute administration of 3.0 mg is not considered feasible based on anticipation of unacceptable tolerability. A 4-week dose escalation regimen was used in all clinical trials in the weight management program.

The primary objective of trial 3630 was to demonstrate equivalence between liraglutide 3.0 mg and 1.8 mg with respect to gastric emptying (Section 4.5.2). The trial was not powered to detect treatment effects, or differences between doses, on secondary endpoints.

### 4.5.1 Appetite, energy intake and energy expenditure

Liraglutide 3.0 mg increased post-prandial satiety and fullness ratings following a standardized mixed breakfast meal compared with placebo at the end of a 5-week treatment period (Figure 4–7), and reduced ratings of hunger and prospective food consumption. Similar results were obtained with liraglutide 1.8 mg. The absence of a dose-response between 1.8 mg and 3.0 mg on appetite ratings and energy intake was not unexpected given that separation of weight loss curves does not occur until after 6–8 weeks of treatment in the clinical trials with liraglutide 3.0 mg (see for example Figure 5–2 and Figure 5–11).



\*p<0.05 vs. placebo. Data are estimated means. Number of patients = 30.

AUC: area under the curve. VAS: visual analog scale.

**Figure 4–7 Mean postprandial appetite ratings during a standardized mixed breakfast meal after 5 weeks of treatment: Trial 3630**

An *ad libitum* lunch meal was served approximately 5 hours after the standardized breakfast meal. The estimated mean energy intake during the *ad libitum* lunch was reduced by approximately 16% for both liraglutide 3.0 mg (-136 kcal; p=0.003) and liraglutide 1.8 mg (-141 kcal; p=0.002) as compared with placebo.

Energy expenditure was assessed during a 24-hour stay in an open-circuit respiratory chamber, also at the end of the 5-week treatment period. Energy expenditure did not increase; indeed, 24-hour energy expenditure was 5% lower (5.8 kcal/hour, p=0.0001) with liraglutide 3.0 mg as compared with placebo, with a relative shift toward increased fat and reduced carbohydrate oxidation.<sup>13</sup> A similar pattern was seen with liraglutide 1.8 mg. The liraglutide-associated reductions in energy expenditure were partly explained by a decrease in body weight with liraglutide (2.5 kg with 3.0 mg and 2.1 kg with 1.8 mg). After adjusting for the weight loss, the placebo-adjusted reduction in

24-hour energy expenditure decreased to 3% (4.1 kcal/hour,  $p=0.02$ ), reflecting metabolic adaptation to reduced body weight.

In conclusion, the weight loss observed with liraglutide was mediated by decreased appetite and subsequent reduction in caloric intake, rather than a treatment-related increase in energy expenditure.

#### 4.5.2 Gastric emptying

Equivalence in gastric emptying was observed over the full 5-hour post-meal period (acetaminophen  $AUC_{0-5h}$ ) for liraglutide 3.0 mg as compared with liraglutide 1.8 mg (AUC ratio and 90% CI: 1.03 [0.92; 1.15]) and placebo (AUC ratio and 90% CI: 0.93 [0.83; 1.04]). Liraglutide 3.0 mg delayed gastric emptying in the first hour after the meal, as reflected by a reduction in mean acetaminophen  $AUC_{0-1h}$  of 23% ( $p=0.007$ ) as compared with placebo. A similar trend was observed with liraglutide 1.8 mg, and is consistent with results seen in the Victoza<sup>®</sup> program. The clinical relevance of this initial delay is unknown, but it may have contributed to the observed reductions in postprandial glucose, as described below.

#### 4.5.3 Fasting and postprandial glucose, glucagon, insulin and C-peptide

Compared with placebo, liraglutide 3.0 mg reduced fasting glucose (by ~9 mg/dL from a baseline value of 97.3 mg/dL), and postprandial glucose AUC in the first hour after the mixed breakfast meal (by 9%), as well as both the total and incremental AUC in the 5-hour period following the mixed breakfast meal (by 13% and 26%, respectively). Moreover, decreases in postprandial glucagon ( $AUC_{0-5h}$ ; by 12%) were observed, and in the first hour after the meal, reductions in postprandial total and incremental insulin (by 16% and 26%, respectively) and C-peptide (by 9% and 21%) were also seen with liraglutide as compared with placebo. Effects on postprandial glycemic parameters were also assessed in overweight and obese patients with or without T2DM in the phase 3 trials (see Section 5.4.7). Consistent improvements in postprandial glycemic excursions were observed in both populations.

#### 4.6 Conclusions

The pharmacokinetic characteristics of liraglutide 3.0 mg in obese individuals were consistent with those for liraglutide doses up to 1.8 mg (Victoza<sup>®</sup>). Exposure increased in a dose proportional manner up to liraglutide 3.0 mg. A clear exposure-response relationship for mean and categorical weight loss was observed for liraglutide, which began to level off at the highest exposure achieved with liraglutide 3.0 mg. The exposure-response relationship was consistently observed across sub-populations, though with women experiencing more weight loss compared to men at comparable exposures. The exposure-response analyses support liraglutide 3.0 mg as the only dose which provides adequate exposures for a clinically relevant weight loss in all investigated sub-populations (categorized by sex, baseline body weight, diabetes status), including at the extremes of the exposure range (i.e., as obtained in the heaviest men and the lightest women).

Weight loss with liraglutide 3.0 mg in overweight or obese patients is mediated by a decrease in appetite and subsequent reduction in caloric intake, and is not due to increased energy expenditure. Gastric emptying assessed during a 5-hour meal was equivalent between liraglutide 3.0 mg and 1.8 mg, and was not different from placebo. The delay in gastric emptying with liraglutide in the first hour after a meal may contribute to the observed reductions in postprandial glucose.

## 5 Clinical Efficacy

### Summary

- In each trial, liraglutide 3.0 mg, as adjunct to diet and exercise, achieved statistical significance on all mean and categorical weight loss endpoints as compared with placebo.
- Treatment with liraglutide 3.0 mg led to a mean weight loss from baseline ranging from 5.7 to 9.2% (6.0–8.8 kg) depending on the trial, whereas patients in the placebo group (on diet and exercise) had a mean weight loss ranging from 0.2 to 3.1% (0.2–3.0 kg).
- More than 35% of patients in the group assigned to liraglutide 3.0 mg achieved the 5% weight loss benchmark in each trial (range 46–78%), and the proportion achieving the benchmark was more than twice the proportion that did so in the placebo group (range 14–30%), consistent with the FDA guidance.<sup>37</sup>
- Weight loss with liraglutide 3.0 mg was consistent across sub-populations, and all met the categorical weight loss criteria stipulated in the FDA guidance.<sup>37</sup>
- Mean weight loss was maintained during treatment in each trial, and was sustained for up to 2 years.<sup>92</sup>
- Weight loss with liraglutide 3.0 mg was accompanied by favorable effects on multiple measures, including blood pressure, lipids and other cardio-metabolic parameters such as glucose homeostasis and obstructive sleep apnea, consistent with the mechanism of action for liraglutide, as well as by meaningful improvements in quality of life, notably physical function.
- More weight loss led to greater improvements in secondary efficacy endpoints.
- In addition to meeting the benchmarks stipulated in the FDA guidance,<sup>37</sup> the combined favorable effects support that the weight loss achieved with liraglutide 3.0 mg, as adjunct to diet and exercise, is clinically relevant.

### 5.1 Introduction

The efficacy evaluation was based on data from the completed phase 2 and 3 randomized, placebo-controlled trials in the global weight management clinical development program. All of the trials were designed to assess the efficacy and safety of liraglutide 3.0 mg, as an adjunct to diet and exercise, in obese patients or overweight patients with at least one weight-related co-morbidity, such as dysglycemia (pre-diabetes and T2DM), hypertension, dyslipidemia, or OSA.

Efficacy was evaluated according to the benchmarks set forth in the current FDA guidance on the development of products for weight management,<sup>37</sup> which states that a product can be considered effective if either of the following occurs after 1 year of treatment:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant.



- The proportion of patients who lose at least 5% of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

Furthermore, the guidance states that improvements in blood pressure, lipids, glycemia, or other parameters commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product.

## 5.2 Phase 2 and 3 clinical development program

**Table 5–1 Phase 2 and 3 clinical trials in the weight management development program**

| Phase 2  |  |   |   |  |
|--|--|---|---|--|
|  |  | Trial 1807 Dose-finding   |   |  |
| Population   |  | Obese   |   |  |
| BMI (kg/m <sup>2</sup> )   |  | 30 - 40   |   |  |
| Total number randomized  |  | 564   |   |  |
| Liraglutide 3.0 mg / 2.4 mg / 1.8 mg / 1.2 mg / Placebo / Orlistat |  | 93 / 93 / 90 / 95 / 98 / 95   |   |  |
| Duration   |  | 20 weeks plus 84-week extension<br>(and interim analysis at 52 weeks) |   |  |
| Phase 3 double-blind randomized, controlled trials                 |  |   |   |  |
|  | Trial 1839<br>With or without<br>pre-diabetes  | Trial 1923<br>Weight maintenance                                      | Trial 1922<br>Type 2 diabetes                                   | Trial 3970<br>Obstructive<br>sleep apnea |
| Population   | Overweight/<br>obese   | Overweight/<br>obese  | Overweight/<br>obese  | Obese                                    |
| BMI (kg/m <sup>2</sup> )   | ≥ 27 with co-<br>morbidities or ≥ 30   | ≥ 27 with co-<br>morbidities or ≥ 30                                  | ≥ 27  | ≥ 30                                     |
| Total number randomized  | 3731   | 422   | 846   | 359                                      |
| Liraglutide 3.0 mg /<br>1.8 mg / Placebo                           | 2487 / 0 / 1244  | 212 / 0 / 210   | 423 / 211 / 212   | 180 / 0 / 179                            |
| Duration   | 56 weeks plus 12-<br>week re-randomized<br>treatment period*<br>(patients with pre-<br>diabetes at enrollment<br>continued in a 2-year<br>extension) | 56 weeks plus 12-<br>week off-treatment<br>observational period       | 56 weeks plus 12-<br>week off-treatment<br>observational period | 32 weeks                                 |
| Lifestyle modification   | All patients were advised on a 500 kcal/day deficit diet and<br>increased physical activity program  |   |   |  |

BMI: body mass index.

\*Re-randomized period was for patients without pre-diabetes.

The phase 2 and 3 trials in the weight management clinical development program ([Table 5–1](#)) were conducted according to current FDA guidance,<sup>37</sup> and are described briefly below:

- **Trial 1807** was the phase 2 dose-finding trial, the data from which guided the selection of the optimal liraglutide dose for inclusion in the phase 3 trials.<sup>92,93</sup>

- **Trial 1839**, the largest in the program, was conducted in overweight or obese patients who did not have T2DM. The ongoing extension will assess new onset of T2DM after 3 years in patients who entered the trial with pre-diabetes.
- **Trial 1923** was designed to assess the ability of liraglutide to maintain weight loss induced by a highly restricted low-calorie diet in overweight or obese patients without T2DM.<sup>94</sup>
- **Trial 1922** focused primarily on the effect of liraglutide on weight loss and glycemic control in patients who had a diagnosis of T2DM, and allowed comparison of the 3.0 mg dose to the maximum approved dose for the treatment of T2DM (1.8 mg).
- **Trial 3970** was conducted in obese patients who had moderate or severe obstructive sleep apnea (OSA), a breathing disorder during sleep that has implications beyond sleep disruption. The trial focused primarily on the ability of liraglutide to improve OSA severity and its related symptoms, through its effects on body weight.

All the trials included a blinded placebo control group; trial 1807 also included orlistat as an open-label active comparator. In each of the trials, liraglutide/placebo treatment was initiated at a dose of 0.6 mg, which was escalated in 0.6 mg weekly intervals until the target dose was achieved. Patients who discontinued from trials 1839, 1923 and 1922, the 56-week phase 3 trials, were asked to return at week 56 to be weighed and to report any AEs that they had experienced (see Section [5.4.2.1](#)).

Diet and exercise represented an active intervention in all treatment groups, and was provided in the form of an energy-restricted diet and exercise counseling. The dietary advice aimed at an energy deficit of approximately 500 kcal/day and a macro-nutrient composition of 30% of energy from fat, 20% from protein, and 50% from carbohydrates. The lifestyle intervention was found to be moderately effective and achievable in a real-world setting. Compliance was encouraged through the use of 3-day food diaries, completed approximately every 8 weeks. Furthermore, patients were encouraged to maintain or increase physical activity (a minimum 150 minutes/week was recommended and encouraged through the use of pedometers and regular counseling). Data from the diaries were not analyzed; rather, the diaries and pedometers were tools for the dietician to encourage compliance. Diet and exercise guidance was similar across the trials as well as the participating trial sites and was provided to patients either in groups or individually by a dietician at approximately monthly intervals (more frequently during dose escalation).

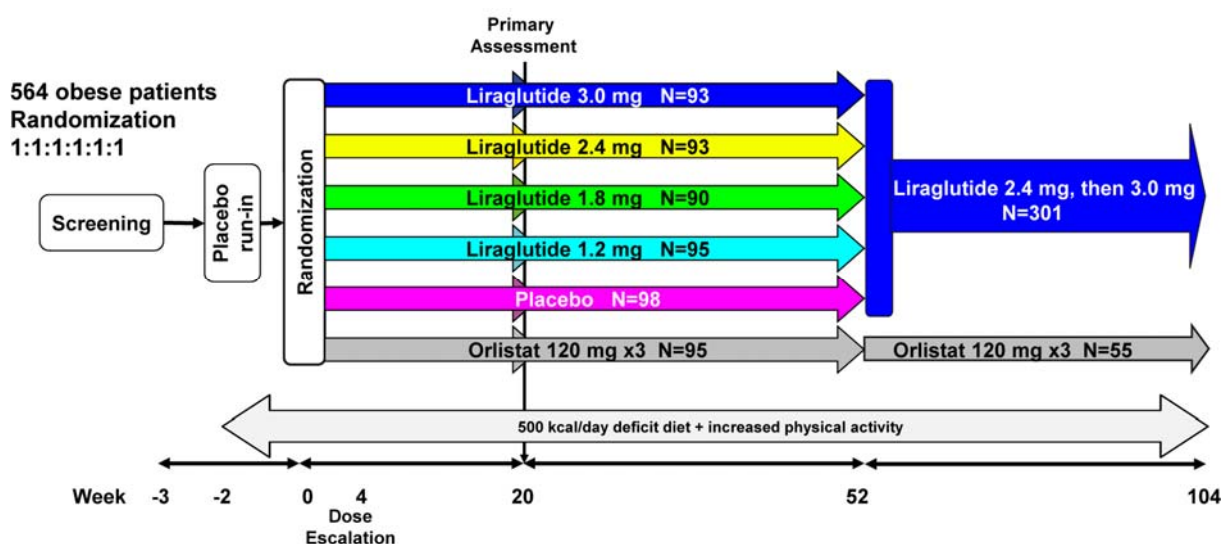
### 5.3 Phase 2 dose-finding trial: Trial 1807

#### 5.3.1 Rationale, primary endpoints and trial design

Liraglutide is currently approved for the treatment of T2DM at a maximum dose of 1.8 mg/day (as Victoza<sup>®</sup>). Data from the Victoza<sup>®</sup> development program suggested that a difference exists in the dose response curves of liraglutide for glycemic control and weight loss, with no evidence of a plateau for weight loss at the highest dose tested. The optimal dose for weight management was investigated in the phase 2, placebo-controlled, dose-finding trial, 1807, with liraglutide doses 1.2, 1.8, 2.4 and 3.0 mg. The aim of the trial was to determine the dose that maximized weight loss and improvements in co-morbidities without substantially changing the safety and tolerability profiles

from those of the doses approved for T2DM (1.2 and 1.8 mg). The maximum dose tested was 3.0 mg, based on assumptions of gastrointestinal intolerance at higher doses. The conclusion of the trial was that liraglutide 3.0 mg/day was the most efficacious of the doses tested, with a tolerability profile that supported its choice as the dose to be used in all phase 3 trials in the weight management clinical development program.

Trial 1807 was a 20-week trial with an 84-week extension period, which included an interim analysis at 52 weeks.<sup>92,93</sup> The trial was conducted at 19 sites across Europe. Patients without T2DM and with a screening BMI between 30 and 40 kg/m<sup>2</sup> were assigned to one of 6 treatment groups: the 4 liraglutide doses, placebo or the active comparator, orlistat (see [Figure 5-1](#)).



Week 0–20 (double blind; orlistat open label): Main trial, stratification by gender. 2-week diet and exercise run-in with daily placebo injections for all patients prior to randomization. Between 0 and 4 weeks liraglutide dose was escalated by weekly 0.6 mg/week increments up to the relevant treatment dose.

Weeks 20–52 (single-blind; patient and investigator blinded, sponsor unblinded): Extension. Patients who chose to enroll provided new informed consent and continued on randomized treatment.

Weeks 52–104 (open-label): Continuing extension for assessment of long-term safety. Liraglutide/placebo-treated patients were initially treated with liraglutide 2.4 mg in the open-label extension period, but were all gradually (as sites received Ethics Committee approval) changed to treatment with liraglutide 3.0 mg based on analysis of the results of the planned 52-week interim analysis. Orlistat-treated patients continued on orlistat.

N: number of randomized patients.

**Figure 5-1 Trial 1807, phase 2 dose-finding trial in obese patients**

After 20 weeks, the sponsor (but not participants or investigators) was unblinded and all patients were asked to re-consent for the subsequent 84-week extension period. Patients who agreed to participate remained in their randomized treatment group up to week 52. After week 52, all patients were unblinded, and those on all doses of liraglutide as well as placebo switched to treatment with the optimal liraglutide dose

was chosen based on consideration of both 20-week (main trial) and 52-week (interim analysis) efficacy and safety results. The interim analysis was included with the purpose of confirming the optimal liraglutide dose to be used in the subsequent phase 3 trials, at the time point considered appropriate to demonstrate the efficacy of a weight-management product.<sup>37</sup>

The primary efficacy analysis was at 20 weeks, and consisted of 2 co-primary endpoints:

- Change in body weight from baseline
- The proportion of patients achieving >5% reduction of baseline body weight (5% responders)

Of the randomized patients, 79% to 90% in each group completed the initial 20-week period and the majority of those (66% to 77%) chose to continue in the extension period ([Appendix Table 1-1](#)). In total, 74 patients chose not to enroll in the extension. Baseline demographics for the participants of trial 1807 are presented in [Table 5-2](#), and were similar across treatment groups.

**Table 5–2 Baseline characteristics for randomized and exposed individuals of trial 1807 (main 20-week period)**

|  | Liraglutide    |                |                |                |                 |  | Orlistat    |
|--|----------------|----------------|----------------|----------------|-----------------|--|-------------|
|  | 1.2 mg<br>N=95 | 1.8 mg<br>N=90 | 2.4 mg<br>N=93 | 3.0 mg<br>N=93 | Placebo<br>N=98 |  | N=95        |
| <b>Age (years) at screening</b>        |                |                |                |                |                 |  |             |
| Mean (SD)                              | 47.2 (9.7)     | 45.5 (10.9)    | 45.0 (11.1)    | 45.9 (10.7)    | 45.9 (10.3)     |  | 45.9 (9.1)  |
| Minimum-maximum                        | 23-65          | 18-63          | 21-65          | 23-63          | 27-64           |  | 27-63       |
| <b>Age group (years)</b>               |                |                |                |                |                 |  |             |
| 18 to <65                              | 94 (98.9)      | 90 (100)       | 92 (98.9)      | 93 (100)       | 98 (100)        |  | 95 (100)    |
| ≥65 to <75                             | 1 (1.1)        | 0 (0.0)        | 1 (1.1)        | 0 (0.0)        | 0 (0.0)         |  | 0 (0.0)     |
| <b>Sex</b>                             |                |                |                |                |                 |  |             |
| Female                                 | 73 (76.8)      | 68 (75.6)      | 71 (76.3)      | 70 (75.3)      | 74 (75.5)       |  | 73 (76.8)   |
| Male                                   | 22 (23.2)      | 22 (24.4)      | 22 (23.7)      | 23 (24.7)      | 24 (24.5)       |  | 22 (23.2)   |
| <b>Race</b>                            |                |                |                |                |                 |  |             |
| White                                  | 94 (98.0)      | 88 (97.8)      | 91 (97.8)      | 92 (98.9)      | 97 (99.0)       |  | 93 (97.9)   |
| Black or African American              | 0 (0.0)        | 2 (2.2)        | 1 (1.1)        | 1 (1.1)        | 1 (1.0)         |  | 1 (1.1)     |
| Asian                                  | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)         |  | 0 (0.0)     |
| American Indian or Alaska Native       | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)         |  | 1 (1.1)     |
| Native Hawaiian/other Pacific Islander | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)         |  | 0 (0.0)     |
| Other                                  | 1 (1.1)        | 0 (0.0)        | 1 (1.1)        | 0 (0.0)        | 0 (0.0)         |  | 0 (0.0)     |
| <b>Ethnicity<sup>a</sup></b>           | –              | –              | –              | –              | –               |  | –           |
| <b>Body weight (kg)</b>                |                |                |                |                |                 |  |             |
| Mean (SD)                              | 96.2 (13.5)    | 98.0 (12.5)    | 98.4 (13.0)    | 97.6 (13.7)    | 97.3 (12.3)     |  | 96.0 (11.7) |
| Minimum-maximum                        | 70.2-141.2     | 74.1-138.5     | 69.2-130.0     | 75.3-132.0     | 74.5-141.3      |  | 72.7-134.8  |
| <b>BMI (kg/m<sup>2</sup>)</b>          |                |                |                |                |                 |  |             |
| Mean (SD)                              | 34.2 (2.7)     | 34.6 (2.7)     | 34.6 (2.8)     | 34.3 (2.8)     | 34.5 (2.8)      |  | 33.7 (2.7)  |
| Minimum-maximum                        | 28.4-40.0      | 29.7-40.0      | 29.1-39.9      | 29.6-40.9      | 29.5-41.0       |  | 29.4-40.4   |
| <b>BMI category (kg/m<sup>2</sup>)</b> |                |                |                |                |                 |  |             |
| <30                                    | 5 (5.3)        | 4 (4.4)        | 2 (2.2)        | 3 (3.2)        | 3 (3.1)         |  | 9 (9.5)     |
| 30–34.9                                | 57 (60.0)      | 53 (58.9)      | 53 (57.0)      | 57 (61.3)      | 56 (57.1)       |  | 55 (57.9)   |
| 35–39.9                                | 33 (34.7)      | 33 (36.7)      | 38 (40.9)      | 31 (33.3)      | 38 (38.8)       |  | 30 (31.6)   |
| ≥40                                    | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 2 (2.2)        | 1 (1.0)         |  | 1 (1.1)     |

|   | Liraglutide    |                |                |                |                 |                  |
|---|----------------|----------------|----------------|----------------|-----------------|------------------|
|   | 1.2 mg<br>N=95 | 1.8 mg<br>N=90 | 2.4 mg<br>N=93 | 3.0 mg<br>N=93 | Placebo<br>N=98 | Orlistat<br>N=95 |
| <b>Glycemic status<sup>b</sup></b>                  |                |                |                |                |                 |                  |
| Normoglycemia                                       | 43 (45.3)      | 44 (48.9)      | 48 (51.6)      | 40 (43.0)      | 45 (45.9)       | 45 (47.4)        |
| Pre-diabetes  | 52 (54.7)      | 46 (51.1)      | 45 (48.4)      | 53 (57.0)      | 53 (54.1)       | 50 (52.6)        |
| T2DM  | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)        | 0 (0.0)         | 0 (0.0)          |
| <b>Co-morbidities present</b>                       |                |                |                |                |                 |                  |
| Dyslipidemia <sup>c</sup>                           | 9 (9.5)        | 15 (16.7)      | 8 (8.6)        | 12 (12.9)      | 14 (14.3)       | 13 (13.7)        |
| Hypertension <sup>d</sup>                           | 27 (28.4)      | 21 (23.3)      | 19 (20.4)      | 12 (12.9)      | 27 (27.6)       | 16 (16.8)        |
| Both  | 6 (6.3)        | 6 (6.7)        | 5 (5.4)        | 4 (4.3)        | 7 (7.1)         | 7 (7.4)          |
| <b>History of cardiovascular disease</b>            |                |                |                |                |                 |                  |
| Based on MedDRA search terms <sup>e</sup>           | 2 (2.1)        | 5 (5.6)        | 2 (2.2)        | 4 (4.3)        | 1 (1.0)         | 8 (8.4)          |
| <b>History of psychiatric disorders<sup>f</sup></b> | 10 (10.5)      | 9 (10.0)       | 9 (9.7)        | 4 (4.3)        | 9 (9.2)         | 13 (13.7)        |

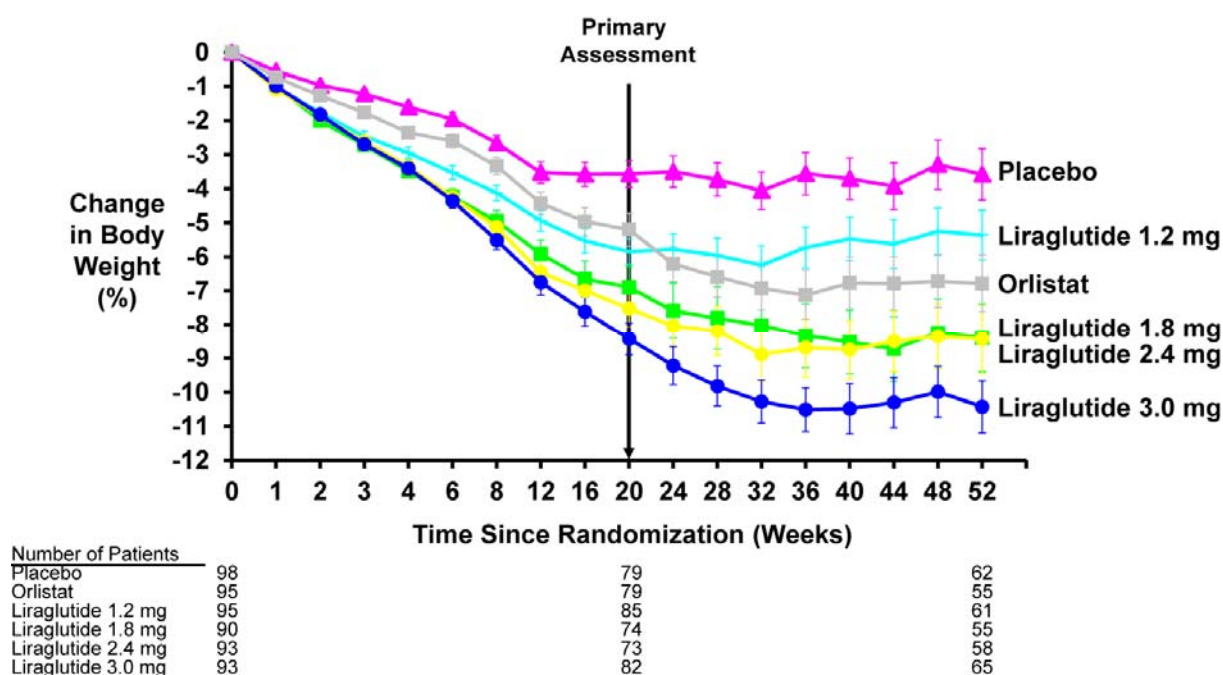
Numbers are for patients in the safety analysis set (all patients receiving at least one dose of the investigational product or comparators), and at randomization unless specified. Data are mean (SD) or number (%). BMI: body mass index. MedDRA: medical dictionary for regulatory activities. N: number of patients. SD: standard deviation. T2DM: type 2 diabetes mellitus.

<sup>a</sup>Ethnicity data were not collected in 1807. <sup>b</sup>Defined according to ADA 2010 criteria.<sup>95</sup> <sup>c</sup>Low density lipoprotein  $\geq 160$  mg/dL, or triglycerides  $\geq 150$  mg/dL, or high density lipoprotein  $< 40$  mg/dL for males and  $< 50$  mg/dL for females.<sup>96,97</sup> <sup>d</sup>Systolic blood pressure  $\geq 140$  or diastolic blood pressure  $\geq 90$  mmHg.<sup>98</sup> <sup>e</sup>Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events. <sup>f</sup>Depression, suicidal behavior, anxiety, mood disorders, insomnia, or sleep disorders.

### 5.3.2 Evidence for liraglutide 3.0 mg as the optimal liraglutide dose

#### 5.3.2.1 Effect of liraglutide dose on body weight

A clear dose-dependent effect on body weight loss was observed with liraglutide in trial 1807 at both 20 weeks and 52 weeks ([Figure 5-2](#)), with maximal weight loss at the highest dose of 3.0 mg at both time points ([Figure 5-3](#)).

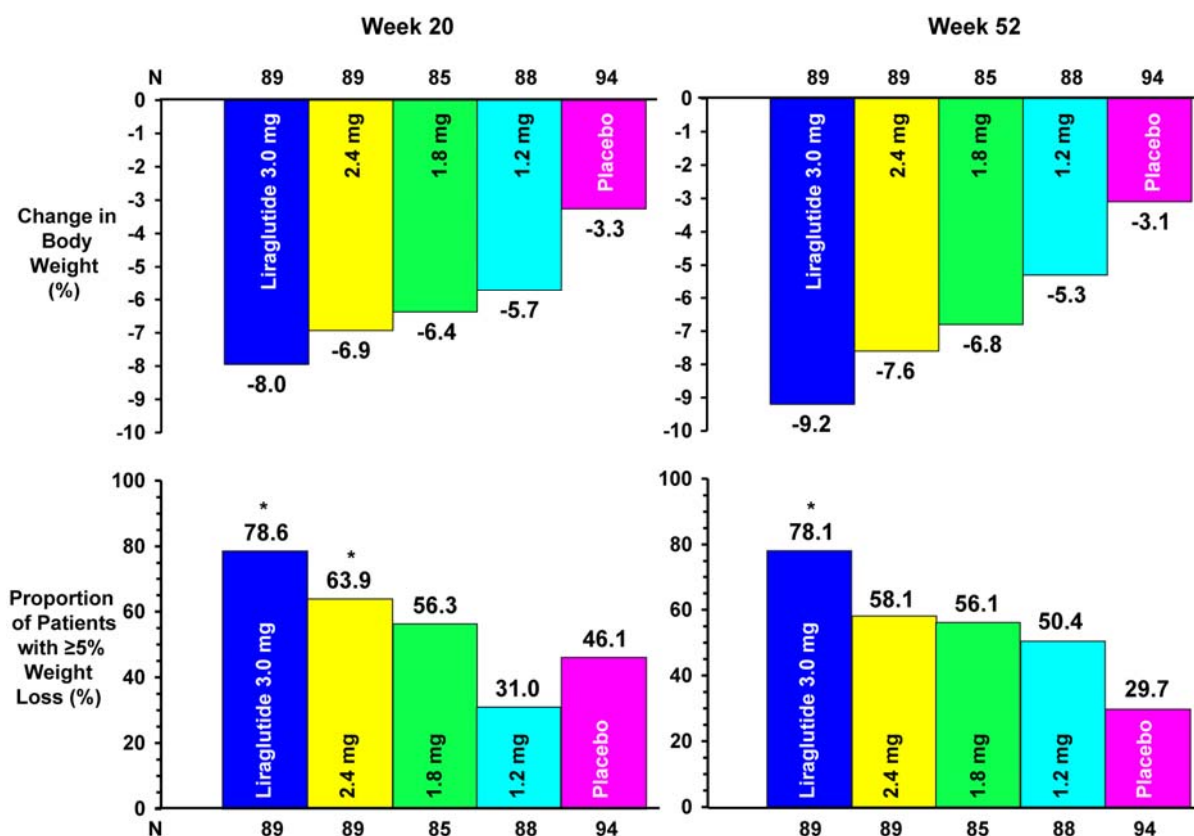


Data are observed means with standard error bars for patients completing each scheduled visit.

**Figure 5-2 Body weight change from baseline (%) by liraglutide dose: Trial 1807**

Importantly, of the doses tested, liraglutide 3.0 mg was the *only* dose that met both the mean and categorical weight loss criteria stipulated in the current FDA weight-management guidance after 52 weeks ([Figure 5-3](#) and [Appendix Table 4-1](#)).<sup>37</sup>





Data shown are estimated means for the full analysis set with last observation carried forward imputation. A dose response was observed in each case ( $p < 0.001$  for all, *post hoc* analyses). \*Achieved FDA benchmark for placebo-subtracted weight loss  $\geq 5\%$  or at least 35% of patients achieving 5% weight loss and twice the % in the placebo group. N: number of patients.

**Figure 5–3 Mean (top) and categorical (bottom) body weight change from baseline by dose: Trial 1807**

### 5.3.2.2 Effect of liraglutide dose on secondary endpoints

In trial 1807, liraglutide 3.0 mg provided not only the greatest weight loss but also had the most beneficial effects overall on a wide range of secondary endpoints. These included cardio-metabolic parameters (glycemic parameters, blood pressure, fasting lipids) and quality of life ([Appendix Table 4-2](#)), as assessed using the Impact of Weight on Quality of Life-Lite questionnaire. This instrument is designed to assess an individual's perceptions of how weight affects their daily life.<sup>39</sup>

### 5.3.2.3 Effect of liraglutide dose on safety

The effects of liraglutide dose on the overall safety profile and selected safety parameters were also evaluated in trial 1807. The only safety parameter for which a consistent dose-response relationship was observed for liraglutide treatment was gastrointestinal disorders ([Table 5–3](#), which shows the 52-week period). This effect was anticipated based on experience in the Victoza<sup>®</sup> program with



doses up to 1.8 mg. No consistent dose relationship was apparent with regard to overall safety profile ([Table 5–3](#)) or other selected safety parameters (hypoglycemia, resting heart rate, or plasma calcitonin levels).

Most of the gastrointestinal events were transient, with onset in the first 4–8 weeks of treatment, were not serious and did not lead to greater withdrawal of patients in the 3.0 mg treatment group as compared with lower dose groups. Moreover, early nausea and vomiting in trial 1807 did not appear to adversely affect liraglutide-associated improvements in quality of life at 20 weeks.<sup>99</sup>

Only small differences in other types of events were apparent between the liraglutide doses; there were no apparent dose-response relationships, although the numbers of events may have been too low to identify such a relationship. Resting heart rate increased with liraglutide treatment as compared with placebo, but there was no clear dose-response effect at the doses tested ([Table 5–4](#);  $p=0.40$  for the response across doses in the second row of the table). This is consistent with the absence of a difference between 1.8 mg and 3.0 mg in trial 1922 (T2DM), and between 1.2 and 1.8 mg in the Victoza<sup>®</sup> program for patients with T2DM.

**Table 5-3 Overall adverse events, and gastrointestinal disorders in 5% or more of patients, by liraglutide dose: Trial 1807 (52-week period)**

| Trial 1807 (obese patients) | Liraglutide 1.2 mg<br>N=95 |     |       | Liraglutide 1.8 mg<br>N=90 |     |       | Liraglutide 2.4 mg<br>N=93 |     |       | Liraglutide 3.0 mg<br>N=93 |     |       | Placebo<br>N=98 |     |       |
|-----------------------------|----------------------------|-----|-------|----------------------------|-----|-------|----------------------------|-----|-------|----------------------------|-----|-------|-----------------|-----|-------|
|                             | N (%)                      | E   | R     | N (%)                      | E   | R     | N (%)                      | E   | R     | N (%)                      | E   | R     | N (%)           | E   | R     |
| Adverse events total        | 88 (92.6)                  | 365 | 500.4 | 85 (94.4)                  | 438 | 662.3 | 88 (94.6)                  | 488 | 700.6 | 89 (95.7)                  | 498 | 657.6 | 87 (88.8)       | 378 | 516.3 |
| Serious adverse events      | 4 (4.2)                    | 4   | 5.5   | 7 (7.8)                    | 7   | 10.6  | 4 (4.3)                    | 6   | 8.6   | 7 (7.5)                    | 10  | 13.2  | 3 (3.1)         | 3   | 4.1   |
| AEs leading to withdrawal   | 6 (6.3)                    | 13  | 17.8  | 9 (10.0)                   | 13  | 19.7  | 12 (12.9)                  | 20  | 28.7  | 7 (7.5)                    | 12  | 15.8  | 3 (3.1)         | 7   | 9.6   |
| Overall withdrawals         | 17 (17.9)                  | –   | –     | 20 (22.2)                  | –   | –     | 27 (29.0)                  | –   | –     | 18 (19.4)                  | –   | –     | 24 (24.5)       | –   | –     |
| Gastrointestinal disorders  | 55 (57.9)                  | 101 | 138.5 | 59 (65.6)                  | 122 | 184.5 | 66 (71.0)                  | 158 | 226.8 | 73 (78.5)                  | 168 | 221.8 | 38 (38.8)       | 62  | 84.7  |
| Nausea                      | 23 (24.2)                  | 27  | 37.0  | 29 (32.2)                  | 33  | 49.9  | 35 (37.6)                  | 48  | 68.9  | 46 (49.5)                  | 69  | 91.1  | 7 (7.1)         | 8   | 10.9  |
| Vomiting                    | 5 (5.3)                    | 6   | 8.2   | 9 (10.0)                   | 18  | 27.2  | 15 (16.1)                  | 18  | 25.8  | 12 (12.9)                  | 16  | 21.1  | 2 (2.0)         | 2   | 2.7   |
| Dyspepsia                   | 6 (6.3)                    | 7   | 9.6   | 7 (7.8)                    | 7   | 10.6  | 10 (10.8)                  | 14  | 20.1  | 8 (8.6)                    | 8   | 10.6  | 3 (3.1)         | 3   | 4.1   |
| Abdominal pain              | 2 (2.1)                    | 2   | 2.7   | 4 (4.4)                    | 4   | 6.0   | 1 (1.1)                    | 1   | 1.4   | 5 (5.4)                    | 5   | 6.6   | 4 (4.1)         | 4   | 5.5   |
| Abdominal pain upper        | 5 (5.3)                    | 6   | 8.2   | 2 (2.2)                    | 3   | 4.5   | 5 (5.4)                    | 5   | 7.2   | 5 (5.4)                    | 7   | 9.2   | 1 (1.0)         | 1   | 1.4   |
| Constipation                | 15 (15.8)                  | 18  | 24.7  | 11 (12.2)                  | 12  | 18.1  | 21 (22.6)                  | 24  | 34.5  | 17 (18.3)                  | 18  | 23.8  | 12 (12.2)       | 14  | 19.1  |
| Diarrhea                    | 8 (8.4)                    | 13  | 17.8  | 9 (10.0)                   | 12  | 18.1  | 12 (12.9)                  | 13  | 18.7  | 14 (15.1)                  | 15  | 19.8  | 10 (10.2)       | 11  | 15.0  |
| Serious gastrointestinal    | 1 (1.1)                    | 1   | 1.4   | 1 (1.1)                    | 1   | 1.5   | 1 (1.1)                    | 2   | 2.9   | 2 (2.2)                    | 3   | 4.0   | 0 (0.0)         | 0   | 0     |

Period: Week 0–52. AE: adverse event. N: number of patients. %: percentage of patients. E: number of events. R: event rate per 100 patient exposure years.

**Table 5-4 Mean and categorical changes in resting heart rate, by liraglutide dose: Trial 1807 (52-week period)**

| Trial 1807 (obese patients)                                    | Liraglutide<br>1.2 mg | Liraglutide 1.8 mg | Liraglutide 2.4 mg | Liraglutide 3.0 mg | Placebo      |
|--|-----------------------|--------------------|--------------------|--------------------|--------------|
| Observed mean (SD) resting heart rate at baseline, bpm         | 70.7 (11.9)           | 69.3 (10.7)        | 70.1 (9.4)         | 68.5 (8.9)         | 68.4 (10.6)  |
| Estimated mean change in heart rate at week 52, bpm            | 2.7                   | 2.2                | 2.5                | 3.7                | -1.6         |
| <b>Persistent heart rate changes at ≥ 2 consecutive visits</b> | <b>N (%)</b>          | <b>N (%)</b>       | <b>N (%)</b>       | <b>N (%)</b>       | <b>N (%)</b> |
| Change in heart rate > 5 bpm                                   | 41 (43.2)             | 37 (41.1)          | 38 (40.9)          | 42 (45.2)          | 24 (24.5)    |
| Change in heart rate > 10 bpm                                  | 20 (21.1)             | 16 (17.8)          | 19 (20.4)          | 22 (23.7)          | 9 (9.2)      |
| Change in heart rate > 20 bpm                                  | 2 (2.1)               | 0 (0.0)            | 3 (3.2)            | 4 (4.3)            | 0 (0.0)      |
| Heart rate >80 bpm   | 20 (21.1)             | 15 (16.7)          | 24 (25.8)          | 19 (20.4)          | 10 (10.2)    |
| Heart rate >90 bpm   | 5 (5.3)               | 0 (0.0)            | 2 (2.2)            | 3 (3.2)            | 2 (2.0)      |

Period: Week 0–52. N: number of patients. %: percentage of patients. bpm: beats per minute. SD: standard deviation.

### 5.3.3 Conclusions

The efficacy and safety results of the dose-finding trial 1807 supported that liraglutide 3.0 mg/day was the dose that maximized weight loss and improvements in co-morbidities with acceptable tolerability. These results were also supported by the exposure-response analyses described in Section 4.4. The 3.0 mg dose was subsequently used in all phase 3 trials in the weight management clinical development program. The safety and tolerability profile for liraglutide 3.0 mg was not substantially different from that of 1.8 mg, the maximum approved dose for T2DM, except that gastrointestinal disorders were more frequent. In order to improve gastrointestinal tolerability, the recommended starting dose of liraglutide is 0.6 mg daily, increasing in increments of 0.6 mg after at least 1 week at each dose level until the final dose level of 3.0 mg/day is reached. This strategy is similar to that approved for Victoza<sup>®</sup> at doses up to 1.8 mg in patients with T2DM.<sup>15</sup>

## 5.4 Phase 3 trials

### 5.4.1 Efficacy evaluation, endpoints and trial design

The evaluation of efficacy was primarily based on the results for the individual trials according to pre-specified statistical analyses, and on a comparison of liraglutide 3.0 mg vs. placebo. The primary endpoints of the 56-week phase 3 trials (1839, 1922 and 1923) were related to body weight, and included both mean and categorical changes in body weight (Table 5-5), as recommended by the FDA guidance.<sup>37</sup> Hierarchical testing of the co-primary endpoints was applied to control for multiple testing, whereby the second and third endpoints were tested only if the previous endpoint(s) had achieved statistical significance.

**Table 5-5 Key efficacy endpoints related to body weight in the phase 3 clinical trials**

| <b>Trial</b>                  | <b>1<sup>st</sup> Co-primary endpoint</b>             | <b>2<sup>nd</sup> Co-primary endpoint</b>   | <b>3<sup>rd</sup> Co-primary endpoint</b>   |
|-------------------------------|---|---|---|
| 1839<br>1922<br>(at 56 weeks) | Change in body weight from baseline (% , kg)          | Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders)   | Proportion of patients achieving $>10\%$ reduction of baseline body weight (10% responders)   |
| 1923<br>(at 56 weeks)         | Change in body weight from baseline (% , kg)          | Proportion of patients that maintained the $\geq 5\%$ reduction in initial body weight achieved during the low calorie diet run-in period | Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders) |
| <b>Trial</b>                  | <b>Key secondary endpoints related to body weight</b> |   |   |
| 3970<br>(at 32 weeks)         | Change in body weight from baseline (% , kg)          | Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders)   | Proportion of patients achieving $>10\%$ reduction of baseline body weight (10% responders)   |

Hierarchical testing of co-primary endpoints was applied in trials 1839, 1922, and 1923. Baseline=randomization.

In trial 3970, conducted in patients with OSA, change in the apnea-hypopnea index (AHI) was the primary endpoint. The AHI is an index of OSA severity that combines apnea episodes (complete cessations in breathing) and hypopnea episodes (partial obstructions), measured as events per hour.

Obesity is a chronic disease associated with increased risk of hypertension, dysglycemia/T2DM, dyslipidemia, and atherosclerosis,<sup>18</sup> and it can also negatively impact physical and mental health and quality of life.<sup>25,27</sup> A reduction of 5–10% of initial body weight has been shown to improve glycemic control and other obesity-related cardiovascular and metabolic abnormalities, as well as physical symptoms, functional limitations and quality of life.<sup>29-32</sup> Accordingly, and in line with the current FDA guidance,<sup>37</sup> pre-specified secondary endpoints were chosen ([Table 5–6](#)) to investigate the effect of liraglutide on those conditions and thus to confirm the clinical relevance of the weight loss achieved.

Results of the phase 3 trials are presented by trial in [Appendix Section 2](#).

**Table 5–6 Pre-specified primary and secondary efficacy endpoints of the phase 3 clinical trials**

| Endpoints (change from baseline)                      | Trial 1839<br>Patients without<br>T2DM<br>56 weeks | Trial 1923<br>Weight<br>maintenance<br>56 weeks | Trial 1922<br>Patients with<br>T2DM<br>56 weeks | Trial 3970<br>Patients with OSA<br>32 weeks |
|---|--|---|---|---|
| <b>Body weight and other weight-related</b>           |  |   |   |   |
| Body weight (mean and categorical)                    | X (primary)  | X (primary)                                     | X (primary)                                     | X   |
| BMI   | X  | X   | X   | X   |
| Waist circumference                                   | X  | X   | X   | X   |
| Binge eating  | X <sup>a</sup>                                     | X   | X <sup>a</sup>                                  | –   |
| <b>Glycemic control parameters</b>                    |  |   |   |   |
| HbA <sub>1c</sub> and fasting parameters <sup>b</sup> | X  | X   | X   | X   |
| HOMA-B  | X  | X   | X   | –   |
| HOMA-IR   | X  | X   | X   | –   |
| Parameters in oral glucose tolerance test             | X  | –   | –   | –   |
| Glycemic status <sup>c</sup>                          | X  | –   | –   | –   |
| Additional glycemic control measures <sup>d</sup>     | X  | –   | X   | –   |
| <b>Cardio-metabolic parameters</b>                    |  |   |   |   |
| Vital signs   | X  | X   | X   | X   |
| Fasting lipids  | X  | X   | X   | X   |
| Cardiovascular biomarkers <sup>e</sup>                | X  | X   | X   | X   |
| <b>Sleep apnea-related endpoints</b>                  |  |   |   |   |
| Apnea-hypopnea index                                  | –  | –   | –   | X (primary)                                 |
| Neck circumference                                    | –  | –   | –   | X   |
| Other sleep-apnea related                             | –  | –   | –   | X   |

| Endpoints (change from baseline)                      | Trial 1839<br>Patients without<br>T2DM<br>56 weeks | Trial 1923<br>Weight<br>maintenance<br>56 weeks | Trial 1922<br>Patients with<br>T2DM<br>56 weeks | Trial 3970<br>Patients with OSA<br>32 weeks |
|---|--|---|---|---|
| <b>Patient reported outcomes</b>                      |  |   |   |   |
| Impact of Weight on Quality of Life-Lite (IWQoL-Lite) | X  | –   | X   | –   |
| 36-item Short-Form health status survey (SF-36)       | X  | –   | –   | X   |
| Treatment Related Impact Measure-Weight (TRIM-Weight) | X  | –   | –   | –   |
| Diabetes Treatment Satisfaction Questionnaire (DTSQs) | –  | –   | X   | –   |
| Epworth Sleepiness Scale (ESS)                        | –  | –   | –   | X   |
| Functional Outcomes of Sleep Questionnaire (FOSQ)     | –  | –   | –   | X   |
| <b>Concomitant medication</b>                         |  |   |   |   |
| Lipid-lowering drugs                                  | X  | X   | X   | –   |
| Anti-hypertensive drugs                               | X  | X   | X   | –   |
| Oral antidiabetic drugs                               | X  | –   | X   | –   |

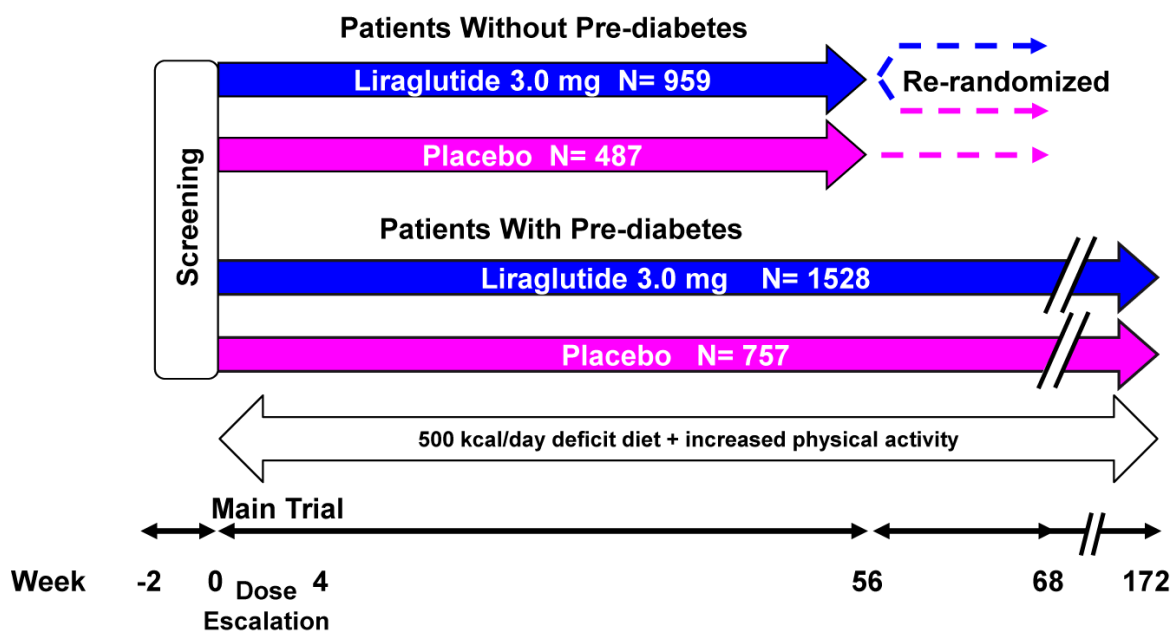
BMI: body mass index. HbA<sub>1c</sub>: glycosylated hemoglobin A<sub>1c</sub>. HOMA: Homeostasis Model Assessment. HOMA-B: a measure of beta-cell function in the fasting state. HOMA-IR: a measure of insulin resistance in the fasting state, mainly at the site of the liver. OSA: obstructive sleep apnea. T2DM: type 2 diabetes mellitus.

<sup>a</sup>Included as a safety endpoint. <sup>b</sup>Fasting glucose (all trials), insulin (1839, 1923, 1922), C-peptide (1839, 1922), glucagon (1922). <sup>c</sup>Normoglycemia, pre-diabetes and T2DM, as defined by ADA 2010 criteria.<sup>95</sup> <sup>d</sup>Fasting proinsulin/insulin ratio, 7-point plasma glucose profile, proportion of patients reaching target HbA<sub>1c</sub> levels (1922).

<sup>e</sup>High sensitivity C-reactive protein (all trials), fibrinogen and adiponectin (1839, 1923, 1922), plasminogen activator inhibitor-1 (1839, 1922), urinary albumin/creatinine ratio (1839, 1922, 3970).

### 5.4.1.1 Trial 1839

Trial 1839 ([Figure 5–4](#)) was the largest in the development program and represented approximately 70% of the total phase 3 trial population. The trial was conducted in overweight or obese patients without T2DM. Participants were obese (with a BMI of at least 30 kg/m<sup>2</sup>), or were overweight (BMI at least 27 kg/m<sup>2</sup>) with a diagnosis of dyslipidemia<sup>96,100</sup> and/or hypertension.<sup>98</sup> Patients were randomized to treatment in a 2:1 ratio and stratified according to whether or not they had a diagnosis of pre-diabetes at screening, according to ADA 2010 criteria.<sup>95</sup> For patients without pre-diabetes, completers on liraglutide were re-randomized at week 56 to continue on liraglutide or switch to placebo in a 12-week re-randomized treatment period with continued lifestyle intervention, to assess the effects of drug cessation on body weight, and possible withdrawal side-effects. Patients on placebo continued on placebo. For patients with pre-diabetes (61% of the randomized population), an additional 2 year extension (currently ongoing; the sponsor was unblinded but patients and investigators remain blinded) was included to investigate the impact of liraglutide 3.0 mg on new onset of T2DM in patients who entered the trial with pre-diabetes. In the 56-week trial, liraglutide 3.0 mg met all 3 pre-specified mean and categorical co-primary weight loss endpoints after 56 weeks ([Table 5–5](#)).

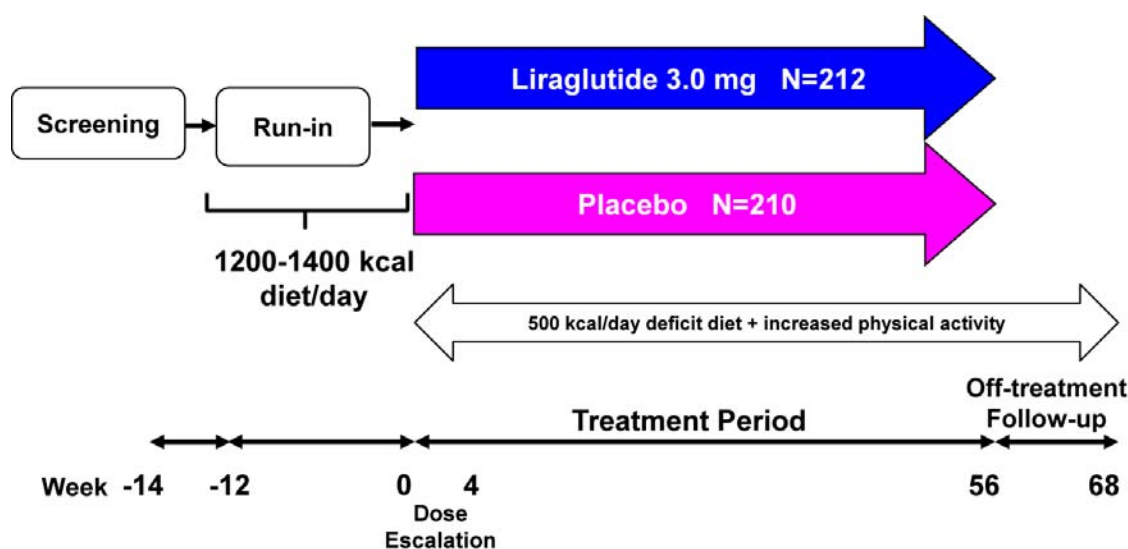


Randomization 2:1. Stratification by pre-diabetes status at screening (2010 criteria<sup>95</sup>) and by BMI ( $\geq 30$  kg/m<sup>2</sup> or  $< 30$  kg/m<sup>2</sup>). Between 0 and 4 weeks liraglutide dose was escalated by 0.6 mg/week increments up to 3.0 mg. N: number of randomized patients.

**Figure 5–4 Trial 1839, 56-week trial in patients without type 2 diabetes**

### 5.4.1.2 Trial 1923

Trial 1923 ([Figure 5-5](#)) was a 56-week, double-blind weight loss and weight maintenance trial<sup>94</sup> conducted in 422 patients without T2DM who were obese (with a BMI of at least 30 kg/m<sup>2</sup>) or who were overweight (BMI at least 27 kg/m<sup>2</sup>) and had a diagnosis of dyslipidemia<sup>96,100</sup> and/or hypertension.<sup>98</sup> As this trial was designed to focus on the role of liraglutide in weight loss maintenance, only patients achieving at least 5% weight loss during a 4–12 week run-in period on a low-calorie diet were subsequently randomized to treatment in a 1:1 ratio. Liraglutide 3.0 mg met all 3 pre-specified mean and categorical co-primary weight loss or weight loss maintenance endpoints at the end of the treatment period ([Table 5-5](#)).



Stratification by co-morbidity status (presence or absence of treated or untreated hypertension or dyslipidemia) and by BMI ( $\geq 30$  kg/m<sup>2</sup> or  $< 30$  kg/m<sup>2</sup>). Randomization 1:1. Between 0 and 4 weeks liraglutide dose was escalated by 0.6 mg/week increments up to 3.0 mg.

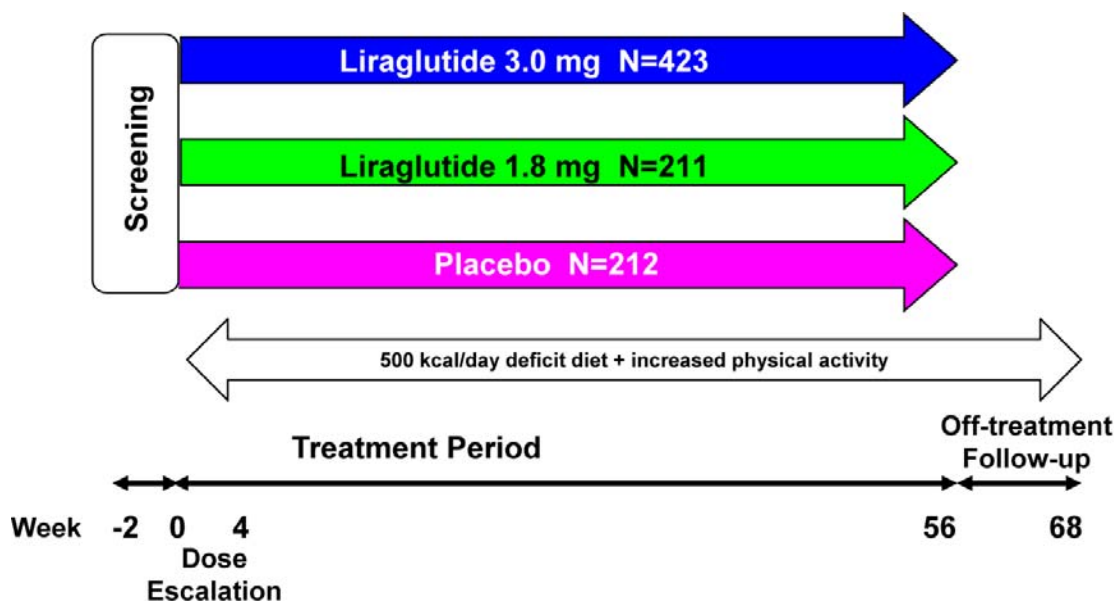
N: number of randomized patients.

**Figure 5-5 Trial 1923, 56-week weight maintenance trial**



### 5.4.1.3 Trial 1922

Trial 1922 ([Figure 5–6](#)) was a 56-week, double-blind weight loss trial conducted in 846 patients with a BMI of at least 27 kg/m<sup>2</sup> and with an established diagnosis of T2DM.<sup>95</sup> Patients were randomized to treatment in a 2:1:1 ratio. Liraglutide 3.0 mg met all 3 pre-specified mean and categorical co-primary weight loss endpoints at the end of the treatment period ([Table 5–5](#)).

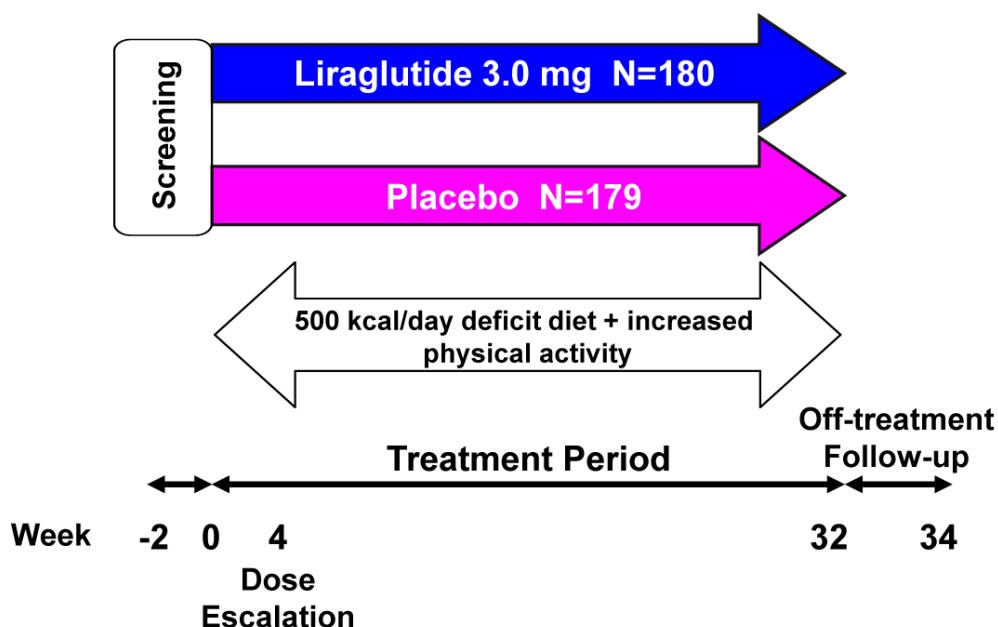


Stratification by background treatment and by baseline HbA<sub>1c</sub> level (<8.5% or ≥8.5%). Allowed background oral anti-diabetic drugs (OADs) were used open-labelled (the proportion with sulfonylurea therapy was restricted to a maximum of 30% of randomized individuals, to ensure adequate exposure to all 3 OAD categories.) Randomization 2:1:1. Between 0 and 4 weeks liraglutide dose was escalated by 0.6 mg/week increments up to 1.8 or 3.0 mg. N: number of randomized patients.

**Figure 5–6 Trial 1922, 56-week trial in patients with type 2 diabetes**

### 5.4.1.4 Trial 3970

Trial 3970 ([Figure 5–7](#)) was a 32-week, double-blind trial conducted in 359 patients with a BMI of at least 30 kg/m<sup>2</sup> and who had moderate or severe obstructive sleep apnea. Patients were randomized to treatment in a 1:1 ratio. The primary objective was to investigate the effects of liraglutide on the severity of OSA in patients who were unwilling or unable to use treatment with continuous positive airway pressure (CPAP). If used correctly CPAP is an effective therapy, but it is not tolerated by many patients (~46–83%<sup>101</sup>) and is associated with discomfort, skin irritation and noise.<sup>73,74</sup> Weight loss is now recommended as first-line intervention for all obese patients with OSA.<sup>74,102</sup> Liraglutide 3.0 mg met the pre-specified primary OSA-related endpoint at the end of the treatment period, and all 3 mean and categorical weight loss endpoints, which were secondary endpoints in this trial ([Table 5–5](#)).



Trial 3970 had a shorter duration than the other phase 3 trials; 32 weeks was expected to allow achievement of maximum weight loss based on the results of trials 1807 and 1923, which were the first trials to be completed. Randomization 1:1. Between 0 and 4 weeks liraglutide dose was escalated by 0.6 mg/week increments up to 3.0 mg. N: number of randomized patients.

**Figure 5–7 Trial 3970, 32-week trial in patients with obstructive sleep apnea**

## 5.4.2 Statistical analyses

### 5.4.2.1 Analyses in individual trials

The sample sizes for each of the clinical trials provided adequate power with respect to the primary efficacy endpoints. Trial 1839 was also powered to investigate the long-term efficacy of liraglutide 3.0 mg in delaying the onset of T2DM in the 2-year extension to this trial, currently ongoing.

The efficacy evaluation was based on a full analysis set (FAS) population, which is defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint, as recommended by FDA guidance.<sup>37</sup> In trials 1839, 1922 and 1923, hierarchical testing of the co-primary endpoints ([Table 5–5](#)) was applied, to control for multiple testing. The individual trials did not control for multiplicity with respect to secondary endpoints.

An analysis of covariance (ANCOVA) model was used to analyze mean changes for the continuous endpoints. The model used in all the trials included treatment, country and sex as fixed effects, as well as baseline value of the variable in question as a covariate. Additional fixed effects were included in the model depending on the trial design. Outcomes for dichotomous endpoints were

analyzed using a logistic regression model, which included the same fixed effects and covariates as for the respective ANCOVA analysis.

The statistical analyses were performed using last observation carried forward (LOCF) imputation for missing data, as pre-specified in the trial protocols. For weight measurements, FPG and triglycerides, the last post-baseline fasting measurement was used. In order to assess the impact of patients withdrawn prematurely and evaluate the robustness of the primary LOCF analyses, a number of sensitivity analyses using different methods for handling missing data were performed for the primary endpoints.<sup>103</sup> For a detailed description of the individual sensitivity analyses, please see [Appendix Section 3](#); the results are presented in [Section 5.4.6.2](#). Furthermore, patients who discontinued from trials 1839, 1923 and 1922, the 56-week phase 3 trials, were asked to return at the time of their scheduled week 56 visit for an assessment of body weight and to report any AEs that they had experienced. These weight values were used in some of the sensitivity analyses, those that included all measurements ([Appendix Table 3-1](#)), to evaluate the impact of missing data on the primary endpoint. Approximately 29% (431 of 1476 patients) of early withdrawn patients in these 3 trials attended the 56-week visit (liraglutide 3.0 mg: 260 of 850 patients [31%]; total liraglutide: 272 of 897 patients [30%]; placebo: 159 of 579 patients [27%]). In addition, the missing data patterns were investigated through Kaplan-Meier plots and by mean curves of weight measurements by time of withdrawal.

#### 5.4.2.2 Pooled analyses

Robustness of efficacy was supported not only by the sensitivity analyses, but also by an assessment of efficacy in sub-populations, performed in a pooled analysis of the 5 phase 2 and 3 trials to maximize the numbers of patients in each specific group. The sub-populations were categorized according to age, sex, BMI, race, ethnicity and region as well as those individuals who achieved a 5% weight loss at the end of the trial (the 5% responders). The pooled analyses were performed using the same general statistical methodology as specified for the individual trials, and included trial as a factor in the model to adjust for heterogeneity across the trials. The analysis population for the pooled data was the FAS from each trial combined. In the pooled analyses, the comparisons made were between liraglutide 3.0 mg and placebo and end-of-trial was at week 56 for trials 1839, 1922 and 1923. For trial 3970, week 32 was used as end-of-trial in the analyses and for trial 1807, week 52 was used.

As the individual trials did not control for multiplicity for secondary endpoints, confirmatory testing of specific pre-specified secondary endpoints was done on pooled data from all 5 trials to confirm the results seen in the individual trials. A statistical analysis plan was pre-specified for the confirmatory testing of the secondary endpoints (selected based on clinical relevance and the presumed likelihood of success) and submitted to the Agency prior to unblinding of the 3 most recent phase 3 trials.

Multiplicity was controlled by a strict hierarchical testing order:

- Waist circumference
- HbA<sub>1c</sub>
- FPG
- Systolic blood pressure
- Triglycerides
- Low-density lipoprotein (LDL) cholesterol
- Total cholesterol
- SF-36 (physical function score)
- IWQoL-Lite (physical function score)
- SF-36 (general health score)
- High-density lipoprotein (HDL) cholesterol
- Use of antihypertensive medication
- Use of lipid lowering medication
- Use of OADs
- Diastolic blood pressure

The endpoints and their order were determined prior to having seen the results of trial 1839, which comprised ~70 of the total population analyzed, albeit after trials 1807 and 1923 (which comprised less than 12% of the population) were completed. Therefore, for each endpoint in the hierarchy, statistical significance in the pooled analysis also had to be seen in trial 1839 alone, the largest trial in the weight management program, which was still blinded at the time of endpoint selection.

The results of the confirmatory analyses confirmed the superiority of liraglutide 3.0 mg vs. placebo on all the endpoints tested in the hierarchy ([Appendix Table 2-15](#)), illustrating the beneficial effects of the weight loss achieved with liraglutide 3.0 mg, as well as the consistency of the effects across all of the trials.

### 5.4.3 Enrolment criteria

All the trials were designed to assess the efficacy and safety of liraglutide 3.0 mg, as an adjunct to diet and exercise, in a representative sample of the patient population expected to be treated with liraglutide. Men and women aged at least 18 years and with stable body weight (less than 5 kg self-reported change during the previous 3 months) were included in all of the trials. Participants were either obese (BMI  $\geq 30$  kg/m<sup>2</sup>) or overweight (BMI  $\geq 27$  kg/m<sup>2</sup>) with at least one weight-related comorbidity, such as dysglycemia (pre-diabetes and T2DM<sup>95</sup>), hypertension,<sup>98</sup> dyslipidemia,<sup>96,100</sup> or OSA. Patients with T2DM were excluded from trials 1839, 3970 and 1923 but a diagnosis of T2DM was required in trial 1922.

Patients were excluded if they had undergone previous treatment with GLP-1 receptor agonists, medications causing significant weight gain or loss, or bariatric surgery in the 3 months prior to trial

initiation, had uncontrolled treated or untreated hypertension (systolic blood pressure  $\geq 160$  mmHg and/or diastolic blood pressure  $\geq 100$  mmHg), or had a history of major depressive disorder or other severe psychiatric disorders.

A full list of inclusion and exclusion criteria is included in [Appendix Tables 1-2 and 1-3](#). Withdrawal criteria are presented in [Appendix Table 1-4](#).

#### 5.4.4 Baseline demographics

Baseline demographic and disease characteristics of participants in the phase 3 trials were well matched between the treatment groups ([Appendix Section 2](#)) and across trials ([Table 5-7](#)), and generally were representative of the patient population expected in the clinical practice for weight management.

In the U.S. trial population, which comprised approximately 50% of the total population, 79% of participants were White, 18% were Black or African American and 1% were Asian, and 11% were of Hispanic or Latino ethnicity, which more closely reflected the racial/ethnic distribution of the U.S. population as compared with the overall trial population ([Table 5-7](#)). More than 500 patients enrolled in the phase 3 trials were Black or African American or of Hispanic/Latino ethnicity, sufficient for making an adequate assessment of efficacy and safety in these populations. An investigation of efficacy and safety data according to region noted a consistent response across all regions, and the non-U.S. data are therefore considered applicable to the U.S. population.

#### 5.4.5 Patient disposition

Patient disposition for the phase 3 trials is presented by treatment in [Table 5-8](#), and was comparable across trials. Approximately 70% of patients completed the phase 3 trials: 73% treated with liraglutide and 67% treated with placebo, which compares favorably with completion rates in other weight-loss trials.<sup>104-106</sup> In trials 1839, 1922 and 3970, more patients treated with liraglutide 3.0 mg (9–12%) than placebo (3–4%) discontinued due to AEs; the proportions were similar between both groups in trial 1923 (~8.5%). Fewer patients on liraglutide 3.0 mg (0–1% across the phase 3 trials) than placebo (1–3%) withdrew due to ineffective therapy, and fewer on liraglutide (6–11%) than placebo (11–20%) withdrew their consent to remain in the trial. Patient withdrawals related to safety are described in more detail in Section [6.1.5](#).

**Table 5–7 Baseline characteristics for randomized and exposed individuals of the phase 3 clinical trials**

|                                  | <b>Trial 1839</b><br>Patients w/o T2DM<br>N=3723 | <b>Trial 1923</b><br>Weight maintenance<br>N=422 | <b>Trial 1922</b><br>Patients with T2DM<br>N=844 | <b>Trial 3970</b><br>Patients with OSA<br>N=355 <sup>a</sup> | <b>All phase 3 trials</b><br>N=5344 | <b>U.S. trial<br/>population</b><br>N=2718 |
|----------------------------------|--|--|--|--|-------------------------------------|--|
| <b>Age (years) at screening</b>  |  |  |  |  |                                     |  |
| Mean (SD)                        | 45.1 (12.0)                                      | 46.2 (11.5)                                      | 54.9 (10.6)                                      | 48.5 (9.7)   | 47.0 (12.2)                         | 47.6 (11.7)                                |
| Min-max                          | 18–78  | 18–73  | 18–82  | 22–64  | 18–82                               | 18–79                                      |
| <b>Age group (years)</b>         |  |  |  |  |                                     |  |
| 18-<65                           | 3519 (94.5)                                      | 401 (95.0)                                       | 687 (81.4)                                       | 355 (100.0)  | 4962 (92.9)                         | 2550 (93.8)                                |
| ≥65-<75                          | 197 (5.3)  | 21 (5.0)   | 142 (16.8)                                       | 0 (0.0)  | 360 (6.7)                           | 160 (5.9)                                  |
| ≥75                              | 7 (0.2)  | 0 (0.0)  | 15 (1.8)   | 0 (0.0)  | 22 (0.4)                            | 8 (0.3)                                    |
| <b>Sex</b>                       |  |  |  |  |                                     |  |
| Female                           | 2921 (78.5)                                      | 343 (81.3)                                       | 419 (49.6)                                       | 98 (27.6)  | 3781 (70.8)                         | 1964 (72.3)                                |
| <b>Race</b>                      |  |  |  |  |                                     |  |
| White                            | 3161 (84.9)                                      | 355 (84.1)                                       | 703 (83.3)                                       | 264 (74.4)   | 4483 (83.9)                         | 2154 (79.2)                                |
| Black/African American           | 355 (9.5)  | 56 (13.3)  | 98 (11.6)  | 66 (18.6)  | 575 (10.8)                          | 476 (17.5)                                 |
| Asian                            | 136 (3.7)  | 1 (0.2)  | 19 (2.3)   | 16 (4.5)   | 172 (3.2)                           | 25 (0.9)                                   |
| American Indian/Alaska Native    | 9 (0.2)  | 0 (0.0)  | 4 (0.5)  | 0 (0.0)  | 13 (0.2)                            | 10 (0.4)                                   |
| Native Hawaiian/Pacific Islander | 4 (0.1)  | 2 (0.5)  | 0 (0.0)  | 3 (0.8)  | 9 (0.2)                             | 8 (0.3)                                    |
| Other                            | 58 (1.6)   | 8 (1.9)  | 20 (2.4)   | 6 (1.7)  | 92 (1.7)                            | 45 (1.7)                                   |
| <b>Ethnicity</b>                 |  |  |  |  |                                     |  |
| Hispanic or Latino               | 393 (10.6)                                       | 28 (6.6)   | 87 (10.3)  | 43 (12.1)  | 551 (10.3)                          | 309 (11.4)                                 |
| Not Hispanic or Latino           | 3330 (89.4)                                      | 394 (93.4)                                       | 754 (89.3)                                       | 312 (87.9)   | 4790 (89.6)                         | 2409 (88.6)                                |
| Not applicable <sup>b</sup>      | 0 (0.0)  | 0 (0.0)  | 3 (0.4)  | 0 (0.0)  | 3 (<0.1)                            | 0 (0.0)                                    |
| <b>Body weight (kg)</b>          |  |  |  |  |                                     |  |
| Mean (SD)                        | 106.3 (21.4)                                     | 99.6 (21.0)                                      | 105.9 (21.5)                                     | 117.9 (24.4)   | 106.5 (21.9)                        | 107.7 (22.8)                               |
| Min-max                          | 62.5–244.0                                       | 65.0–191.9                                       | 60.1–199.4                                       | 70.8–244.9   | 60.1–244.9                          | 60.1–244.9                                 |

|   | <b>Trial 1839</b><br>Patients w/o T2DM<br>N=3723 | <b>Trial 1923</b><br>Weight maintenance<br>N=422 | <b>Trial 1922</b><br>Patients with T2DM<br>N=844 | <b>Trial 3970</b><br>Patients with OSA<br>N=355 <sup>a</sup> | <b>All phase 3 trials</b><br>N=5344 | <b>U.S. trial<br/>population</b><br>N=2718 |
|---|--|--|--|--|-------------------------------------|--|
| <b>BMI (kg/m<sup>2</sup>)</b>                       |  |  |  |  |                                     |  |
| Mean (SD)   | 38.3 (6.4)                                       | 35.6 (5.9)                                       | 37.1 (6.7)                                       | 39.2 (6.9)   | 38.0 (6.5)                          | 38.3 (6.7)                                 |
| Min-max   | 27.0–77.2  | 25.7–62.0  | 27.0–67.6  | 28.7–75.3  | 25.7–77.2                           | 26.2–75.3                                  |
| <b>BMI category (kg/m<sup>2</sup>)</b>              |  |  |  |  |                                     |  |
| 27–29.9   | 110 (3.0)  | 67 (15.9)  | 116 (13.7)                                       | 1 (0.3)  | 294 (5.5)                           | 163 (6.0)                                  |
| 30–34.9   | 1194 (32.1)                                      | 164 (38.9)                                       | 259 (30.7)                                       | 106 (29.9)   | 1723 (32.2)                         | 816 (30.0)                                 |
| 35–39.9   | 1183 (31.8)                                      | 103 (24.4)                                       | 218 (25.8)                                       | 121 (34.1)   | 1625 (30.4)                         | 816 (30.0)                                 |
| ≥40   | 1236 (33.2)                                      | 88 (20.9)  | 251 (29.7)                                       | 127 (35.8)   | 1702 (31.8)                         | 923 (34.0)                                 |
| <b>Glycemic status<sup>c</sup></b>                  |  |  |  |  |                                     |  |
| Normoglycemia                                       | 1444 (38.8)                                      | 150 (35.5)                                       | 0 (0.0)  | 126 (35.5)   | 1720 (32.2)                         | 940 (34.6)                                 |
| Pre-diabetes  | 2279 (61.2)                                      | 272 (64.5)                                       | 0 (0.0)  | 229 (64.5)   | 2780 (52.0)                         | 1360 (50.0)                                |
| T2DM  | 0 (0.0)  | 0 (0.0)  | 844 (100)  | 0 (0.0)  | 844 (15.8)                          | 418 (15.4)                                 |
| <b>Co-morbidities present</b>                       |  |  |  |  |                                     |  |
| Dyslipidemia <sup>d</sup>                           | 1096 (29.4)                                      | 124 (29.4)                                       | 562 (66.6)                                       | 120 (33.8)   | 1900 (35.6)                         | 1113 (40.9)                                |
| Hypertension <sup>e</sup>                           | 1295 (34.8)                                      | 130 (30.8)                                       | 585 (69.3)                                       | 150 (42.3)   | 2160 (40.4)                         | 1110 (40.8)                                |
| Both  | 629 (16.9)                                       | 65 (15.4)  | 421 (49.9)                                       | 76 (21.4)  | 1191 (22.3)                         | 692 (25.5)                                 |
| <b>History of cardiovascular disease</b>            |  |  |  |  |                                     |  |
| Based on MedDRA search terms <sup>f</sup>           | 321 (8.6)  | 41 (9.7)   | 126 (14.9)                                       | 21 (5.9)   | 509 (9.5)                           | 311 (11.4)                                 |
| <b>History of psychiatric disorders<sup>g</sup></b> | 540 (14.5)                                       | 68 (16.1)  | 100 (11.8)                                       | 59 (16.6)  | 767 (14.4)                          | 521 (19.2)                                 |

All phase 3 trials enrolled patients at U.S. sites. Numbers are for patients in the safety analysis set (all patients receiving at least one dose of the investigational product or comparators), and at randomization unless specified. Data are mean (SD) or number (%). BMI: body mass index. Max: maximum value. MedDRA: medical dictionary for regulatory activities. Min: minimum value. N: number of patients. OSA: obstructive sleep apnea. SD: standard deviation. T2DM: type 2 diabetes mellitus. W/o: without.

<sup>a</sup>An additional 4 patients were randomized but not exposed in 3970. <sup>b</sup>Ethnicity data were not collected at French sites in trial 1922. <sup>c</sup>Defined according to ADA 2010 criteria.<sup>95</sup> <sup>d</sup>Low density lipoprotein ≥160 mg/dL, or triglycerides ≥150 mg/dL, or high density lipoprotein <40 mg/dL for males and <50 mg/dL for females.<sup>96,97</sup> <sup>e</sup>Systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg.<sup>98</sup> <sup>f</sup>Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events. <sup>g</sup>Depression, suicidal behavior, anxiety, mood disorders, insomnia, or sleep disorders.



**Table 5–8 Patient disposition in the phase 3 clinical trials, by treatment**

|                         | Trial 1839<br>Patients without T2DM<br>(56 weeks) |              | Trial 1923<br>Weight maintenance<br>(56 weeks) |             | Trial 1922<br>Patients with T2DM<br>(56 weeks) |             | Trial 3970<br>Patients with OSA<br>(32 weeks) |            | All phase 3<br>trials |
|-------------------------|---|--------------|--|-------------|--|-------------|---|------------|-----------------------|
|                         | Liraglutide<br>3.0 mg                             | Placebo      | Liraglutide<br>3.0 mg                          | Placebo     | Liraglutide<br>3.0 mg                          | Placebo     | Liraglutide<br>3.0 mg                         | Placebo    | Total                 |
| Screened                |   |              |  |             |  |             |   |            | 7841                  |
| Screening failures      |   |              |  |             |  |             |   |            | 2483                  |
| Randomized              | 2487 (100.0)                                      | 1244 (100.0) | 212 ( 100)                                     | 210 ( 100)  | 423 (100.0)                                    | 212 (100.0) | 180 ( 100)                                    | 179 ( 100) | 5358 (100.0)          |
| Exposed                 | 2481 ( 99.8)                                      | 1242 (99.8)  | 212 ( 100)                                     | 210 ( 100)  | 422 ( 99.8)                                    | 212 (100.0) | 176 ( 97.8)                                   | 179 ( 100) | 5344 (99.7)           |
| Full analysis set       | 2437 ( 98.0)                                      | 1225 (98.5)  | 207 ( 97.6)                                    | 206 ( 98.1) | 412 ( 97.4)                                    | 211 ( 99.5) | 180 ( 100)                                    | 179 ( 100) | 5261 (98.2)           |
| Safety analysis set     | 2481 ( 99.8)                                      | 1242 (99.8)  | 212 ( 100)                                     | 210 ( 100)  | 422 ( 99.8)                                    | 212 (100.0) | 176 ( 97.8)                                   | 179 ( 100) | 5344 (99.7)           |
| Withdrawn               | 698 ( 28.1)                                       | 443 ( 35.6)  | 53 ( 25.0)                                     | 64 ( 30.5)  | 99 ( 23.4)                                     | 72 ( 34.0)  | 46 ( 25.6)                                    | 37 ( 20.7) | 1559 (29.1)           |
| Adverse events          | 238 ( 9.6)  | 45 ( 3.6)    | 18 ( 8.5)                                      | 18 ( 8.6)   | 39 ( 9.2)                                      | 7 (3.3)     | 20 (11.1)                                     | 6 ( 3.4)   | 412 (7.7)             |
| Protocol non-compliance | 65 ( 2.6)   | 38 ( 3.1)    | 8 ( 3.8)                                       | 5 ( 2.4)    | 12 ( 2.8)                                      | 13 (6.1)    | 8 ( 4.4)                                      | 5 ( 2.8)   | 162 (3.0)             |
| Ineffective therapy     | 23 ( 0.9)   | 36 ( 2.9)    | 0 ( 0.0)                                       | 2 (1.0)     | 0 (0.0)  | 3 (1.4)     | 2 (1.1)                                       | 1 ( 0.6)   | 132 (2.5)             |
| Withdrawal criteria     | 294 ( 11.8)                                       | 261 (21.0)   | 17 ( 8.0)                                      | 24 ( 11.4)  | 32 ( 7.6)                                      | 37 (17.5)   | 14 ( 7.8)                                     | 20 ( 11.2) | 649 (12.1)            |
| Other                   | 78 ( 3.1)   | 63 ( 5.1)    | 10 ( 4.7)                                      | 15 ( 7.1)   | 16 ( 3.8)                                      | 12 ( 5.7)   | 2 ( 1.1)                                      | 5 ( 2.8)   | 204 (3.8)             |
| Adverse event total*    | 246 (9.9)   | 47 (3.8)     | 18 ( 8.5)                                      | 18 ( 8.6)   | 39 ( 9.2)                                      | 7 ( 3.3)    | 22 (12.2)                                     | 6 ( 3.4)   | 424 (7.9)             |
| Completers              | 1789 ( 71.9)                                      | 801 ( 64.4)  | 159 ( 75.0)                                    | 146 ( 69.5) | 324 ( 76.6)                                    | 140 ( 66.0) | 134 (74.4)                                    | 142 (79.3) | 3799 (70.9)           |

Data are presented as number of patients (% of randomized).

\*Adverse events including 'target dose not tolerated, acute pancreatitis and psychiatric disorder'.

The full analysis set is defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint. The safety analysis set is defined as all patients receiving at least one dose of trial product.

OSA: obstructive sleep apnea. T2DM: type 2 diabetes mellitus.



#### 5.4.6 Effect of liraglutide 3.0 mg on body weight

In each of the phase 3 trials, liraglutide 3.0 mg, as adjunct to diet and exercise, succeeded on all 3 mean and categorical weight-loss endpoints compared to placebo (Table 5–9). Treatment with liraglutide 3.0 mg led to a mean weight loss from baseline ranging from 5.7 to 8.0% (6.0–8.4 kg) depending on the trial, whereas patients in the placebo group had a mean weight loss ranging from 0.2 to 2.6% (0.2–2.8 kg). Consistent with the FDA guidance,<sup>37</sup> more than 35% of patients in the group assigned to liraglutide 3.0 mg achieved the 5% weight loss benchmark in each trial, and the proportion achieving the benchmark was more than twice the proportion that did so in the placebo group. In two of the phase 3 trials (1839 and 1923), the other efficacy benchmark was achieved as the difference in mean weight loss between patients treated with liraglutide 3.0 mg and those treated with placebo was greater than 5% and statistically significant.

**Table 5–9 Mean and categorical changes in body weight at end of treatment: Phase 3 trials**

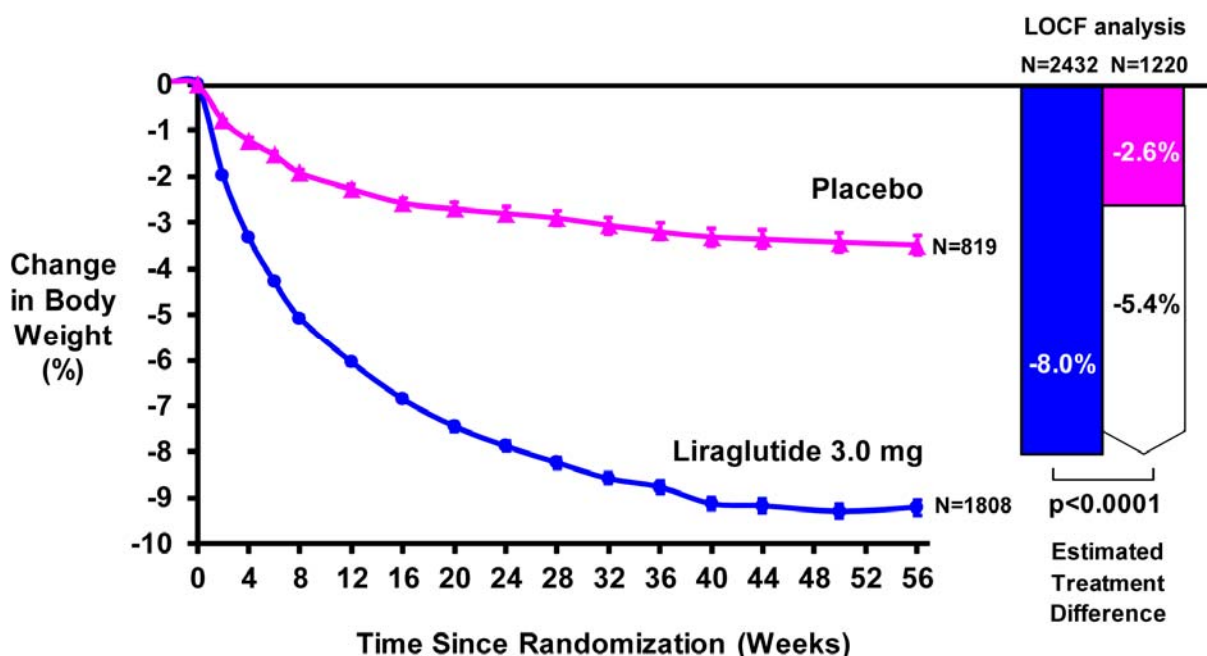
|                                  | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1923</b><br>Weight maintenance<br>(56 weeks) | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|----------------------------------|--|---|---|--|
|                                  | Lira 3.0 mg, N=2432<br>/ Placebo, N=1220             | Lira 3.0 mg, N=194 /<br>Placebo, N=188                | Lira 3.0 mg, N=411 /<br>Placebo, N=210                | Lira 3.0 mg, N=175 /<br>Placebo, N=178               |
| Body weight (%)                  |  |   |   |  |
| Mean estimates                   | -7.99 / -2.60  | -6.26 / -0.20   | -5.93 / -1.98   | -5.73 / -1.58  |
| Treatment difference<br>[95% CI] | -5.39* [-5.82; -4.95]<br>Met FDA benchmark           | -6.06* [-7.50; -4.62]<br>Met FDA benchmark            | -3.95* [-4.82; -3.08]                                 | -4.15* [-5.21; -3.09]                                |
| ≥5% weight loss<br>(% patients)  |  |   |   |  |
| Mean estimates                   | 63.5 / 26.6  | 50.7 / 21.3   | 49.8 / 13.5   | 46.4 / 18.1  |
| Odds ratios [95% CI]             | 4.80* [4.12; 5.60]<br>Met FDA benchmark              | 3.81* [2.42; 5.99]<br>Met FDA benchmark               | 6.39* [4.10; 9.96]<br>Met FDA benchmark               | 3.92* [2.41; 6.38]<br>Met FDA benchmark              |
| >10% weight loss<br>(% patients) |  |   |   |  |
| Mean estimates                   | 32.8 / 10.1  | 27.4 / 6.8  | 22.9 / 4.2  | 22.4 / 1.5   |
| Odds ratios [95% CI]             | 4.34* [3.54; 5.32]                                   | 5.14* [2.72; 9.71]                                    | 6.81* [3.35; 13.84]                                   | 18.96* [5.69; 63.14]                                 |

\*p<0.0001. Data are for the full analysis set with the last observation carried forward. Mean changes are analyzed by ANCOVA and categorical changes by logistic regression.

ANCOVA: analysis of covariance. CI: confidence interval. N: number of patients. OSA: obstructive sleep apnea.

T2DM: type 2 diabetes mellitus. w/o: without.

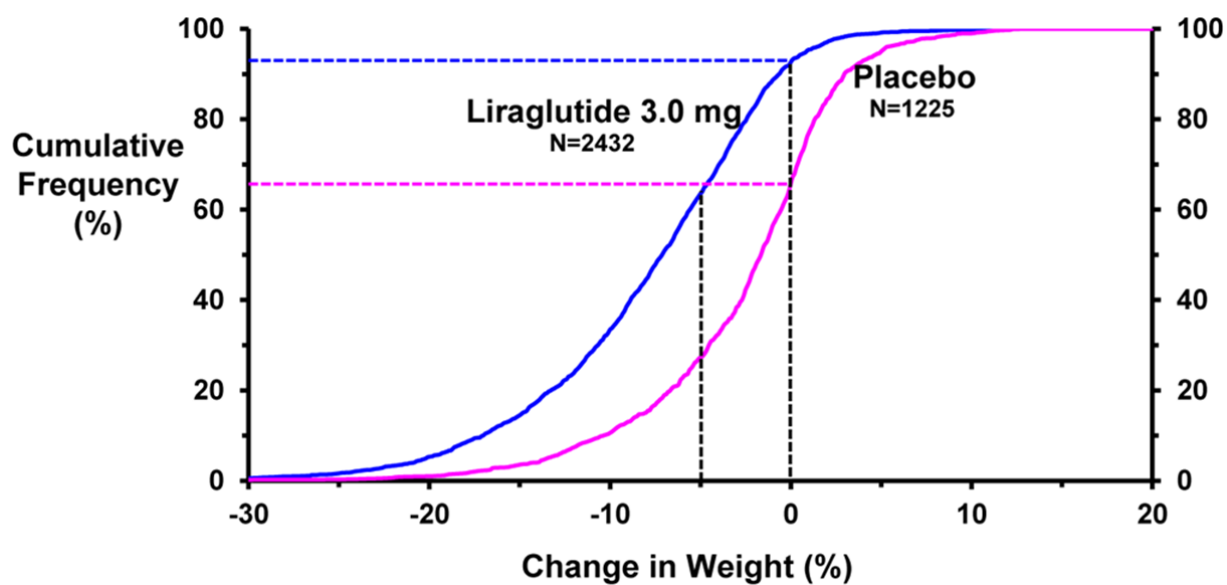
**Trial 1839 in patients without T2DM:** Changes in body weight from baseline to week 56 for trial 1839, the largest phase 3 trial, are illustrated in [Figure 5–8](#). The weight loss achieved with liraglutide 3.0 mg plateaued at about 40 weeks and was maintained over the full 56-week period.



Data are observed means with standard error bars for patients completing each visit (numbers [N] completing are shown at the end of the curves). The estimated mean weight loss and treatment difference for patients included in the analysis (N shown above the bars) with the last observation carried forward (LOCF) to end of trial are shown at the right.

**Figure 5–8 Body weight change from baseline (%): Trial 1839**

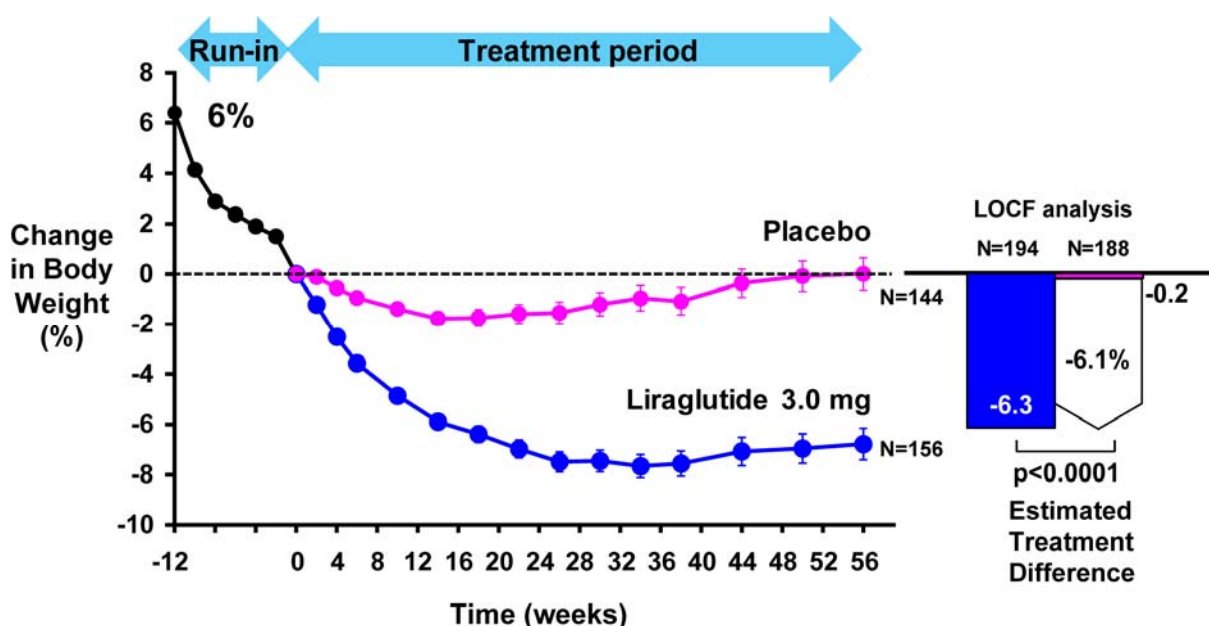
Approximately 90% of patients treated with liraglutide 3.0 mg lost some weight from baseline in trial 1839, compared to approximately 65% of those treated with placebo ([Figure 5–9](#)). A comparable distribution of weight loss was also observed in the other trials. In addition to more patients losing at least 5% or more than 10% of their initial body weight ([Table 5–9](#)), 13% of patients treated with liraglutide 3.0 mg achieved a weight loss of more than 15% of their baseline weight in the largest trial, 1839, compared with 3% in the placebo group.



Data are presented for the full analysis set with last observation carried forward imputation. N: number of patients.

**Figure 5–9 Cumulative distribution of weight loss at week 56: Trial 1839**

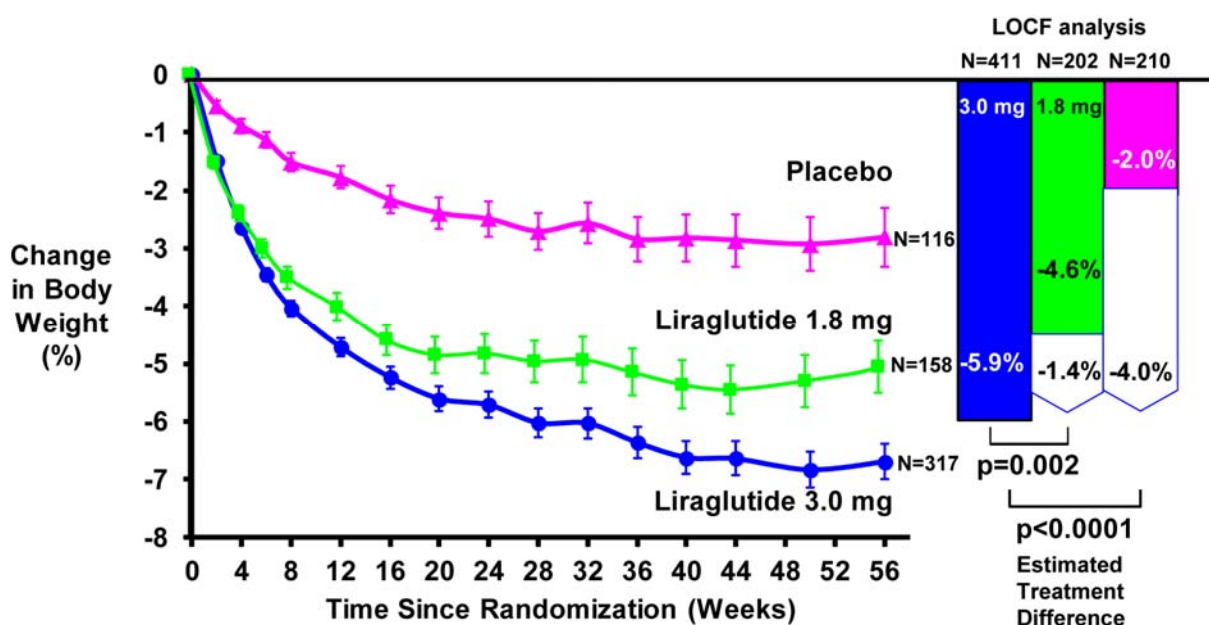
**Trial 1923 weight maintenance trial:** In trial 1923, liraglutide 3.0 mg induced further substantial weight loss in patients who had already lost a mean 6.0% (6.3 kg) of their initial body weight during the highly restricted low-calorie dietary pre-randomization run-in period ([Figure 5–10](#)). The patients in the liraglutide group not only maintained their weight loss at week 56, but went on to achieve an additional weight loss of 6.3% (6.0 kg) ([Table 5–9](#)). A larger proportion of patients treated with liraglutide 3.0 mg (81.4%) as compared with placebo (48.9%) maintained their run-in weight loss at week 56 ( $p<0.0001$ ). Thus, this trial not only confirmed the ability of liraglutide 3.0 mg to maintain weight loss but also indicated the ability of liraglutide to promote clinically significant weight loss after achieving a minimum 5% body weight loss with a highly restricted dietary intervention.



Data are observed means with standard error bars for patients completing each visit (numbers [N] completing are shown at the end of the curves). The estimated mean weight loss and treatment difference for patients included in the analysis (N shown above the bars) with the last observation carried forward (LOCF) to end of trial are shown at the right.

**Figure 5–10 Body weight change from baseline (%): Trial 1923**

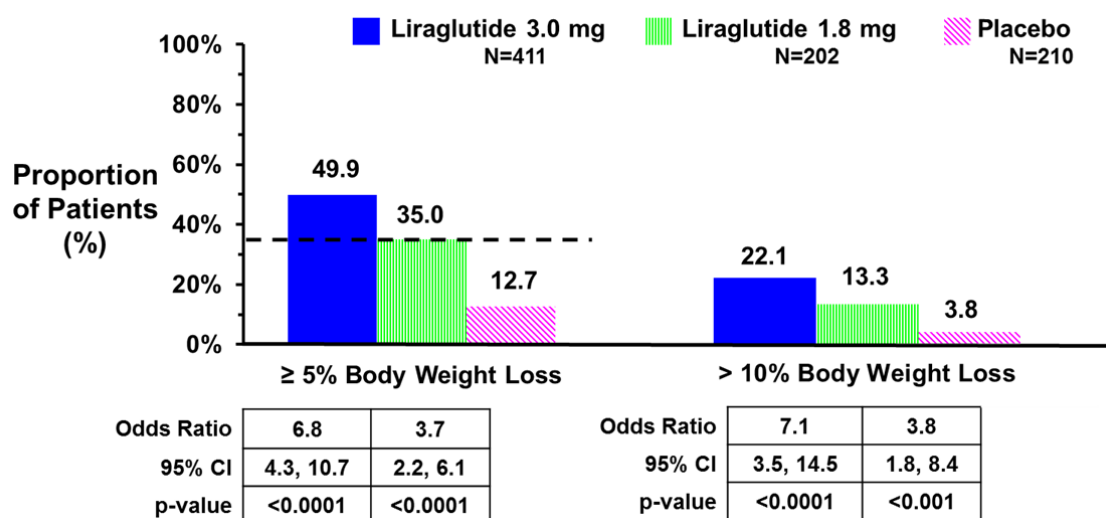
**Trial 1922 in patients with T2DM:** A mean weight loss from baseline in the range recommended by ADA treatment guidelines (5–7%)<sup>95</sup> was achieved with liraglutide 3.0 mg (Table 5–9). Weight loss plateaued at approximately 40–50 weeks and was maintained over the full 56-week period (Figure 5–11). It should be recognized that individuals with T2DM often respond less favorably to weight management pharmacotherapy than those without T2DM.<sup>107</sup> In trial 1922, the weight loss with liraglutide 3.0 mg was independent of background diabetes medication, including sulfonylurea mono- or combination therapy ( $p=0.61$ , indicating no significant effect of background OADs) and baseline HbA<sub>1c</sub> quartile ( $p=0.22$ ).



Data are observed means with standard error bars for patients completing each visit (numbers [N] completing are shown at the end of the curves). The estimated mean weight loss and treatment difference for patients included in the analysis (N shown above the bars) with the last observation carried forward (LOCF) to end of trial are shown at the right.

**Figure 5–11 Body weight change from baseline (%): Trial 1922**

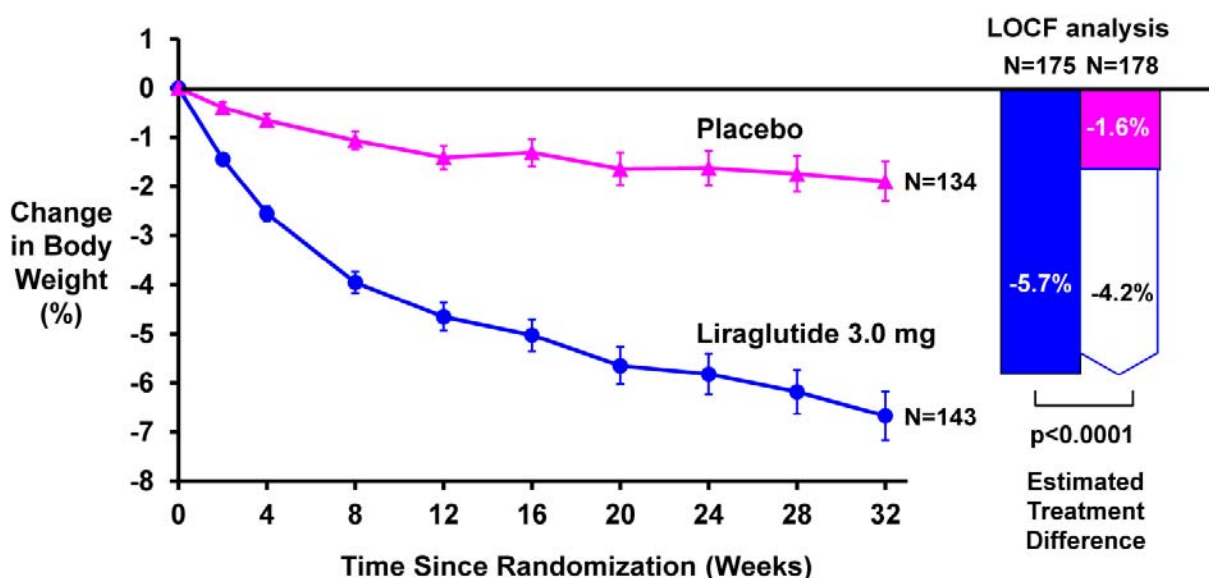
Trial 1922 was designed to investigate comparative efficacy and safety of liraglutide 3.0 mg and 1.8 mg after 56 weeks of treatment in overweight and obese patients with T2DM. Compared to the dose-finding trial, 1807, considerably more patients were included in each of the treatment groups. Trial 1922 confirmed findings from the phase 2 dose-finding trial, conducted in patients without T2DM, that liraglutide 3.0 mg promoted statistically significantly greater weight loss than the 1.8 mg dose, the maximum approved dose for the treatment of T2DM. This was both in terms of mean weight loss (Figure 5–11,  $p=0.002$  for the comparison between doses) and categorical weight loss (Figure 5–12,  $p=0.0008$  for the between-dose comparison of  $\geq 5\%$  weight loss, and  $p=0.01$  for the  $>10\%$  weight loss comparison).



Data shown are estimated means for the full analysis set with last observation carried forward imputation. N: number of patients.

**Figure 5–12 Categorical body weight change from baseline (%): Trial 1922**

**Trial 3970 in patients with moderate or severe OSA:** Weight change was a secondary endpoint in trial 3970 and is presented in [Figure 5–13](#). In this trial of 32 weeks duration, weight loss in the liraglutide group had not yet plateaued and the observed weight loss may not have been the maximal weight loss possible with treatment in this population.



Data are observed means with standard error bars for patients completing each visit (numbers [N] completing are shown at the end of the curves). The estimated mean weight loss and treatment difference for patients included in the analysis (N shown above the bars) with the last observation carried forward (LOCF) to end of trial are shown at the right.

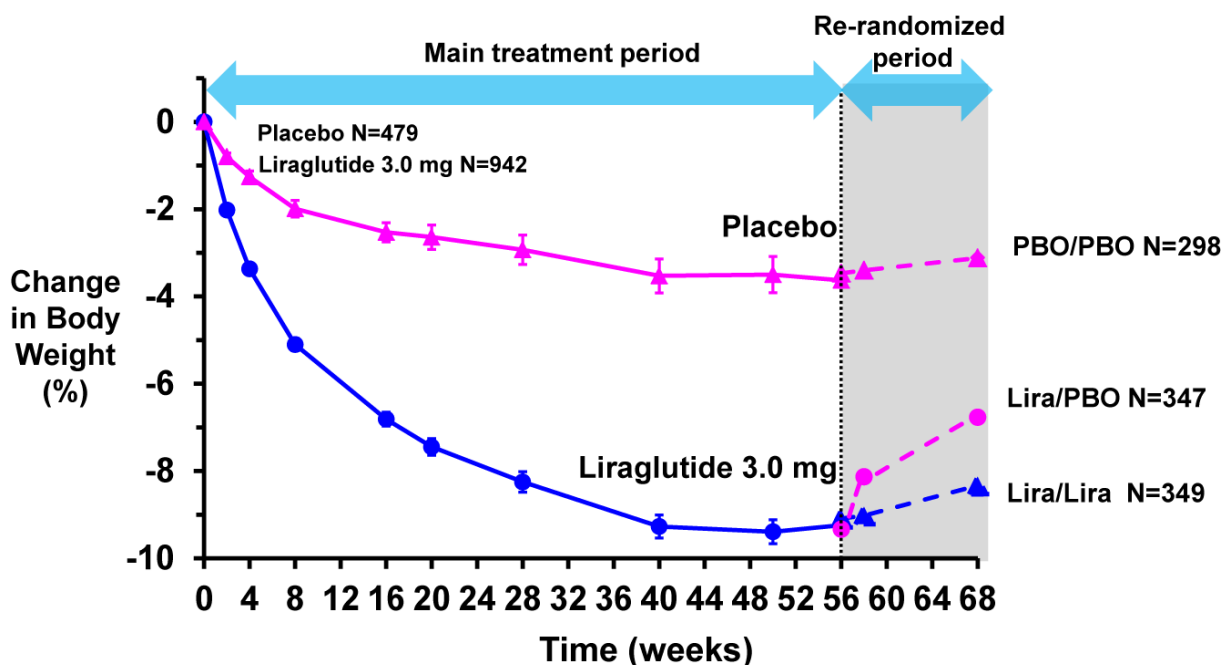
**Figure 5–13 Body weight change from baseline (%): Trial 3970**

#### 5.4.6.1 Maintenance of weight loss

As mentioned above, in each of the three 56-week trials (1839, 1923 and 1922), maximum weight loss was achieved between 40 and 50 weeks with liraglutide 3.0 mg, as adjunct to diet and exercise ([Figure 5–8](#), [Figure 5–10](#) and [Figure 5–11](#)). Mean weight loss with liraglutide was maintained over the 56-week treatment period and was generally maintained only as long as patients remained on treatment. As soon as liraglutide treatment was discontinued, mean weight regain started to occur. This effect is illustrated in the 12-week re-randomized treatment period of trial 1839, in which completing patients without pre-diabetes in the liraglutide group were re-randomized at week 56 to continue on liraglutide or switch to placebo (see [Figure 5–4](#)). The weight regain after treatment discontinuation is shown in [Figure 5–14](#). The mean weight regain after 12 weeks of 2.9% (2.6 kg) for patients who were re-randomized to placebo was significantly greater than the mean regain of 0.7% (0.6 kg) for patients who were re-randomized to continue liraglutide (treatment difference of -2.2% [95% CI -2.6; -1.8];  $p<0.0001$ ). Similar findings were observed in the off-treatment observational follow-up periods of trials 1923 and 1922. These follow-up data illustrate the drug-



dependent effect of liraglutide on both weight loss and the maintenance of weight loss, and support that continued liraglutide treatment is necessary to maintain weight loss.

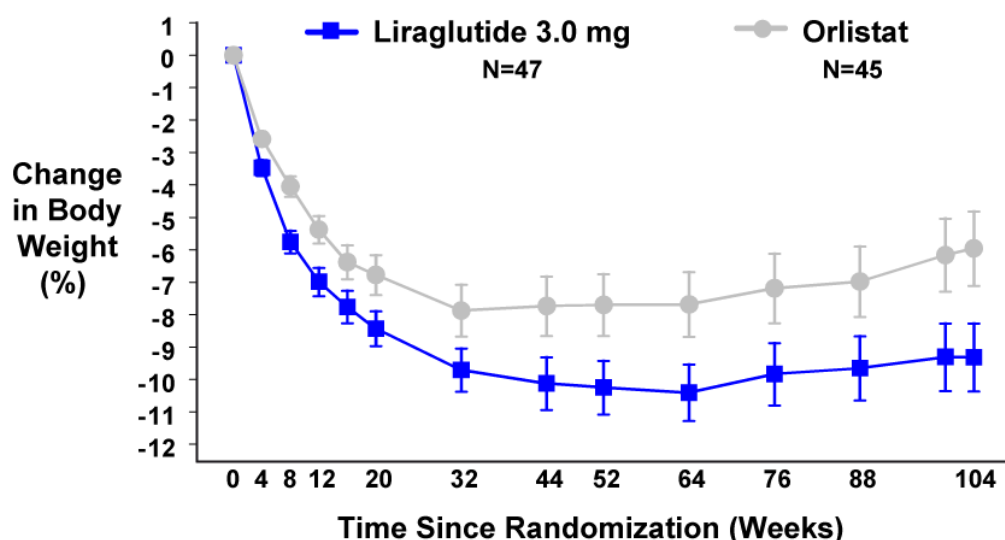


Lira/Lira: patients in the liraglutide group were re-randomized to liraglutide. Lira/PBO: patients in the liraglutide group were re-randomized to placebo. N: number of patients. PBO/PBO: patients in the placebo group continued on placebo. Data are observed means with standard error bars and numbers of completing patients are shown at the far right. Diet and exercise continued during the re-randomized period.

**Figure 5–14 Body weight change during re-randomized treatment period for patients without pre-diabetes: Trial 1839**

Liraglutide treatment continued up to 2 years in the phase 2 trial, 1807. Approximately 50% of patients (n=47) who were randomized to liraglutide 3.0 mg completed the full 2-year treatment period, as did 45 patients (~47%) who were randomized to orlistat (a comparison to placebo was not possible after 2 years as all patients on liraglutide or placebo were switched to treatment with liraglutide after 52 weeks). Weight loss with liraglutide 3.0 mg, as adjunct to diet and exercise, was sustained for up to 2 years of treatment ([Figure 5–15](#)).



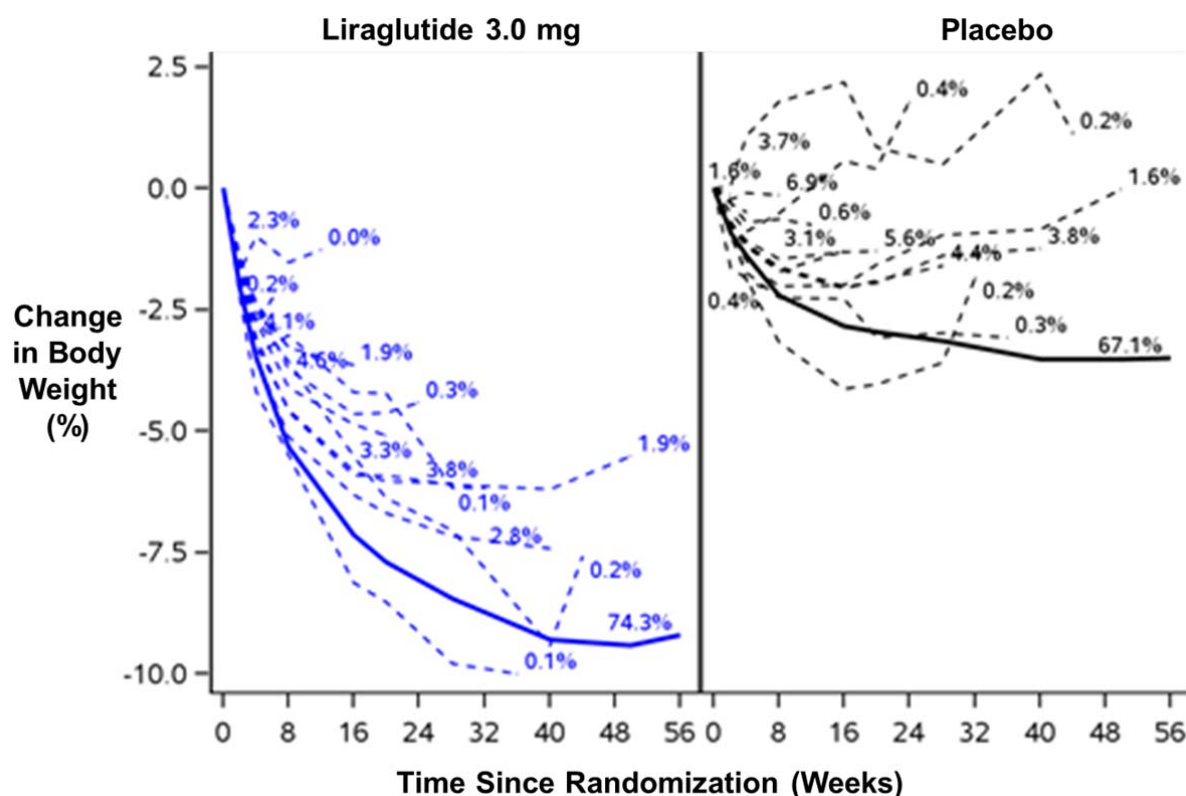


Data are observed means with standard error bars for patients who completed 104 weeks. N: number of patients.

**Figure 5–15 Body weight change from baseline (%): Trial 1807, completers of 104 weeks**

#### 5.4.6.2 Sensitivity analyses for primary endpoints

LOCF imputation was the pre-specified primary endpoint for all trials and, thus, was utilized as planned. The LOCF imputation is considered somewhat conservative, as illustrated in [Figure 5–16](#), which shows the mean body weight response for the completing patients (represented by the solid lines) versus the mean response profiles for patients who withdrew from the trial at a specific time point (represented by the dashed lines). In general, the average body weight of patients in either treatment group who withdrew from the trial was lower than that of the completer population at any time of withdrawal. The measurements at the time of withdrawal were used in the calculation of LOCF.

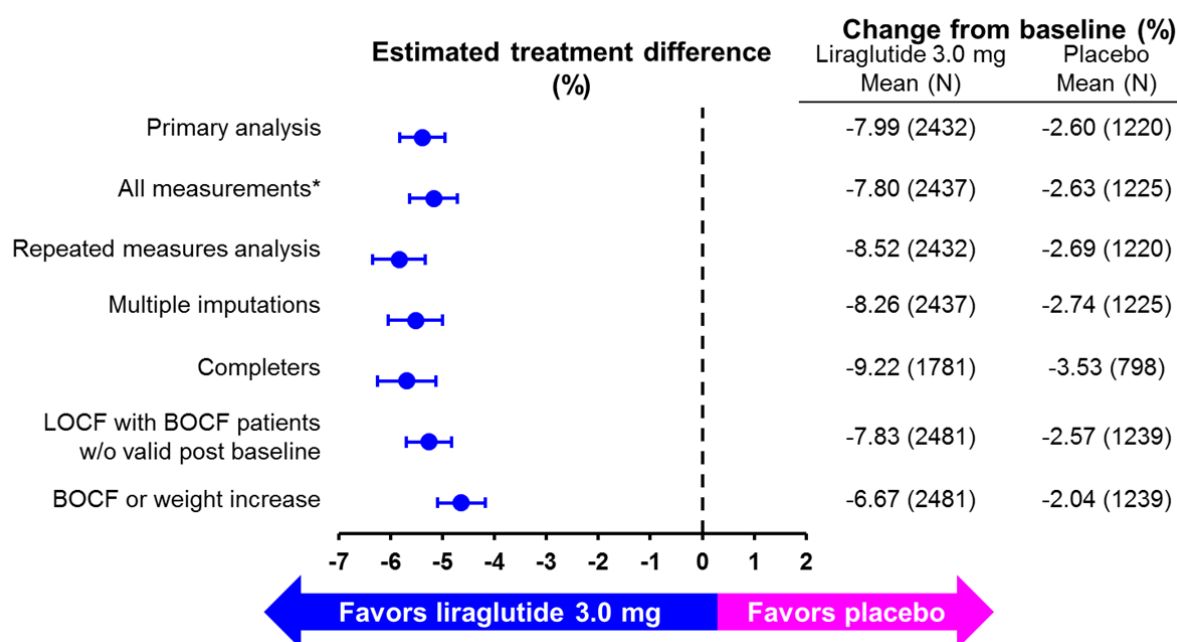


Data are observed fasting values for the full analysis set. The dashed lines illustrate the mean weight loss for patients discontinuing treatment up to a specific time point (at the end of the line). The number at the end of each line indicates the proportion of patients who withdrew at that time point. The two solid lines illustrate the mean weight loss for patients that completed 56 weeks of treatment (74.3% of patients treated with liraglutide 3.0 mg and 67.1% of those treated with placebo).

**Figure 5-16 Body weight response profile (%) by last available measurement: Trial 1839**

However, recognizing the limitations of the use of LOCF imputation,<sup>103</sup> a number of sensitivity analyses were performed to evaluate the impact of the anticipated large number of patient discontinuations typical of long-term weight management trials on the interpretation of the results, as described in Section 5.4.2. These analyses used alternative imputation methods to account for the missing data, and are described in more detail in Appendix Section 3. Each of the analyses confirmed the superiority of liraglutide 3.0 mg over placebo for the primary endpoints, giving similar estimated treatment differences (Appendix Tables 3-2 to 3-4), thus confirming the robustness of the primary analyses. The sensitivity analyses for body weight change in trial 1839 are shown in Figure 5-17; similar results were seen in the other trials. Even using a conservative imputation, in which either a weight loss of zero or a weight gain, if applicable, was assumed for the withdrawn patients (for analysis of mean weight loss) or when withdrawn patients were treated as non-responders (for analysis of categorical weight loss), a statistically significant difference was observed for liraglutide 3.0 mg vs. placebo. Using this conservative imputation, which is shown in

the bottom row of [Figure 5–17](#) for weight loss, the proportions of patients achieving at least a 5% weight loss was 54% vs. 23% for liraglutide 3.0 mg vs. placebo in trial 1839 (compared with the primary analysis of 64% vs. 27%) and 47% vs. 11% for liraglutide 3.0 mg vs. placebo in trial 1922 (compared with the primary analysis of 50% vs. 13.5%).



A description of the sensitivity analyses can be found in [Appendix Section 3](#). The panel at the right shows the estimated means for liraglutide and placebo (ANCOVA analysis).

\*All measurements included fasting and non-fasting weight measurements, off drug measurements, and follow-up measurements after 56 weeks of randomization for patients who discontinued.

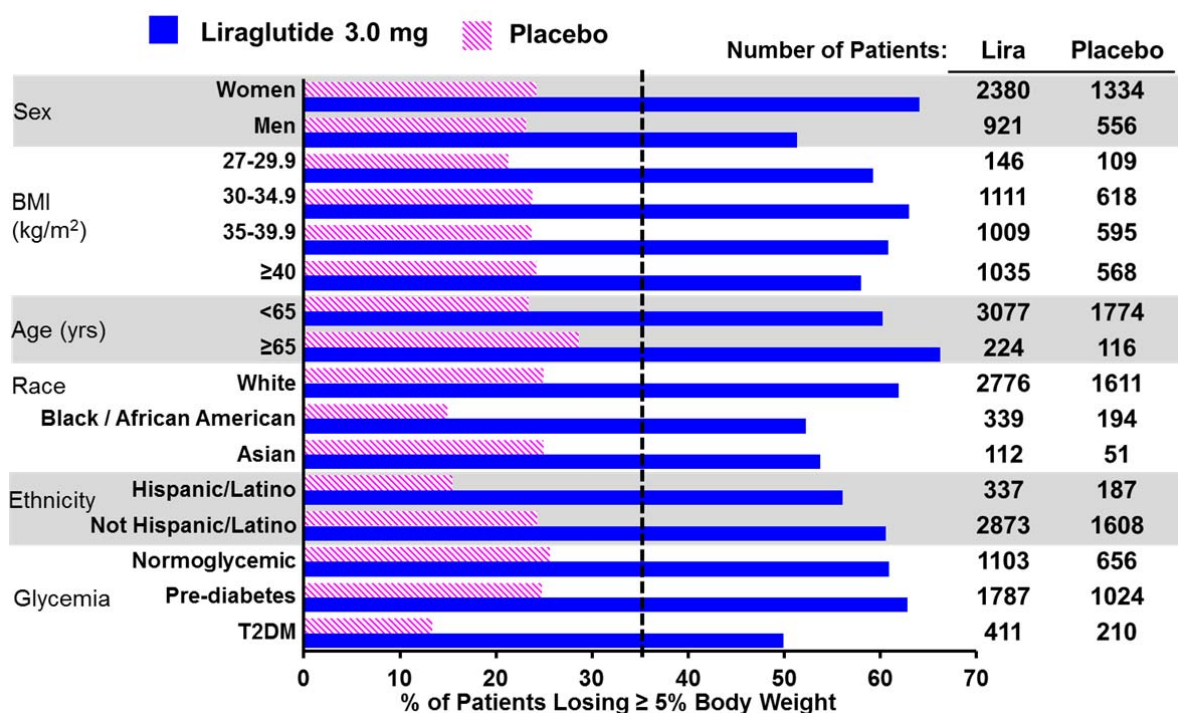
BOCF: baseline observation carried forward. LOCF: last observation carried forward imputation. N: number of patients.

**Figure 5–17 Sensitivity analyses of change in body weight (%) after 56 weeks: Trial 1839**

#### 5.4.6.3 Weight loss efficacy in patient sub-populations

Overall, the response to treatment with liraglutide 3.0 mg was consistent across demographic sub-populations, as assessed in pooled analyses, and the categorical FDA benchmark was met in each of the sub-populations ([Figure 5–18](#)).

Weight loss was statistically significantly greater in women as compared with men in the pooled analysis. Importantly, both men and women experienced a clinically meaningful weight loss with liraglutide 3.0 mg and met the categorical weight loss criteria stipulated in the FDA weight management guidance.<sup>37</sup> When adjusted for differences in the distribution of men and women between trials (see [Table 5–7](#)), there were no significant effects of trial or baseline glycemic status (normoglycemia, pre-diabetes or T2DM) on weight loss.



Sub-population analysis in a pooled population of patients from all 5 phase 2 and 3 trials. The vertical dashed line represents the FDA benchmark of at least 35% of patients achieving at least 5% weight loss. BMI: body mass index. T2DM: type 2 diabetes mellitus.

**Figure 5–18 Weight loss with liraglutide 3.0 mg in patient sub-populations: Phase 2 and 3 trials pooled**

Despite similar mean baseline BMIs, men and women had different mean baseline body weights (~119 kg and ~101 kg, respectively). In light of the relatively higher plasma liraglutide exposure in women as compared to men at comparable body weights (as described in Section 4.3.1), *post hoc* analyses were done to further assess the influence of baseline body weight on weight loss with liraglutide 3.0 mg in men and women. Results were consistent with those seen in the exposure-response analyses (Section 4.4), with greater mean and categorical weight loss in the lighter as compared with the heavier women, whereas there was no effect of baseline body weight in men. Women in the lowest baseline body weight quartile (mean body weight ~80 kg) had a statistically significantly greater mean placebo-adjusted weight loss of 6.8%, as compared with 4.8% for women in the heaviest baseline body weight quartile (mean body weight ~126 kg) ( $p=0.02$ ). In comparison, men in the heaviest baseline body weight quartile (~151 kg) had a placebo-adjusted weight loss of 4.5% vs. 3.1% for men in the lowest baseline body weight quartile (mean body weight ~94 kg) ( $p=0.28$ ). Despite an overall lower mean weight loss, the heaviest men still met the FDA categorical weight-loss benchmark,<sup>37</sup> with 51.5% of those on liraglutide 3.0 mg and 17.6% of those on placebo losing at least 5% of their initial body weight (odds ratio 4.7 [95% CI 2.9; 7.8],  $p<0.0001$ ).

#### **5.4.7 Effect of liraglutide 3.0 mg on glycemic control parameters**

Obesity is associated with impaired glucose regulation and increased risk of T2DM, and weight loss can have a beneficial impact on glycemic control, by improving insulin sensitivity and delaying the onset of T2DM.<sup>29</sup> Effects of liraglutide, particularly at the higher doses, are likely to be mediated by both direct (weight-loss independent) and weight-loss dependent mechanisms (see Section [5.4.11.3](#)).

As expected, based on the pharmacology of the compound, liraglutide 3.0 mg was associated with improvements in fasting and postprandial glycemia, as well as overall glycemic control compared to placebo across the weight management trials ([Table 5–10](#)). The effects were most pronounced in patients with T2DM (trial 1922) or in those with pre-diabetes at enrolment ([Figure 5–19](#), panels on the right).

**Table 5–10 Change from baseline in HbA<sub>1c</sub>, FPG and prandial increment: Phase 3 trials**

|  | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1923</b><br>Maintenance<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|--|---|--|--|--|
|  | Lira 3.0 mg, N=412 /<br>Placebo, N=211                | Lira 3.0 mg, N=2437<br>/ Placebo, N=1225             | Lira 3.0 mg, N=207<br>/ Placebo, N=206         | Lira 3.0 mg, N=180<br>/ Placebo, N=179               |
| Baseline HbA <sub>1c</sub> (%)                     | 7.9 / 7.9   | 5.6 / 5.6  | 5.6 / 5.6                                      | 5.7 / 5.6  |
| HbA <sub>1c</sub> (%-points)                       |   |  |  |  |
| Mean estimates                                     | -1.32 / -0.38   | -0.29 / -0.07  | -0.14 / 0.13                                   | -0.36 / -0.17  |
| Treatment differences                              | -0.93 [-1.08; -0.79]                                  | -0.23 [-0.25; -0.21]                                 | -0.27 [-0.33; -0.21]                           | -0.19 [-0.25; -0.12]                                 |
| [95% CI] p-value                                   | p<0.0001  | p<0.0001   | p<0.0001                                       | p<0.0001   |
| Baseline FPG (mg/dL)                               | 158.4 / 155.5   | 95.9 / 95.5  | 97.5 / 98.5                                    | 97.1 / 97.0  |
| FPG (mg/dL)  |   |  |  |  |
| Mean estimates                                     | -34.10 / -2.18  | -7.00 / -0.10  | -9.57 / -2.73                                  | -2.52 / 2.90   |
| Treatment differences                              | -31.92 [-38.18; -25.65]                               | -6.90 [-7.50; -6.31]                                 | -6.84 [-8.97; -4.71]                           | -5.42 [-7.99; -2.86]                                 |
| [95% CI] p-value                                   | p<0.0001  | p<0.0001   | p<0.0001                                       | p<0.0001   |
| Baseline glucose<br>(mg/dL)                        | 41.4 / 43.9   |  |  |  |
| Prandial glucose<br>increment (mg/dL) <sup>a</sup> |   |  |  |  |
| Mean estimates                                     | -15.3 / -5.4  | N/A  | N/A  | N/A  |
| Treatment differences                              | -9.9 [-15.2; -4.6]                                    |  |  |  |
| [95% CI] p-value                                   | p=0.0003  |  |  |  |
| Baseline glucose<br>(h×mg/dL)                      |   | 277.0 / 278.0  |  |  |
| Post-load plasma<br>glucose (h×mg/dL) <sup>b</sup> |   |  |  |  |
| Mean estimates                                     | N/A   | 231.4 / 267.7  | N/A  | N/A  |
| Treatment differences                              |   | -36.4 [-39.6; -33.2]                                 |  |  |
| [95% CI] p-value                                   |   | p<0.0001   |  |  |

Data are estimated means (ANCOVA) and treatment differences for the full analysis set with the last observation carried forward. Baseline values are observed means.

<sup>a</sup>Based on 7-point self-measured plasma glucose profile, 90 minutes after meal initiation. <sup>b</sup>Based on plasma glucose during OGTT (2-h area under the curve).

ANCOVA: analysis of covariance. CI: confidence interval. FPG: fasting plasma glucose. HbA<sub>1c</sub>: glycosylated hemoglobin A1c. Lira: liraglutide. N: number of patients. N/A: not applicable for this trial. OGTT: oral glucose tolerance test. OSA: obstructive sleep apnea. SD: standard deviation. T2DM: type 2 diabetes mellitus. W/o: without.

The beneficial effects were accompanied by improvements in measures of insulin resistance (HOMA-IR, Matsuda index) and beta-cell function (HOMA-B, disposition index, pro-insulin/insulin ratio; [Table 5–11](#)), as well as reduction in fasting glucagon with liraglutide 3.0 mg as compared with placebo (assessed only in trial 1922, p<0.0001).



**Table 5–11 Measures of insulin resistance and beta-cell function: Trials 1922 and 1839**

|  | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) |
|--|---|--|
|  | Liraglutide 3.0 mg, N=412 /<br>Placebo, N=211         | Liraglutide 3.0 mg, N=2437 /<br>Placebo, N=1225      |
| HOMA-IR (%)  |   |  |
| Relative change (%)                                  | -20.0 / -3.3  | -19.1 / -4.5   |
| Relative difference [95% CI]                         | -16 [-25; -6]   | -15 [-18; -11]                                       |
| p-value  | p=0.003   | p<0.0001   |
| Matsuda index (insulin sensitivity) (%) <sup>a</sup> |   |  |
| Relative change (%)                                  | N/A   | 21 / 10  |
| Relative difference [95% CI]                         |   | 10 [5.5; 14.7]                                       |
| p-value  |   | p<0.0001   |
| HOMA-B (%)   |   |  |
| Relative change (%)                                  | 94.3 / 9.1  | 13.7 / -3.9  |
| Relative difference [95% CI]                         | 71 [52; 92]   | 18 [13; 22]  |
| p-value  | p<0.0001  | p<0.0001   |
| Disposition index (%) <sup>b</sup>                   |   |  |
| Relative change (%)                                  | N/A   | 35 / 11  |
| Relative difference [95% CI]                         |   | 20 [13.3; 26.5]                                      |
| p-value  |   | p<0.0001   |
| Pro-insulin/insulin ratio (%)                        |   |  |
| Relative change (%)                                  | -38.4 / -2.2  | N/A  |
| Relative difference [95% CI]                         | -37 [-42; -31]  |  |
| p-value  | p<0.0001  |  |

Data are relative changes from baseline and % relative treatment differences (ANCOVA on a log scale) for the full analysis set with the last observation carried forward.

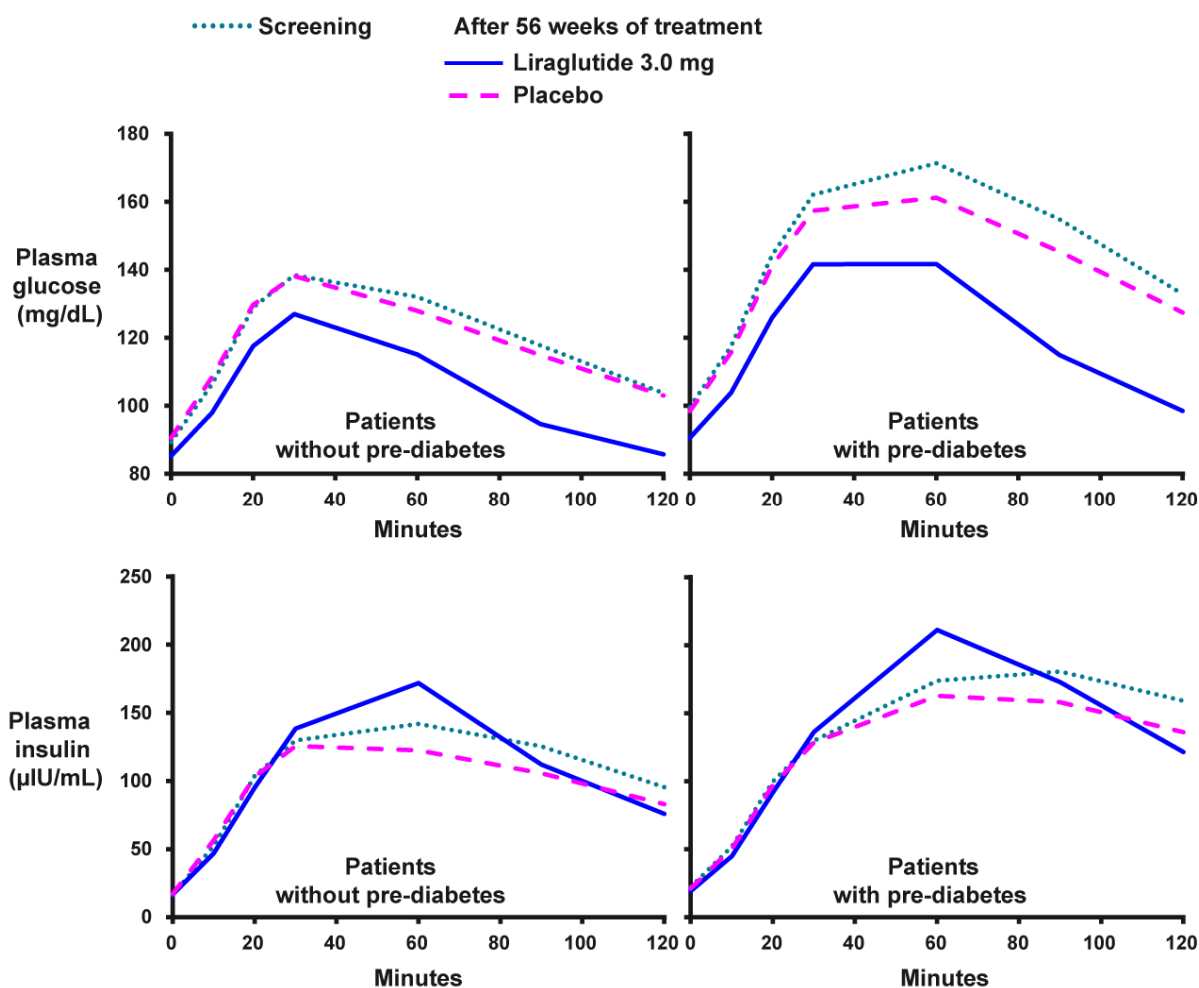
<sup>a</sup>Completer exploratory analysis (ANOVA), based on estimation of the Matsuda index during an 75-g OGTT.<sup>108</sup>

<sup>b</sup>Completer exploratory analysis (ANOVA), estimated as the product of the insulin secretion ratio and the Matsuda index during a 75-g OGTT. The disposition index is a measure of dynamic insulin secretion adjusted for the ambient degree of insulin resistance.<sup>109</sup>

AN(C)OVA: analysis of (co)variance. CI: confidence interval. HOMA: Homeostasis Model Assessment. HOMA-B: a measure of beta-cell function in the fasting state. HOMA-IR: a measure of insulin resistance in the fasting state, mainly at the site of the liver. N: number of patients. N/A: not applicable for this trial. OGTT: oral glucose tolerance test.

With the exception of trial 1922 (patients with T2DM) in which no difference was observed with treatment, liraglutide 3.0 mg was associated with reduction of mean fasting insulin compared to placebo in the phase 3 trials 1839 and 1923 (fasting insulin was not measured in 3970), consistent with the observed improvement in insulin sensitivity and overall glycemic control. Insulin concentrations were also measured following a 75 g oral glucose tolerance test (OGTT) in trial 1839, as illustrated by [Figure 5–19](#) (bottom panels). Liraglutide 3.0 mg was associated with a more physiological profile (earlier and higher insulin peak with more rapid decrease in insulin levels)

compared with placebo.<sup>110</sup> These results supplement those obtained in a similar obese population in trial 3630 during the more physiological mixed meal test, where postprandial insulin (and glucose) concentrations increased less so in response to the meal with liraglutide as compared with placebo (see Section 4.5.3).



Data are observed means for the full analysis set with last observation carried forward imputation.

**Figure 5–19 Mean plots of glucose (top) and insulin (bottom) during oral glucose tolerance test at screening and week 56 by pre-diabetes status at screening: Trial 1839**

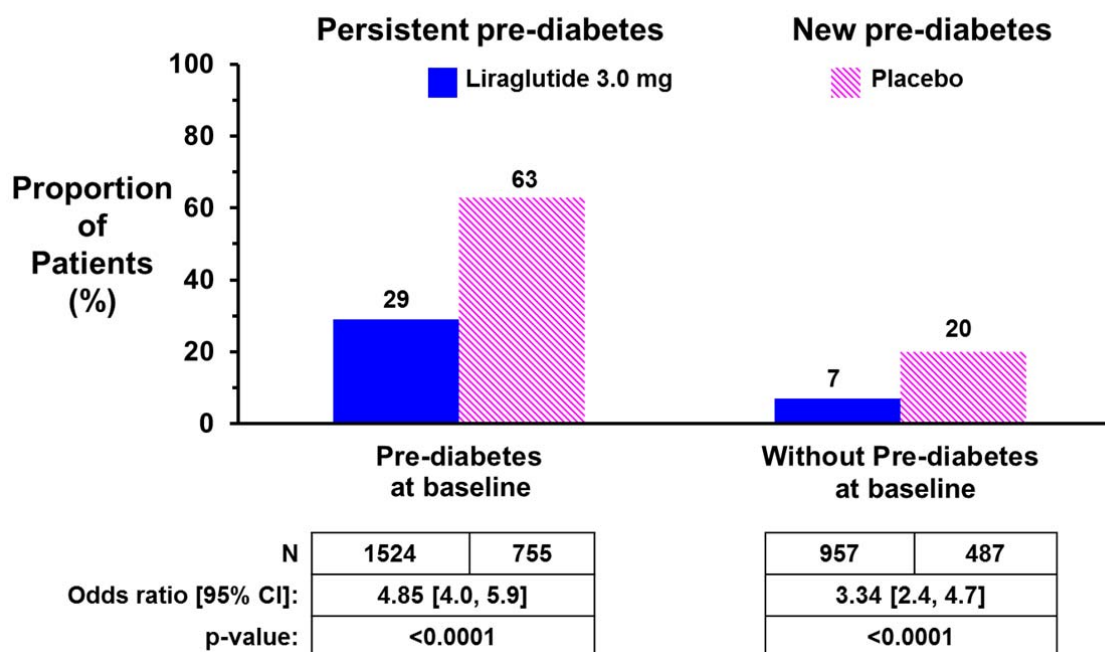
The clinical consequences of the above effects are described in more detail below.

#### 5.4.7.1 Pre-diabetes prevalence and new onset of type 2 diabetes: Trial 1839

In trial 1839, liraglutide 3.0 mg, as adjunct to diet and exercise, reduced the prevalence of pre-diabetes (as defined by ADA 2010 criteria).<sup>95</sup> Of the 61.2% of patients who had pre-diabetes at



screening, only 29% of those treated with liraglutide 3.0 mg met the diagnostic criteria for pre-diabetes after 56 weeks compared with 63% of placebo-treated patients ([Figure 5–20](#)). Moreover, of patients without pre-diabetes at screening, 20% of those treated with placebo had progressed to pre-diabetes after 56 weeks compared with 7% of those treated with liraglutide 3.0 mg.



Data are estimated means for the full analysis set with last observation carried forward imputation.

CI: confidence interval. N: number of patients.

**Figure 5–20 Pre-diabetes prevalence at week 56: Trial 1839**

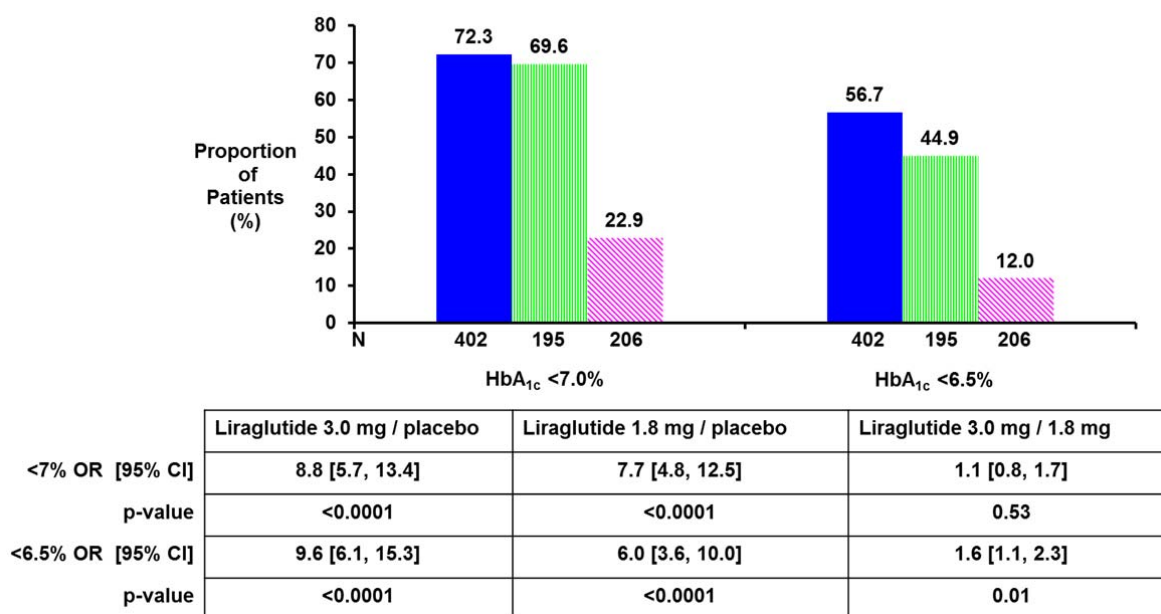
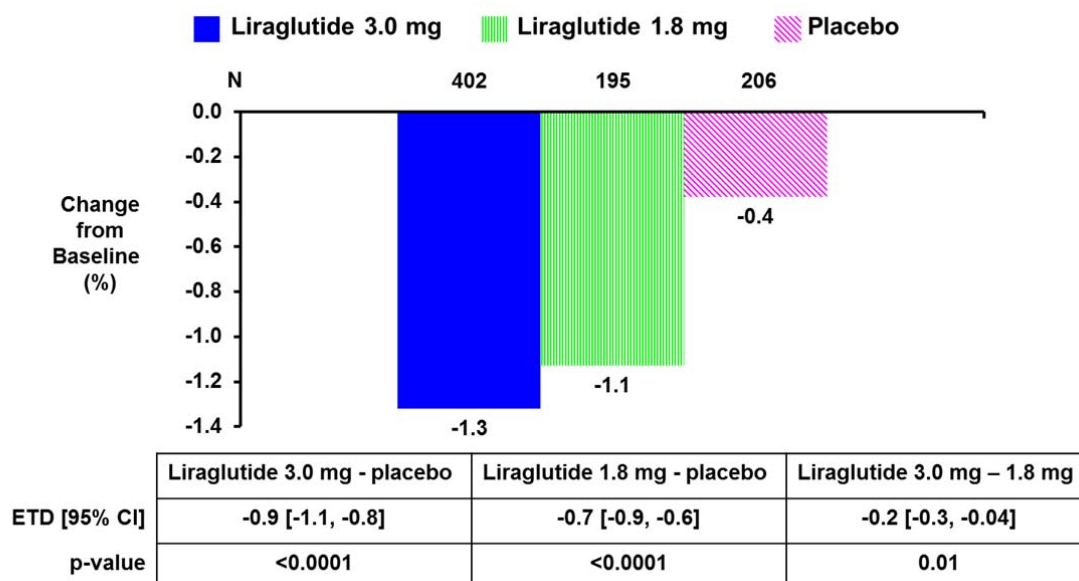
Few patients developed T2DM during trial 1839, whether they were treated with liraglutide 3.0 mg (4 patients, 0.2%) or placebo (14, 1.1%). These proportions corresponded to an annualized incidence rate of 1.3 per 100 patient years in the placebo group and 0.2 per 100 patient years in the liraglutide group. The likelihood of developing T2DM during the 56-week trial was 86% lower in the liraglutide group than in the placebo group (odds ratio 0.12 [95% CI 0.04; 0.39],  $p=0.0003$ ).

#### 5.4.7.2 Improvements in glycemic control in patients with type 2 diabetes: Trial 1922

##### HbA<sub>1c</sub>, FPG and prandial increment

In trial 1922, liraglutide 3.0 mg significantly reduced both HbA<sub>1c</sub> and FPG compared to placebo, as well as the mean postprandial glucose increment (90 minutes after the meal, average over 3 daily meals) ([Table 5–10](#)). As illustrated by [Figure 5–21](#), the effects on HbA<sub>1c</sub> were dose-dependent.

Mean baseline HbA<sub>1c</sub>: liraglutide 3.0 mg 7.9%, 1.8 mg 8.0%, placebo 7.9%



Data are estimated means for the full analysis set with last observation carried forward imputation. ETD: estimated treatment difference. CI: confidence interval. N: number of patients. OR: odds ratio.

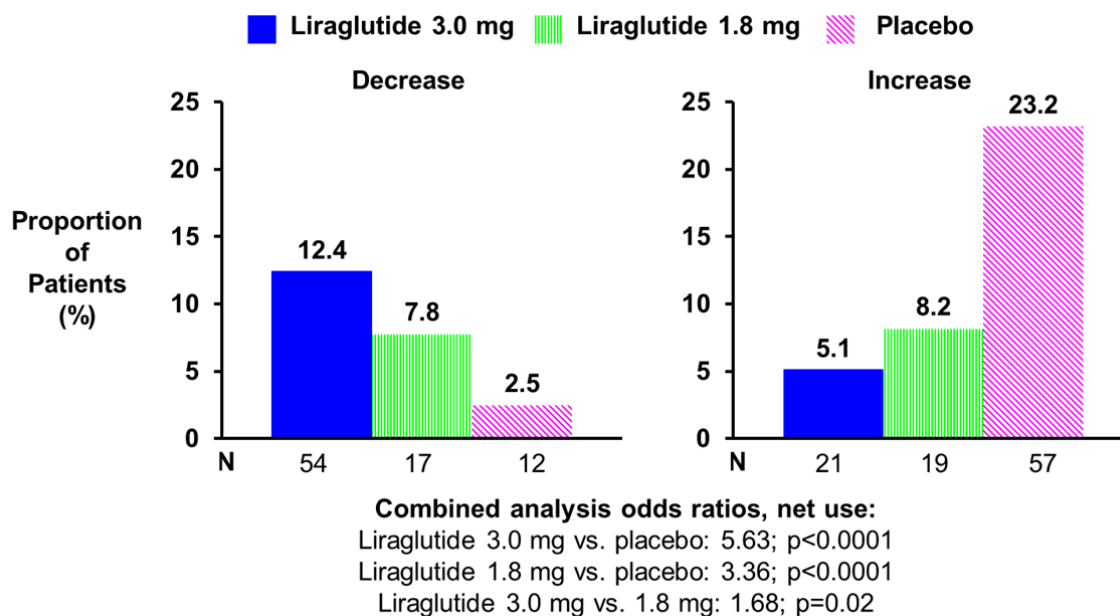
**Figure 5–21 Change from baseline in HbA<sub>1c</sub> (top) and the proportion of patients achieving HbA<sub>1c</sub> targets (bottom): Trial 1922**

Greater mean reductions were achieved with liraglutide 3.0 mg as compared with 1.8 mg ( $p=0.01$ , upper panel), and more patients on liraglutide 3.0 mg (57%) than 1.8 mg (45%) achieved a target  $HbA_{1c} \leq 6.5\%$  ( $p=0.01$ , lower panel). These results confirmed the findings from the phase 2 dose-finding trial, 1807, in patients without T2DM ([Appendix Table 4-1](#)). Greater improvements in  $HbA_{1c}$  were also observed with greater weight loss ([Figure 5–29](#)).

The effects on  $HbA_{1c}$  were independent of diabetes duration and baseline  $HbA_{1c}$  quartile (giving  $p$ -values of 0.89 and 0.85, respectively, for the interaction between the variables).

The improvements in FPG occurred rapidly and were sustained throughout the 56-week treatment period, suggestive of a direct (weight-loss independent) effect of liraglutide. When treatment was discontinued, FPG reverted to placebo levels within 2 weeks.

The beneficial effects on glycemic control occurred concomitantly with a greater proportion of patients treated with liraglutide 3.0 mg as compared with placebo reducing their net use of oral anti-diabetic drugs after 56 weeks ([Figure 5–22](#)). This further emphasizes the positive effect of liraglutide on glycemic control.



Data are estimated means (ordinal regression) for the full analysis set with last observation carried forward imputation. Change in net use of drug was defined as a change in dose or number of medications prescribed. N: number of patients.

**Figure 5–22 Change in use of oral antidiabetic drugs: Trial 1922**

#### 5.4.8 Effect of liraglutide 3.0 mg on cardio-metabolic parameters

A reduction of 5–10% of initial body weight has been shown to improve not only glycemic control, but also other obesity-related cardiovascular and metabolic abnormalities.<sup>29-32</sup> The effect of liraglutide treatment on many of those conditions, including blood pressure, fasting lipids, cardiovascular biomarkers and obstructive sleep apnea, was investigated, in order to confirm the clinical relevance of the weight loss achieved.

##### 5.4.8.1 Waist circumference and abdominal obesity

Waist circumference is a measure of abdominal obesity and is associated with cardiovascular disease in both men and women.<sup>111</sup> Consistent with its effects on body weight, liraglutide had positive statistically significant effects on waist circumference in all the trials, as well as on BMI (Table 5–12).

**Table 5–12 Change from baseline in waist circumference and BMI: Phase 3 trials**

|   | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1923</b><br>Weight maintenance<br>(56 weeks) | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|---|--|---|---|--|
|   | Lira 3.0 mg,<br>N=2437 / Placebo,<br>N=1225          | Lira 3.0 mg, N=207<br>/ Placebo, N=206                | Lira 3.0 mg, N=412<br>/ Placebo, N=211                | Lira 3.0 mg, N=180<br>/ Placebo, N=179               |
| <b>Waist circumference (cm)</b>           |  |   |   |  |
| Mean estimates                            | -8.17 / -3.97  | -4.68 / -1.19   | -6.02 / -2.81   | -6.35 / -3.14  |
| Treatment differences<br>[95% CI] p-value | -4.20 [-4.68; -3.72]<br>p<0.0001                     | -3.49 [-4.83; -2.15]<br>p<0.0001                      | -3.21 [-4.20; -2.22]<br>p<0.0001                      | -3.22 [-4.45; -1.98]<br>p<0.0001                     |
| <b>BMI (kg/m<sup>2</sup>)</b>             |  |   |   |  |
| Mean estimates                            | -3.04 / -1.00  | -2.07 / -0.02   | -2.24 / -0.74   | -2.21 / -0.62  |
| Treatment differences<br>[95% CI] p-value | -2.04 [-2.21; -1.87]<br>p<0.0001                     | -2.05 [-2.53; -1.57]<br>p<0.0001                      | -1.50 [-1.83; -1.16]<br>p<0.0001                      | -1.59 [-2.00; -1.17]<br>p<0.0001                     |

Data are estimated means (ANCOVA) and treatment differences for the full analysis set with the last observation carried forward.

BMI: body mass index. CI: confidence interval. N: number of patients. OSA: obstructive sleep apnea. T2DM: type 2 diabetes mellitus. W/o: without.

The weight loss and reduction in waist circumference with liraglutide were primarily due to reduction in fat mass rather than lean body mass, as observed after 20 weeks in a sub-population of 113 patients in trial 1807 (16-21 randomized patients across groups) using dual energy x-ray absorptiometry (DEXA) and computerized axial tomography (CT) scans (Table 5–13).<sup>92,112</sup> Both visceral and subcutaneous adipose tissue decreased from baseline. Results of the substudy also demonstrated the beneficial effects of weight loss with regard to the liver-to-spleen attenuation ratio, a measure of liver fat (hepatic steatosis) that is often increased in obese individuals and is associated with dyslipidemia and insulin resistance.<sup>113,114</sup> The liver-to-spleen attenuation ratio

increased from baseline to week 20 in both the liraglutide 3.0 mg and placebo treatment groups, with no difference between treatments, indicating beneficial reductions in liver fat with weight loss.

**Table 5–13 Body composition in a sub-population of patients: Trial 1807**

| Body composition at randomization (mean ± SD)         | Liraglutide 3.0 mg<br>(N=15/16) | Placebo<br>(N=14/21) |
|---|---------------------------------|----------------------|
| Body weight, kg (DEXA)                                | 100.0 ± 15.4                    | 99.6 ± 12.8          |
| Fat tissue, kg (DEXA)                                 | 43.9 ± 8.4                      | 45.8 ± 10.5          |
| Lean tissue, kg (DEXA)                                | 53.1 ± 10.3                     | 51.0 ± 11.0          |
| Visceral fat, cm <sup>2</sup> (CT)                    | 144.9 ± 69.5                    | 136.2 ± 37.6         |
| Subcutaneous fat, cm <sup>2</sup> (CT)                | 433.6 ± 116.2                   | 474.3 ± 106.5        |
| <b>Change from randomization to week 20 (mean±SD)</b> |                                 |                      |
| Body weight, kg (DEXA)                                | -7.1 ± 4.0                      | -4.8 ± 3.6           |
| Fat tissue,% of baseline fat (DEXA) <sup>a</sup>      | -14.2 ± 8.4                     | -9.4 ± 6.9           |
| Lean tissue,% of baseline lean (DEXA) <sup>a</sup>    | -2.0 ± 3.9                      | -1.7 ± 3.1           |
| Visceral fat,% of baseline (CT) <sup>a</sup>          | -16.5 ± 18.5                    | -7.8 ± 15.9          |
| Subcutaneous fat,% of baseline (CT) <sup>a</sup>      | -11.8 ± 9.9                     | -8.6 ± 12.2          |

Completers, per protocol analysis. N numbers show the number of completers included in the analysis out of the total number of patients enrolled in the sub-population.

<sup>a</sup>Relative changes. CT: computerized axial tomography. DEXA: dual energy x-ray absorptiometry. SD: standard deviation.

#### 5.4.8.2 Vital signs

Liraglutide 3.0 mg statistically significantly decreased mean systolic blood pressure as compared with placebo in each of the trials ([Table 5–14](#)). The reduction in blood pressure is already apparent at the first study visit, and appears to precede weight loss. Diastolic blood pressure was also significantly reduced in trial 1839, with a similar trend in trials 1922 and 3970. In trial 1923, a mean reduction in systolic blood pressure of 5.7 mmHg occurred during the low-calorie dietary run-in period, with no further decrease after baseline ([Appendix Table 2-9](#)). The reduction in systolic blood pressure was maintained with liraglutide in this trial, while systolic blood pressure increased in the placebo group, despite patients in this group maintaining their pre-randomization weight loss.

**Table 5–14 Change from baseline in systolic and diastolic blood pressure: Phase 3 trials**

|                       | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1923</b><br>Maintenance<br>(56 weeks) | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|-----------------------|--|--|---|--|
|                       | Lira 3.0 mg, N=2437<br>/ Placebo, N=1225             | Lira 3.0 mg, N=207<br>/ Placebo, N=206         | Lira 3.0 mg, N=412 /<br>Placebo, N=211                | Lira 3.0 mg, N=180<br>/ Placebo, N=179               |
| Systolic BP (mmHg)    |  |  |   |  |
| Mean estimates        |  |  |   |  |
| Treatment differences | -4.28 / -1.46  | 0.13 / 2.86                                    | -2.98 / -0.40   | -3.74 / 0.38   |
| [95% CI] p-value      | -2.82 [ -3.56 ; -2.09]<br>p<0.0001                   | -2.72 [ -4.71 ; -0.74]<br>p=0.007              | -2.58 [ -4.55 ; -0.61]<br>p=0.01                      | -4.12 [ -6.33 ; -1.90]<br>p=0.0003                   |
| Diastolic BP (mmHg)   |  |  |   |  |
| Mean estimates        |  |  |   |  |
| Treatment differences | -2.68 / -1.79  | 1.13 / 1.47                                    | -1.00 / -0.63   | -1.03 / -0.06  |
| [95% CI] p-value      | -0.89 [ -1.41 ; -0.37]<br>p=0.0009                   | -0.33 [ -1.74 ; 1.07]<br>p=0.64                | -0.37 [ -1.70 ; 0.96]<br>p=0.59                       | -0.97 [ -2.45 ; 0.51]<br>p=0.20                      |

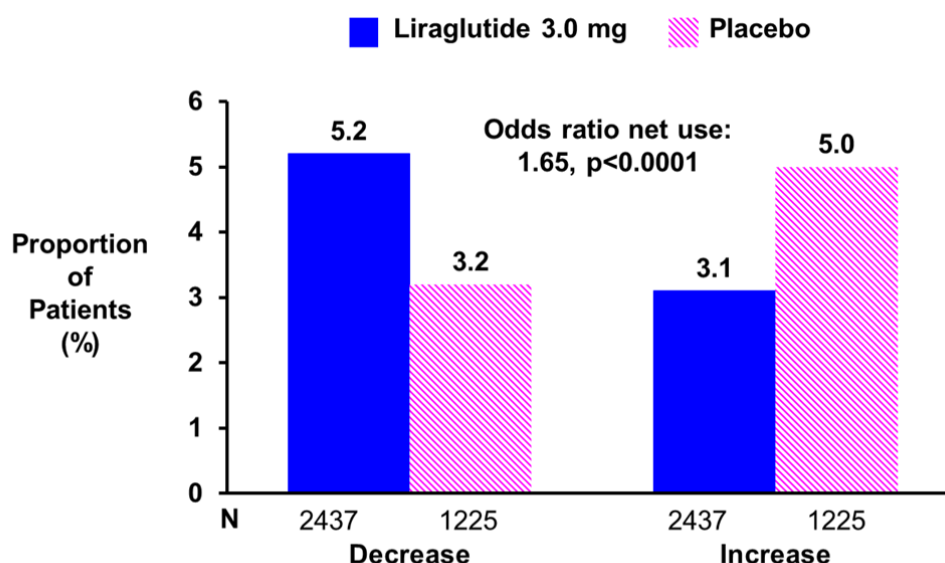
Data are estimated means (ANCOVA) and treatment differences for the full analysis set with the last observation carried forward.

Changes in trial 1923 were after pre-randomization low-calorie dietary run-in period, during which mean weight loss of 6% was achieved.

ANCOVA: analysis of covariance. BP: blood pressure. CI: confidence interval. N: number of patients. OSA: obstructive sleep apnea. T2DM: type 2 diabetes mellitus. W/o: without.

In trial 1839, the beneficial effects on blood pressure occurred concomitantly with a greater proportion of patients treated with liraglutide 3.0 mg as compared with placebo reducing their net use of anti-hypertensive medications after 56 weeks ([Figure 5–23](#)) (the protocol did not include a pre-specified algorithm for when to increase or decrease the medication). A similar, non-significant trend was observed in trials 1923 and 1922.





Data are estimated means (ordinal regression) for the full analysis set with last observation carried forward imputation. Change in net use of drug was defined as a change in dose or number of medications prescribed. N: number of patients.

**Figure 5–23 Change in use of anti-hypertensive drugs: Trial 1839**

The observed improvements in blood pressure were generally greater in those patients with higher baseline values in both treatment groups. Moreover, greater improvements in blood pressure ([Figure 5–30](#)) were observed with greater weight loss.

An increase in resting heart rate was observed with liraglutide 3.0 mg as compared with placebo in all of the trials. This is a known effect of liraglutide and has been shown to be non dose-dependent at doses between 1.2 mg and 3.0 mg ([Table 5–4](#)). Heart rate data are presented in more detail in [Section 6.3.4.3](#).

#### 5.4.8.3 Fasting lipid profile

Dyslipidemia was relatively well-controlled at randomization in most patients. Across trials, most of the patients with hypertension or dyslipidemia were on anti-hypertensive (84%) or lipid-lowering (58%) medications. Liraglutide 3.0 mg statistically significantly improved all components of the fasting lipid profile vs. placebo in trial 1839, the largest trial in the weight management program ([Table 5–15](#)). That is, all lipids were reduced compared with placebo, except for HDL-cholesterol, which was increased. Furthermore, non-HDL cholesterol was also significantly reduced with liraglutide 3.0 mg as compared with placebo (with a relative treatment difference of -4% [95% CI -5; -3] ) in a *post hoc* analysis. Non-HDL cholesterol has been suggested to give a better assessment of the risk for heart disease than measuring only LDL-cholesterol,<sup>100</sup> and is calculated by subtracting HDL-cholesterol from total cholesterol.

In trial 1922, conducted in patients with T2DM, similar significantly positive effects of liraglutide 3.0 mg as compared with placebo were observed on all lipids, except LDL cholesterol and free fatty acids ([Table 5–15](#)). The trends with respect to lipids consistently favored liraglutide 3.0 mg vs. placebo in all the trials.

**Table 5–15 Relative change from baseline in fasting lipids: Phase 3 trials**

|                       | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1923</b><br>Weight maintenance<br>(56 weeks) | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|-----------------------|--|---|---|--|
|                       | Lira 3.0 mg, N=2437<br>/ Placebo, N=1225             | Lira 3.0 mg, N=207 /<br>Placebo, N=206                | Lira 3.0 mg, N=412 /<br>Placebo, N=211                | Lira 3.0 mg, N=180 /<br>Placebo, N=179               |
| Triglycerides (%)     |  |   |   |  |
| Relative change (%)   | -13.61 / -4.76                                       | -4.69 / 4.25  | -14.63 / -1.12  | -9.41 / -4.09  |
| Relative difference   | -9.3 [-11.5; -7.0]                                   | -8.6 [-14.3; -2.4]                                    | -13.7 [-19.5; -7.4]                                   | -5.5 [-12.5; 2.0]                                    |
| [95% CI] p-value      | p<0.0001   | p=0.007   | p<0.0001  | p=0.14   |
| Total cholesterol (%) |  |   |   |  |
| Relative change (%)   | -3.19 / -0.89  | 4.36 / 6.58   | -1.39 / 2.28  | -3.86 / -1.43  |
| Relative difference   | -2.3 [-3.3; -1.3]                                    | -2.1 [-4.8; 0.7]                                      | -3.6 [-6.3; -0.8]                                     | -2.5 [-5.4; 0.6]                                     |
| [95% CI] p-value      | p<0.0001   | p=0.15  | p=0.01  | p=0.11   |
| LDL (%)               |  |   |   |  |
| Relative change (%)   | -3.15 / -0.71  | 7.80 / 11.51  | 0.82 / 3.13   | -5.00 / -0.86  |
| Relative difference   | -2.4 [-4.0; -0.9]                                    | -3.3 [-7.3; 0.8]                                      | -2.2 [-7.0; 2.8]                                      | -4.2 [-8.7; 0.5]                                     |
| [95% CI] p-value      | p=0.002  | p=0.11  | p=0.38  | p=0.08   |
| HDL (%)               |  |   |   |  |
| Relative change (%)   | 2.33 / 0.46  | 12.66 / 11.94   | 4.84 / 2.03   | 1.45 / 1.56  |
| Relative difference   | 1.9 [0.7; 3.0]                                       | 0.6 [-2.3; 3.6]                                       | 2.8 [0.2; 5.3]  | -0.1 [-3.2; 3.1]                                     |
| [95% CI] p-value      | p=0.001  | p=0.67  | p=0.03  | p=0.94   |
| VLDL (%)              |  |   |   |  |
| Relative change (%)   | -13.46 / -4.78                                       | -24.01 / -20.20                                       | -13.94 / -0.89  | -9.44 / -4.57  |
| Relative difference   | -9.1 [-11.4; -6.8]                                   | -4.8 [-12.3; 3.4]                                     | -13.2 [-18.7; -7.2]                                   | -5.1 [-11.9; 2.2]                                    |
| [95% CI] p-value      | p<0.0001   | p=0.24  | p<0.0001  | p=0.17   |
| Free fatty acids (%)  |  |   |   |  |
| Relative change (%)   | 0.79 / 5.17  | -24.48 / -23.18                                       | -13.68 / -8.49  | N/A  |
| Relative difference   | -4.2 [-7.3; -0.9]                                    | -1.7 [-11.5; 9.2]                                     | -5.7 [-11.9; 1.0]                                     |  |
| [95% CI] p-value      | p=0.01   | p=0.75  | p=0.09  |  |

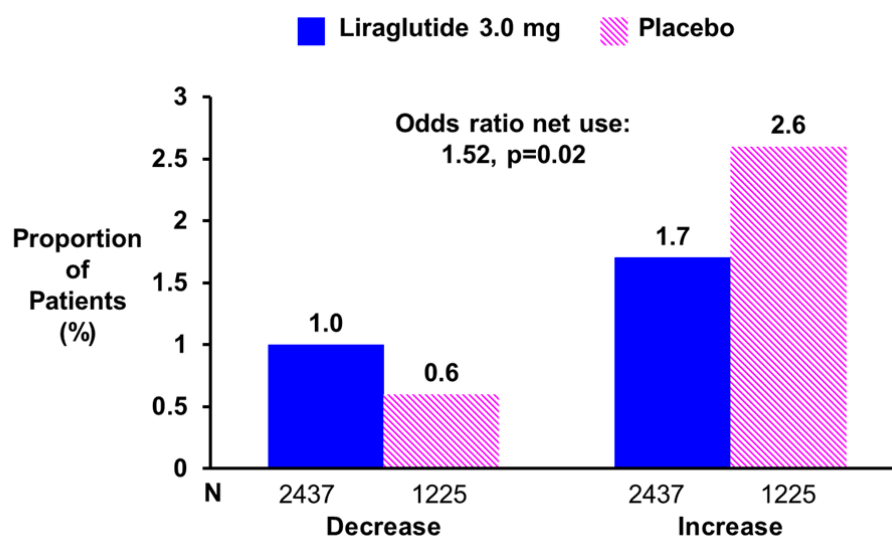
Data are relative changes from baseline and % relative treatment differences (ANCOVA on a log scale) for the full analysis set with the last observation carried forward.

ANCOVA: analysis of covariance. CI: confidence interval. HDL: high-density lipoprotein cholesterol. Lira: liraglutide. LDL: low-density lipoprotein cholesterol. N: number of patients. N/A: not applicable for this trial. OSA: obstructive sleep apnea. T2DM: type 2 diabetes mellitus. VLDL: very low-density lipoprotein cholesterol. W/o: without.



In trial 1923, the initial  $\geq 5\%$  weight loss that was achieved during the low-calorie dietary run-in period prior to randomization was accompanied by reductions in the concentrations of several lipids, including triglycerides ([Appendix Table 2-9](#)). These reductions were maintained with liraglutide 3.0 mg. It is reported that the concentrations of many lipids, notably total and LDL cholesterol, typically reach their nadir during the early weeks of dieting.<sup>115,116</sup>

In trial 1839, the beneficial effects on lipids occurred concomitantly with a greater proportion of patients treated with liraglutide 3.0 mg as compared with placebo reducing their net use of lipid-lowering medications after 56 weeks ([Figure 5–24](#)) (the protocol did not include a pre-specified algorithm for when to increase or decrease the medication). A similar, non-significant trend was observed in trials 1923 and 1922.



Data are estimated means (ordinal regression) for the full analysis set with last observation carried forward imputation. Change in net use of drug was defined as a change in dose or number of medications prescribed. N: number of patients.

**Figure 5–24 Change in use of lipid-lowering drugs: Trial 1839**

The observed improvements in fasting lipids were generally greater in those patients with higher baseline values (lower baseline values for HDL-cholesterol) in both treatment groups. For VLDL-, HDL-cholesterol and triglycerides, the treatment effects by baseline quartile were statistically significant ( $p \leq 0.02$  for all interactions), and better effects of liraglutide treatment were seen in those patients with the greatest need of improvement, i.e., the lowest HDL quartile, and the highest VLDL and triglyceride quartiles. Greater improvements in fasting lipids ([Figure 5–31](#)) were also observed with greater weight loss.

Furthermore, the beneficial treatment effects were greatest with liraglutide 3.0 mg as compared with 1.8 mg for VLDL and triglycerides in patients with T2DM ([Appendix Table 4-3](#)), with a non-significant trend for improvement in the other lipids. These findings confirmed the findings from the phase 2 dose-finding trial, 1807, in patients without T2DM ([Appendix Table 4-2](#)).

#### 5.4.8.4 Cardiovascular biomarkers

Obesity, especially the accumulation of excess visceral fat, is related to an increased risk of cardiovascular disease. A number of metabolic and inflammatory abnormalities are associated with this increased risk profile.<sup>117</sup> High sensitivity C-reactive protein, a marker of inflammation associated with increased cardiovascular risk,<sup>118</sup> was statistically significantly reduced by liraglutide 3.0 mg vs. placebo in trials 1839, 1923 and 1922, with a similar trend in trial 3970 ( $p=0.054$ ) ([Table 5-16](#)). Furthermore, significant reductions in plasminogen activator inhibitor-1, which contributes to arterial thrombosis and is an indicator of inflammation and hence cardiovascular risk,<sup>118</sup> with liraglutide vs. placebo were observed in both trials in which this biomarker was measured. Adiponectin, a modulator of key metabolic processes including glucose regulation and fatty acid oxidation,<sup>119</sup> was significantly increased with liraglutide 3.0 mg compared to placebo in trial 1839, with a similar trend in the other trials, indicating an improvement in this biomarker. No treatment effects on fibrinogen were observed. Finally, urinary albumin/creatinine ratio, a marker for kidney disease that is associated with increased risk of cardiovascular mortality,<sup>120</sup> was significantly reduced with liraglutide 3.0 mg as compared with placebo in trial 1922, in patients with T2DM, but not in trials 1839 or 3970, which was as expected since patients in these trials did not have T2DM.

**Table 5–16 Relative change from baseline in cardiovascular biomarkers: Phase 3 trials**

|  | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1923</b><br>Weight maintenance<br>(56 weeks) | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|--|--|---|---|--|
|  | Lira 3.0 mg, N=2437<br>/ Placebo, N=1225             | Lira 3.0 mg, N=207 /<br>Placebo, N=206                | Lira 3.0 mg, N=412 /<br>Placebo, N=211                | Lira 3.0 mg, N=180 /<br>Placebo, N=179               |
| hsCRP (%)                                |  |   |   |  |
| Relative change (%)                      | -37.60 / -10.24                                      | -33.21 / -8.49  | -34.21 / -9.75  | -20.62 / -8.51                                       |
| Relative difference                      | -30.5 [-34.3; -26.5]                                 | -27.0 [-38.0; -14.0]                                  | -27.1 [-36.0; -16.9]                                  | -13.2 [-24.9; 0.3]                                   |
| [95% CI] p-value                         | p<0.0001   | p=0.0002  | p<0.0001  | p=0.054  |
| PAI-1 (arb. unit/mL)                     |  |   |   |  |
| Relative change (%)                      | –  |   | –   |  |
| Relative difference                      | -21.3 [-25.7; -16.7]                                 | N/A   | -21.1 [-31.1; -9.7]                                   | N/A  |
| [95% CI] p-value                         | p<0.0001   |   | p=0.0006  |  |
| Adiponectin (%)                          |  |   |   |  |
| Relative change (%)                      | 11.94 / 3.20   | 33.89 / 28.24   | 5.60 / 0.03   | N/A  |
| Relative difference                      | 8.5 [5.5; 11.6]                                      | 4.4 [-2.4; 11.7]                                      | 5.6 [-3.0; 14.9]                                      |  |
| [95% CI] p-value                         | p<0.0001   | p=0.21  | p=0.21  |  |
| Fibrinogen (%)                           |  |   |   |  |
| Relative change (%)                      | 0.91 / 0.46  | 1.52 / -2.25  | 3.27 / -1.21  | N/A  |
| Relative difference                      | 0.5 [-1.2; 2.1]                                      | 3.9 [-0.3; 8.2]                                       | 4.5 [0; 9.3]  |  |
| [95% CI] p-value                         | p=0.59   | p=0.07  | p=0.052   |  |
| Urinary albumin/<br>creatinine ratio (%) |  |   |   |  |
| Relative change (%)                      | 11.49 / 15.63  | N/A   | -20.47 / -0.18  | 8.39 / 6.81  |
| Relative difference                      | -3.6 [-10.1; 3.4]                                    |   | -20.3 [-32.6; -5.8]                                   | 1.5 [-14.6; 20.6]                                    |
| [95% CI] p-value                         | p=0.31   |   | p=0.008   | p=0.87   |

Data are relative changes from baseline (except for PAI-1 where the mean at end of treatment is presented) and % relative differences (ANCOVA on a log scale) for the full analysis set with the last observation carried forward.

\*PAI-1 was analyzed using different methods at baseline and week 56, therefore relative changes cannot be calculated.

ANCOVA: analysis of covariance. arb.: arbitrary. CI: confidence interval. hsCRP: high sensitivity C-reactive protein.

Lira: liraglutide. N: number of patients. N/A: not applicable for this trial. OSA: obstructive sleep apnea.

PAI-1: plasminogen activator inhibitor-1. T2DM: type 2 diabetes mellitus. W/o: without.

Greater improvements in cardiovascular biomarkers were observed with greater weight loss ([Figure 5–31](#)).

#### 5.4.8.5 Moderate or severe obstructive sleep apnea: Trial 3970

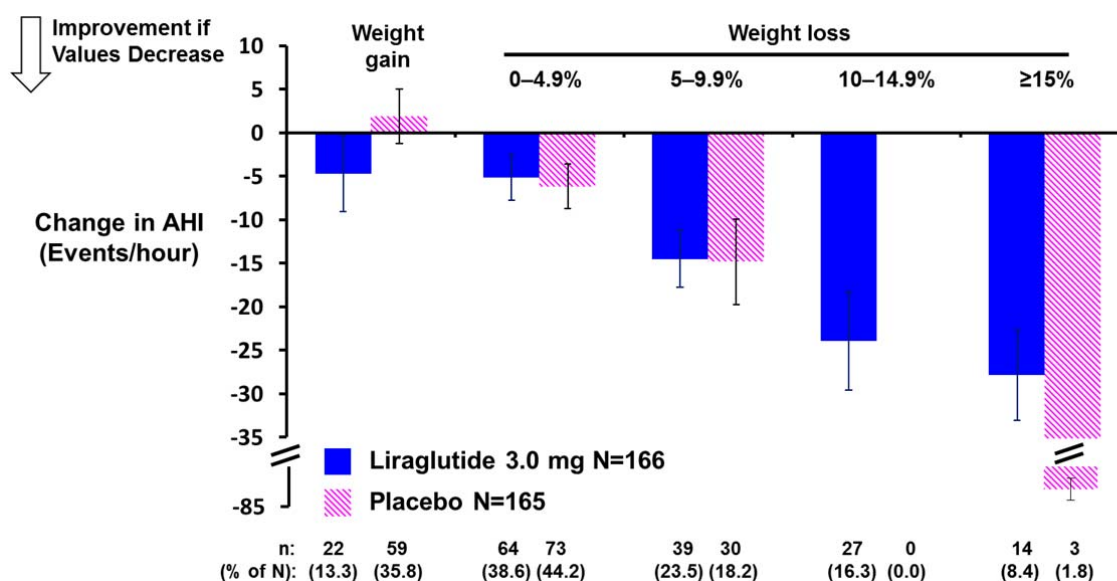
Untreated OSA is recognized as an independent risk factor for the development of certain comorbid conditions, such as hypertension and other cardiovascular morbidities.<sup>69,70</sup> However, OSA remains undiagnosed in up to 20% of middle-aged adults in the general population.<sup>69,70</sup> Weight loss is one of the few treatments for OSA, other than CPAP, that improves OSA symptoms, as assessed by the apnea-hypopnea index, or AHI.<sup>73,74</sup> The AHI is the number of apnea or hypopnea episodes recorded

per hour of sleep, expressed as the number of events per hour. In trial 3970, conducted in patients who were unwilling or unable to use CPAP and who had either moderate OSA (defined as an AHI of 15.0–29.9 events/hour) or severe OSA (defined as an AHI of at least 30 events/hour), the mean baseline AHI was 49.2 events/hour. Liraglutide 3.0 mg, as adjunct to diet and exercise, statistically significantly reduced the severity of OSA, with a mean reduction in the AHI as compared with placebo of 12.2 vs. 6.1 episodes/hour ( $p=0.015$ ). The reduction in AHI was consistent with that which has been seen in other weight loss interventions for patients with OSA.<sup>74,121,122</sup> The treatment effect was similar irrespective of whether the OSA was moderate or severe at baseline ( $p=0.74$ ), albeit with greater absolute reductions in patients with severe OSA at baseline.

Non-significant improvements in most secondary sleep-related endpoints consistently were seen with liraglutide as compared with placebo; these included OSA severity-related endpoints, endpoints on oxygen saturation and sleep architecture (related to sleep patterns; see [Appendix Figures 2-1](#) and [2-2](#)), as well as the patient reported outcome questionnaires Epworth Sleepiness Scale (ESS), which measures a patient's usual level of daytime sleepiness, and the Functional Outcomes of Sleep Questionnaire (FOSQ), which assesses the impact of daytime sleepiness on multiple activities of everyday living.

As expected, *post hoc* analyses demonstrated that improvements in the primary and most of the secondary sleep-related endpoints were related to weight loss, regardless of the treatment group ([Figure 5–25](#)); these effects were most pronounced in individuals with severe OSA at baseline. Nevertheless, while similar effects on AHI were seen in the two treatment groups with comparable weight losses, many more patients on liraglutide 3.0 mg than on placebo achieved a weight loss of 5% or greater, thereby significantly increasing their chances of clinically meaningful improvement in OSA severity or other OSA-related symptoms such as oxygen saturation, total sleep time, or sleepiness.

Improvements in sleep-related endpoints were accompanied by statistically significant improvements in systolic blood pressure ([Table 5–14](#)), FPG and HbA<sub>1c</sub> ([Table 5–10](#)), and similar trends for hsCRP ([Table 5–16](#)) and fasting lipids ([Table 5–15](#)), all of which are considered highly clinically relevant in this population.



Change in AHI (events/hour) in patients with moderate and severe AHI at baseline vs. 5 weight change categories. Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. AHI: apnea-hypopnea index. N: Number of patients in the full analysis set; n: number of patients contributing to the analysis. Percentages are based on the total N.

**Figure 5–25 Change from baseline in the apnea-hypopnea index by weight-change category: Trial 3970**

#### 5.4.9 Effect of liraglutide 3.0 mg on patient reported outcomes

Obese individuals often have lower self-esteem and poorer quality of life than normal-weight individuals.<sup>38</sup> Moreover, obesity can adversely affect physical function and mental health.<sup>39,27</sup> Obese individuals often suffer from physical symptoms, such as joint pain, and psycho-social problems.<sup>23–26</sup> Therefore, multiple and diverse questionnaires were used to assess patient perspectives in the weight management clinical development program. The IWQoL-Lite questionnaire was used in trials 1839 and 1922, and the SF-36 was used in trials 1839 and 3970 (both had a score range of 0–100, where higher scores indicate greater quality of life). Trial 1839 also employed the Treatment Related Impact Measure-Weight (TRIM-Weight) questionnaire and trial 1922 employed the Diabetes Treatment Satisfaction Questionnaire (DTSQs). In addition, the two sleep related questionnaires ESS and FOSQ were used in trial 3970.

The IWQoL-Lite questionnaire is a 31-item self-reported measure of health-related quality of life that assesses patients' perceptions of how weight affects their daily lives.<sup>39</sup> The questionnaire has a total score, and 5 domain scores (physical function, self-esteem, sexual life, public distress and work).

Statistically significant increases, indicating improvements, in the validated total score for the IWQoL-Lite were observed with liraglutide 3.0 mg as compared with placebo in both of the trials in which this questionnaire was used ([Table 5–17](#)).

**Table 5–17 Change from baseline in IWQoL-Lite and SF-36 total scores: Trials 1839, 1922 and 3970**

|  | <b>Trial 1839</b><br>Patients w/o T2DM<br>(56 weeks) | <b>Trial 1922</b><br>Patients with T2DM<br>(56 weeks) | <b>Trial 3970</b><br>Patients with OSA<br>(32 weeks) |
|--|--|---|--|
|  | Liraglutide 3.0 mg, N=2437<br>/ Placebo, N=1225      | Liraglutide 3.0 mg,<br>N=412 / Placebo, N=211         | Liraglutide 3.0 mg,<br>N=180 / Placebo, N=179        |
| IWQoL-Lite (total score) <sup>a</sup>        |  |   |  |
| Mean estimates                               | 10.66 / 7.54   | 11.16 / 8.43  | N/A  |
| Treatment differences [95% CI]               | 3.13 [2.24; 4.01]                                    | 2.73 [0.53; 4.92]                                     |  |
| p-value                                      | p<0.0001   | p=0.015   |  |
| SF-36 (overall physical health) <sup>b</sup> |  |   |  |
| Mean estimates                               | 3.66 / 1.93  | N/A   | 2.84 / 1.99  |
| Treatment differences [95% CI]               | 1.73 [1.22; 2.24]                                    |   | 0.86 [-0.49; 2.20]                                   |
| p-value                                      | p<0.0001   |   | p=0.21   |
| SF-36 (overall mental health) <sup>b</sup>   |  |   |  |
| Mean estimates                               | 0.14 / -0.76   | N/A   | 1.47 / 0.88  |
| Treatment differences [95% CI]               | 0.90 [0.30; 1.50]                                    |   | 0.59 [-0.86; 2.04]                                   |
| p-value                                      | p=0.003  |   | p=0.43   |

Data are estimated means (ANCOVA) and treatment differences for the full analysis set with the last observation carried forward. Trial 1923 did not employ these questionnaires.

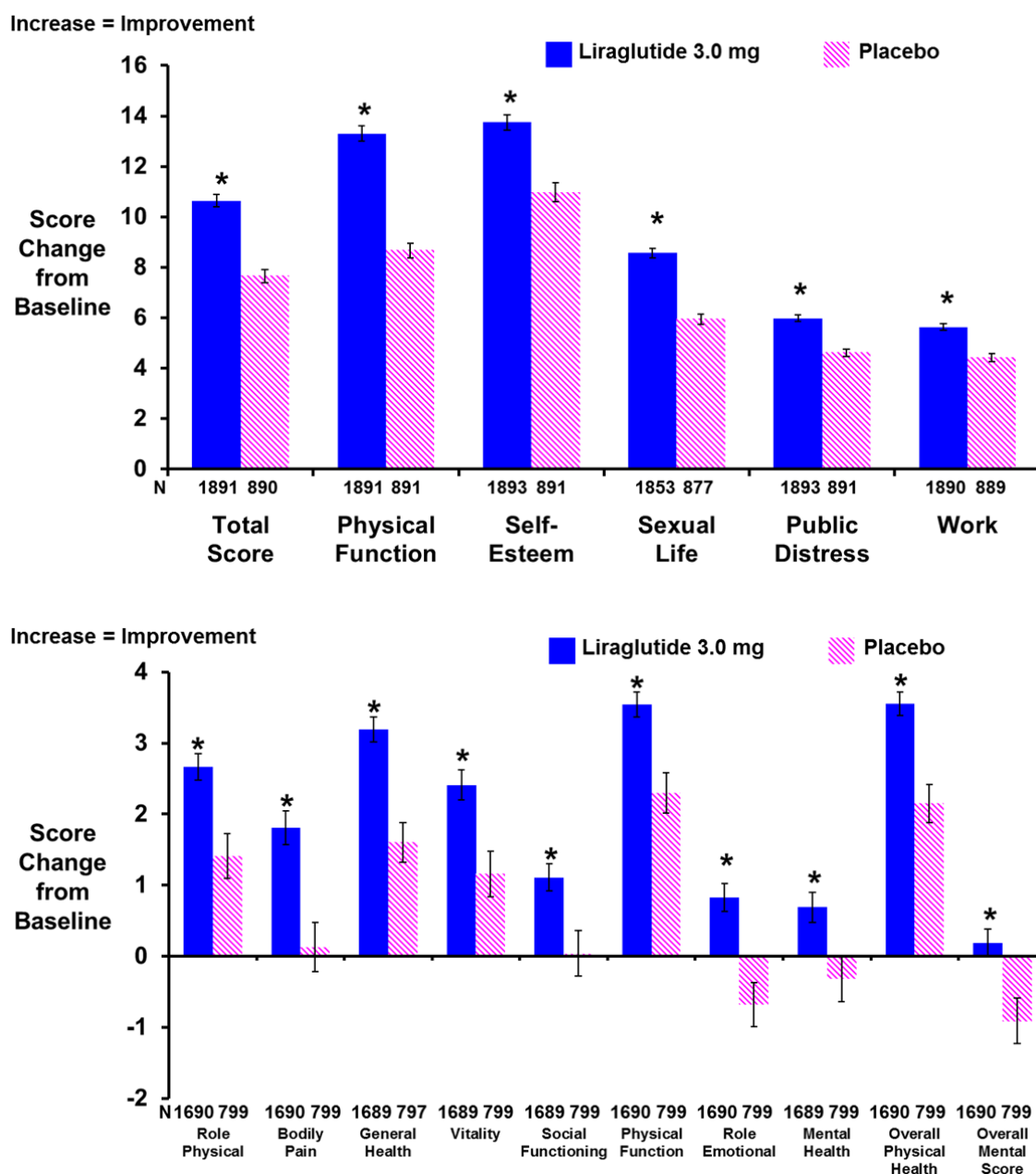
<sup>a</sup>A change of 7.7–12 points from baseline to 1 year, depending on baseline severity, represents a meaningful improvement.<sup>39</sup> Baseline values for all groups were in the moderate range (72–79), and an increase of 7.2 is then considered clinically meaningful.

<sup>b</sup>Score increases of 2 points for overall physical health and 3 points for overall mental health are considered to be clinically meaningful.<sup>40</sup>

ANCOVA: analysis of covariance. IWQoL-Lite: Impact of Weight on Quality of Life-Lite. N: number of patients. N/A: not applicable for this trial. OSA: obstructive sleep apnea. SF-36: 36-item Short-Form health status survey. T2DM: type 2 diabetes mellitus. W/o: without.

The improvements in the IWQoL-Lite total score were primarily driven by the significantly improved physical function scores ([Figure 5–26](#)). In the IWQoL-Lite validation paper, an increase in 7.7–12 points from baseline to 1 year, depending on baseline severity, was considered to be a clinically meaningful improvement.<sup>39</sup> For the IWQoL-Lite mean total score, a clinically meaningful improvement was observed in both of the trials, in patients with or without T2DM ([Table 5–17](#)). A greater proportion of patients in the liraglutide group (49%) as compared with the placebo group (38%) achieved a clinically meaningful improvement in the total score ([Figure 5–27](#), p<0.0001 by *post hoc* analysis).

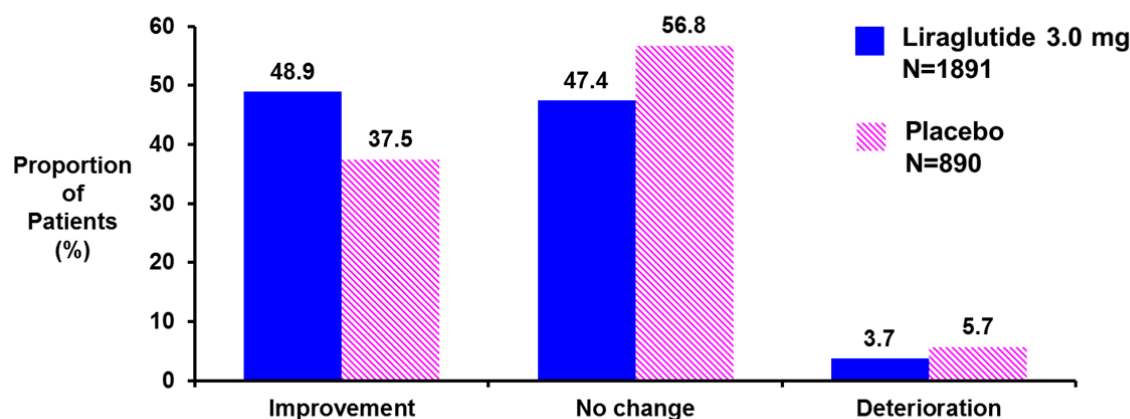




\* $p < 0.001$ . Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. Overall physical and mental health scores (SF-36) are shown at the right. N: number of patients.

**Figure 5–26 Improvements in health-related quality of life and health status (top: IWQoL-Lite and bottom: SF-36): Trial 1839**

**Odds ratio for overall better outcome 1.59 [1.35, 1.88]**  
**Liraglutide 3.0 mg / Placebo p<0.0001**



Data are estimated means for the full analysis set with last observation carried forward imputation. Improvement denotes an increase from baseline of  $\geq$  the individual MID; no change is a change from baseline  $<$  the individual MID; and deterioration is a reduction from baseline  $\geq$  the individual MID. The odds ratio is a combination of the three. CI: confidence interval. IWQoL-Lite: Impact of Weight on Quality of Life-Lite. MID: minimal important difference. N: number of patients.

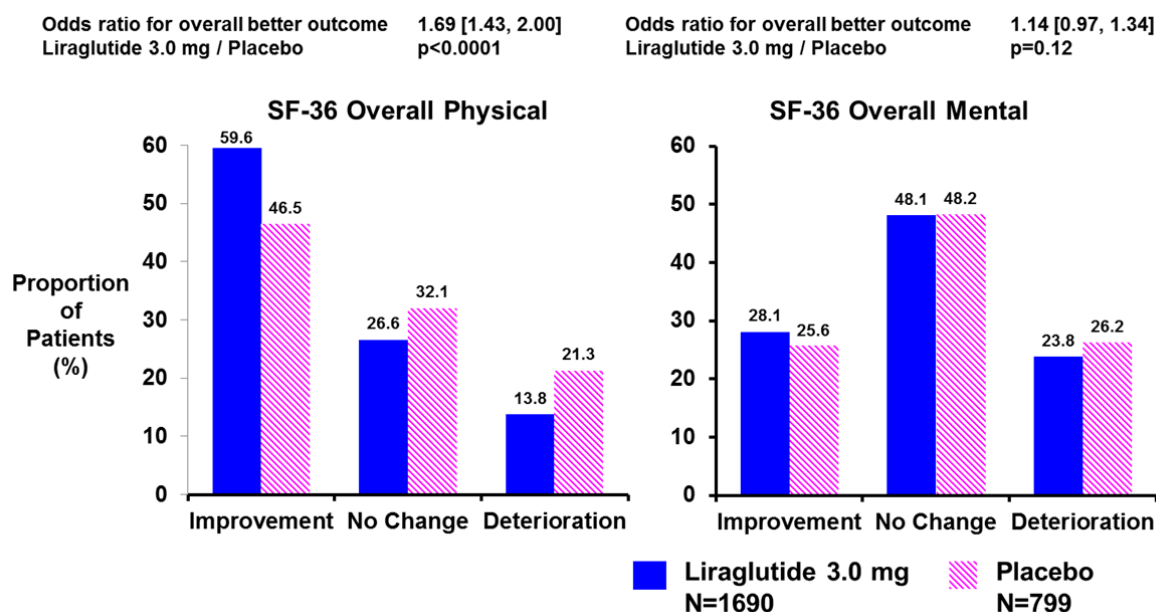
**Figure 5–27 Proportion of patients achieving clinically meaningful improvements in IWQoL-Lite total score: Trial 1839**

The SF-36 assesses general health status and has 36 questions grouped into 8 domains: role-physical, bodily pain, general health, vitality, social functioning, physical function, role-emotional and mental health, which again can be combined to give two summary component scores.

Significant improvements in the SF-36 overall physical and mental health scores were also seen with liraglutide vs. placebo in trial 1839, with a similar positive trend in trial 3970 ([Table 5–17](#)). Furthermore, significant improvements were observed in all domains in trial 1839 with liraglutide 3.0 mg as compared with placebo, again indicating favorable effects on physical function and also mental health ([Figure 5–26](#)). Similar trends were observed in trial 3970, with a statistically significant improvement in general health perceptions for liraglutide 3.0 mg vs. placebo.

In the SF-36 user manual, score increases of 2 points for overall physical health and 3 points for overall mental health are considered to be clinically meaningful.<sup>40</sup> In trial 1839, a greater proportion of patients in the liraglutide group (60%) as compared with the placebo group (47%) achieved a clinically meaningful improvement in the overall physical health score ([Figure 5–28](#),  $p<0.0001$  *post hoc*). The proportion of patients who achieved a meaningful improvement in the overall mental health score did not differ between the liraglutide group (28%) and the placebo group (26%) ( $p=0.11$ ).





Data are estimated means for the full analysis set with last observation carried forward imputation. Improvement denotes an increase from baseline of  $\geq$  the individual MID; no change is a change from baseline  $<$  the individual MID; and deterioration is a reduction from baseline  $\geq$  the individual MID. The odds ratio is a combination of the three. CI: confidence interval. MID: minimal important difference. N: number of patients. SF-36: 36-item Short-Form health status survey.

**Figure 5–28 Proportion of patients achieving clinically meaningful improvements in SF-36 overall physical and mental health: Trial 1839**

Trial 1839 also employed the Treatment Related Impact Measure-Weight questionnaire (TRIM-Weight), which assesses the key impacts of anti-obesity medications and evaluates a patient's functioning and well-being.<sup>123</sup> It contains 22 items divided into five domains: daily life, weight management, treatment burden, experience of side effects and psychological health, which are combined into a total score. Significant improvements from baseline were observed for liraglutide 3.0 mg vs. placebo in the weight management and treatment burden scores. The experience of side effects score was significantly higher for patients on liraglutide 3.0 mg as compared with placebo, indicating non-favorable effects, however these effects did not reverse the positive effects on other domains in establishing the total score ([Appendix Table 2-3](#)).

Finally, the Diabetes Treatment Satisfaction Questionnaire (DTSQs) was used in trial 1922, in patients with T2DM, to assess the impact of treatment on the patients' treatment satisfaction, including perceived frequencies of hyper- and hypoglycemia.<sup>124</sup> Liraglutide 3.0 mg significantly improved the DTSQs total score from baseline as compared with placebo.

In summary, improvements in health-related quality of life from baseline were observed both for patients treated with liraglutide 3.0 mg and for those treated with placebo in all the above trials, as

expected with weight loss, demonstrating the effectiveness of the lifestyle intervention. The effect increased with greater weight loss (as illustrated in [Figure 5–32](#)), and the addition of liraglutide 3.0 mg further enhanced the benefit of the lifestyle intervention in many of the domains, notably physical function, and provided clinically meaningful improvements. Improvements in physical function occurred consistently across the different trial populations, including patients with T2DM and OSA, in which improvements in activity level of the FOSQ questionnaire were observed (as described in Section [5.4.8.5](#)). Such improvements may be translated into benefits for the individual in terms of enhanced mobility, greater ease in dressing and undressing, having less painful or stiff joints and having fewer health worries generally.<sup>40,41</sup>

#### **5.4.10 Secondary efficacy endpoints in patient sub-populations**

Overall, the efficacy response to liraglutide 3.0 mg was consistent across sub-populations and the beneficial effect of liraglutide as compared with placebo was generally seen across all sub-populations and secondary efficacy endpoints, as assessed in pooled analyses ([5.4.2.2](#)). As expected, the treatment effect on glycemic parameters (FPG, HbA<sub>1c</sub>) was greater in patients with T2DM than in those without.

#### **5.4.11 Secondary efficacy endpoints, relationship with weight loss**

The beneficial effects of liraglutide 3.0 mg on secondary endpoints were consistently greater with greater body weight loss. This was demonstrated by an evaluation of secondary endpoints in the ‘5% responders’ who lost 5% or more of their body weight, as compared with the 5% ‘non-responders’ who did not achieve this weight-loss benchmark, as well as by an assessment of secondary endpoints by weight change category, as outlined in the sections below. Furthermore, as illustrated by the results of a ‘mediator analysis’, the relative contribution of weight loss to the effect of treatment on key secondary efficacy endpoints at the end of treatment appears to vary between endpoints ([5.4.11.3](#)).

##### **5.4.11.1 Efficacy in the 5% responder population**

In the pooled group of patients who achieved a weight loss of at least 5% across all 5 trials, the ‘5% responders’, mean weight loss with liraglutide 3.0 mg at end of trial was 11.5% (12.0 kg) as compared with a weight loss of 1.6% (1.7 kg) in the ‘5% non-responders’ group ([Table 5–18](#)).

**Table 5–18 Change from baseline in efficacy endpoints for 5% responders vs. non-responders, by treatment group: All 5 trials pooled**

| Parameter                             | Liraglutide 3.0 mg              |                                  | Placebo                        |                                  |
|---------------------------------------|---------------------------------|----------------------------------|--------------------------------|----------------------------------|
|                                       | 5% responders<br>N=1989 (60.3%) | Non responders<br>N=1312 (39.7%) | 5% responders<br>N=462 (24.4%) | Non-responders<br>N=1428 (75.6%) |
| <b>Body weight related parameters</b> |                                 |                                  |                                |                                  |
| Body weight (%)                       | -11.48                          | -1.56                            | -9.80                          | 0.21                             |
| Body weight (kg)                      | -11.99                          | -1.67                            | -10.48                         | 0.21                             |
| BMI (kg/m <sup>2</sup> )              | -4.32                           | -0.61                            | -3.72                          | 0.08                             |
| Waist circumference (cm)              | -10.78                          | -3.00                            | -9.71                          | -1.48                            |
| <b>Glycemic control parameters</b>    |                                 |                                  |                                |                                  |
| HbA <sub>1c</sub> (%-points)          |                                 |                                  |                                |                                  |
| Excluding trial 1922                  | -0.35                           | -0.19                            | -0.14                          | -0.02                            |
| Trial 1922 (only)                     | -1.59                           | -1.04                            | -1.14                          | -0.21                            |
| FPG (mg/dL)                           |                                 |                                  |                                |                                  |
| Excluding trial 1922                  | -8.32                           | -4.72                            | -3.02                          | 1.19                             |
| Trial 1922 (only)                     | -44.68                          | -24.07                           | -29.33                         | 4.51                             |
| <b>Vital signs</b>                    |                                 |                                  |                                |                                  |
| Systolic BP (mmHg)                    | -5.25                           | -1.48                            | -2.97                          | -0.11                            |
| Diastolic BP (mmHg)                   | -2.92                           | -0.72                            | -2.79                          | -0.66                            |
| <b>Lipids</b>                         |                                 |                                  |                                |                                  |
| HDL (%)                               | 5.0                             | 0.11                             | 6.94                           | 0.37                             |
| LDL (%)                               | -3.35                           | -0.39                            | -1.91                          | 1.11                             |
| VLDL (%)                              | -14.74                          | -2.21                            | -13.13                         | 3.65                             |
| Triglycerides (%)                     | -17.60                          | -2.12                            | -18.42                         | 2.64                             |
| Total cholesterol (%)                 | -3.21                           | -0.72                            | -2.12                          | 1.10                             |
| Free fatty acids (%)                  | -3.98                           | -1.37                            | -10.20                         | 0.12                             |
| <b>Cardiovascular biomarkers</b>      |                                 |                                  |                                |                                  |
| hsCRP (%)                             | -44.89                          | -14.98                           | -30.47                         | 0.51                             |
| Fibrinogen (%)                        | 0.17                            | 2.99                             | -2.21                          | 0.06                             |
| Adiponectin (%)                       | 18.80                           | 2.65                             | 20.35                          | 2.64                             |
| Urinary albumin/creatinine ratio (%)  | 10.63                           | -0.43                            | 16.40                          | 10.40                            |
| <b>Patient reported outcome</b>       |                                 |                                  |                                |                                  |
| IWQoL-Lite (total score)              | 12.93                           | 7.11                             | 12.54                          | 5.97                             |
| SF-36 (overall physical health score) | 4.19                            | 2.14                             | 4.23                           | 1.25                             |

5% responder: pooled population of patients achieving  $\geq 5\%$  weight loss. Data are mean estimates for the full analysis set with the last observation carried forward.

All 5 trials pooled: 1839, 1923, 1922, 3970 and 1807 (52-week period).

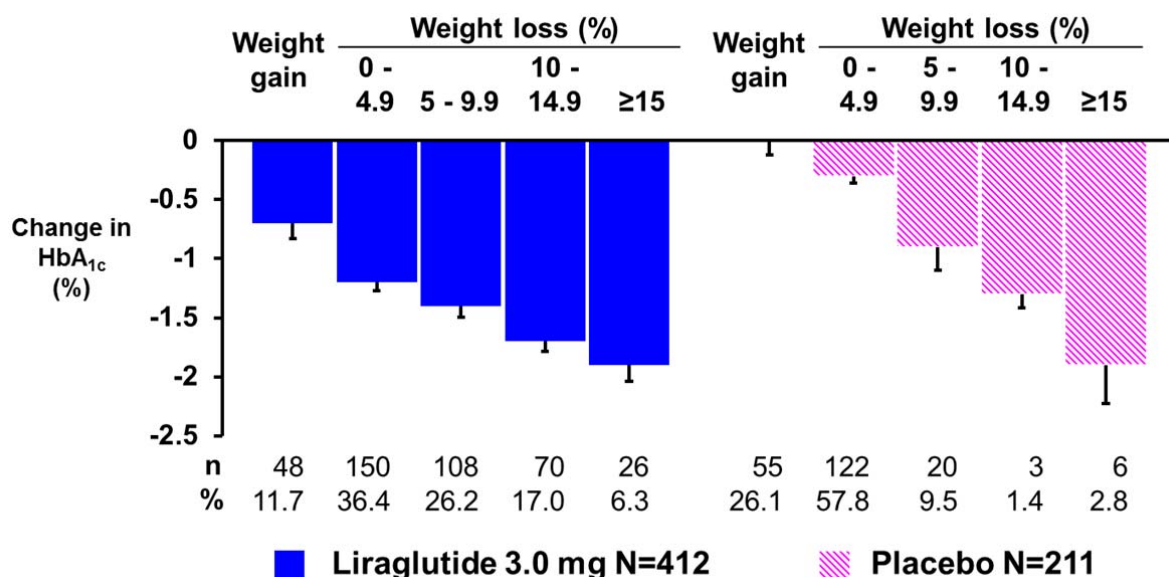
With diet and exercise alone (placebo), the 5% responders were fewer in number (24% of the treatment group as compared with 60% for the liraglutide group) and they achieved a mean weight loss of 9.8% (10.5 kg), compared with a mean weight gain of 0.21% (0.21 kg) in the non-responder population.

Consistently across secondary endpoints, the improvements achieved in the 5% responder population with liraglutide 3.0 mg, as adjunct to diet and exercise, were greater than or comparable with those achieved in the non-responder population. These results emphasize the beneficial effects of liraglutide 3.0 mg not only on weight loss, but also on a range of cardio-metabolic parameters and quality of life measures.

#### 5.4.11.2 Change in secondary endpoints by weight change categories

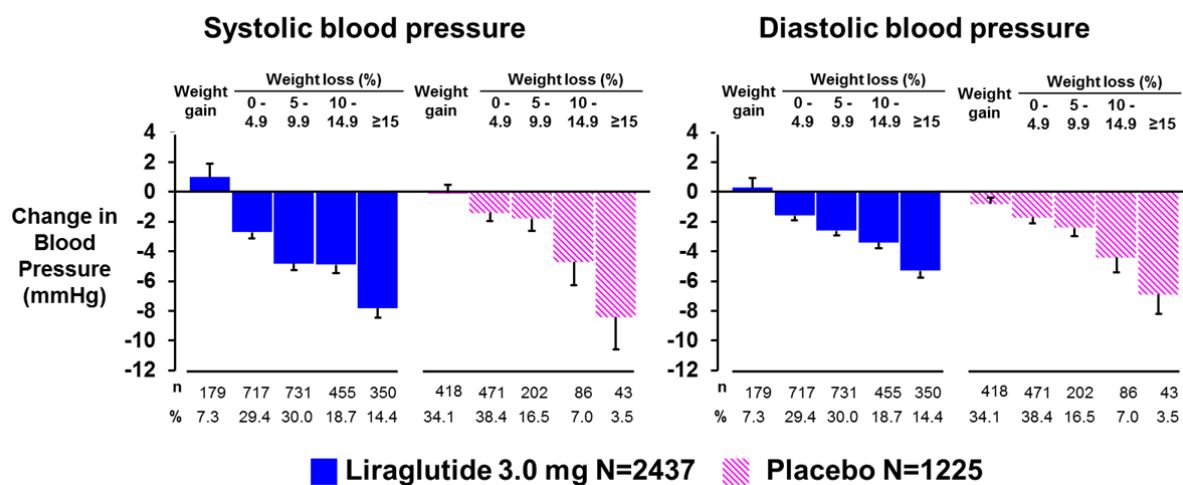
The evaluation of the relationship between weight loss and change in secondary endpoints was further expanded to include 5 weight-change categories (weight gain, 0-4.9%, 5-9.9%, 10-14.9%, ≥15%). Representative examples of the figures that illustrate the results of the evaluation are presented below.

Greater improvements in glycemic control were observed with greater weight loss in patients with T2DM in trial 1922 ([Figure 5–29](#)) and greater improvements in blood pressure ([Figure 5–30](#)), fasting lipids and cardiovascular biomarkers ([Figure 5–31](#)), OSA ([Figure 5–25](#)) as well as quality of life ([Figure 5–32](#)) were also observed. Furthermore, at the same mean weight change category, the changes with liraglutide 3.0 mg were generally greater than those seen with placebo.



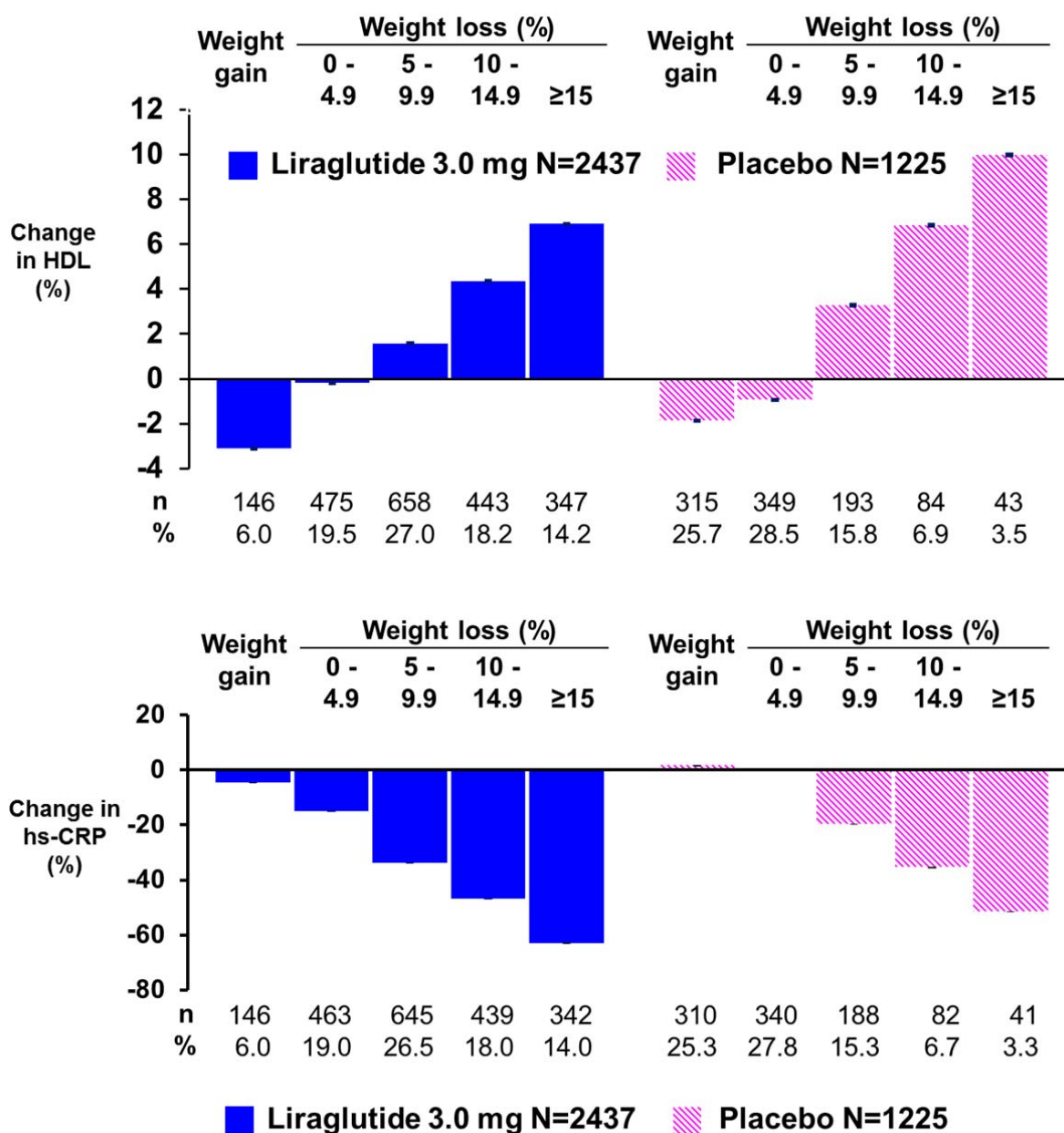
Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. N: Number of patients in the full analysis set; n: number of patients contributing to the analysis. Percentages are based on the total N.

**Figure 5–29 Change from baseline in HbA<sub>1c</sub> by weight-change category: Trial 1922**



Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. N: Number of patients in the full analysis set; n: number of patients contributing to the analysis. Percentages are based on the total N.

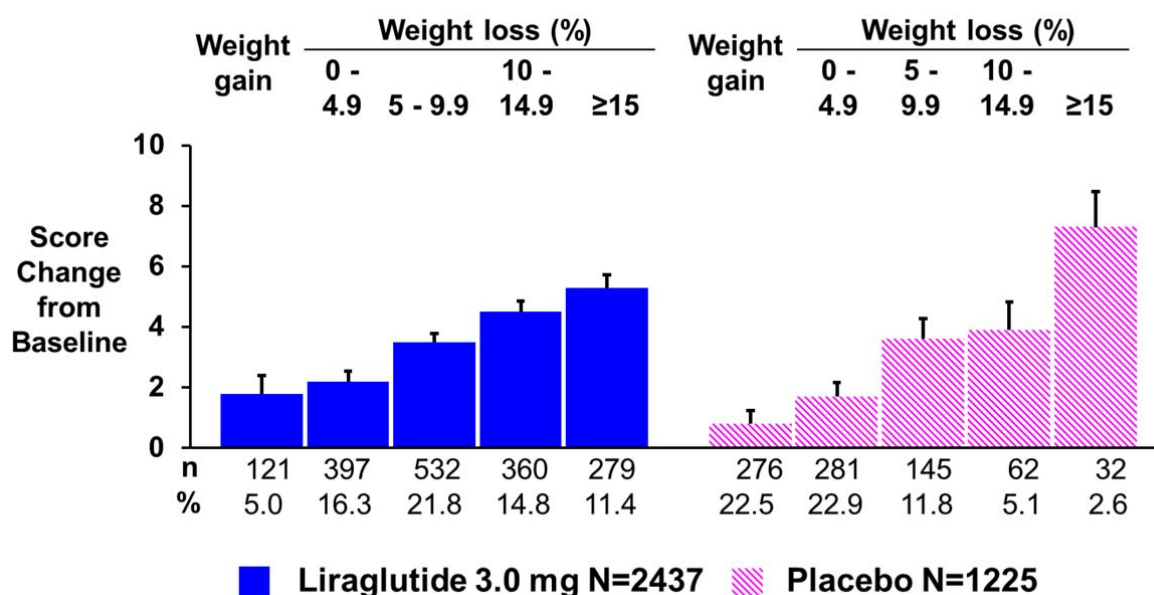
**Figure 5–30 Change from baseline in blood pressure by weight-change category: Trial 1839**



Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. N: Number of patients in the full analysis set; n: number of patients contributing to the analysis. Percentages are based on the total N. HDL: high-density lipoprotein. hsCRP: high-sensitivity C-reactive protein. Similar results were seen for other lipids and cardiovascular biomarkers.

**Figure 5–31 Change from baseline in HDL-cholesterol (top) and hsCRP (bottom) by weight-change category: Trial 1839**





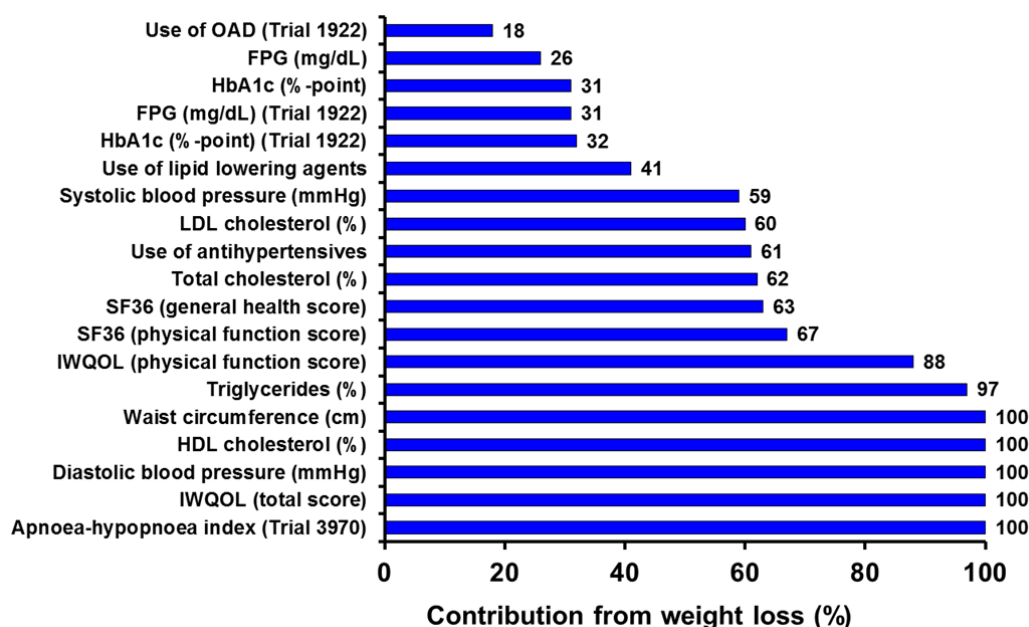
Data are observed means with standard error bars for the full analysis set with last observation carried forward imputation. N: Number of patients in the full analysis set; n: number of patients contributing to the analysis. Percentages are based on the total N. SF-36: 36-item Short-Form health status survey.

**Figure 5–32 Change from baseline in SF-36 overall physical health score by weight-change category: Trial 1839**

#### 5.4.11.3 Direct and indirect effects of treatment

Liraglutide 3.0 mg is believed to mediate its effects through weight-loss dependent and weight-loss independent mechanisms. In an attempt to better understand and quantify the relative contribution of weight loss on key secondary efficacy endpoints, a *post hoc* mediator analysis was performed, based on assessments of change in body weight and the secondary endpoints at the end of treatment. The pre-specified analysis of the endpoints was expanded to include weight loss as a covariate in the model. While the mediator analysis cannot be conclusive with respect to a causal relationship between weight loss and effects on secondary endpoints, its assumptions rely on such a relationship. The analysis has its limitations, including the fact that weight loss is a post-randomization observation, and the results shown below should therefore be interpreted with caution.

The results of the analysis are illustrated by [Figure 5–33](#) below, which ranks the effects of liraglutide on secondary endpoints at end-of-treatment by the relative contribution of weight loss. A rank of 100% indicates that all of the effect may be mediated by weight loss (e.g., the effect on AHI), and lower ranks suggest that weight loss has a lesser contribution. For example, a rank of 31% for FPG indicates that the treatment effect is likely to be predominantly, but not entirely, mediated via direct effects of liraglutide.



Results are from trial 1839, unless otherwise indicated.

Data are for the full analysis set with the last observation carried forward for liraglutide 3.0 mg vs. placebo. Results are based on the original statistical model used for each endpoint with the last observation carried forward including relative change in body weight at end of trial (56 weeks for 1839 and 1922, 32 weeks for 3970) as an additional covariate. The range for the adjusted mediator estimate is restricted to between 0 and 100%.

FPG: fasting plasma glucose. HDL: high-density lipoprotein cholesterol. IWQoL-Lite: Impact of Weight on Quality of Life-Lite. LDL: low-density lipoprotein cholesterol. SF-36: 36-item Short-Form health status survey.

**Figure 5–33 Mediator analysis of secondary endpoints: Trial 1839**

Overall, results of the above analyses demonstrate the relationship between liraglutide-induced weight loss and effects on secondary endpoints, with greater weight loss leading to greater benefits on weight-related co-morbidities and health-related quality of life measures. Based on results of the above analysis, liraglutide mediates its effects on secondary efficacy endpoints through weight-loss dependent (indirect) and weight loss independent (direct) mechanisms.

## 5.5 Efficacy conclusions

Treatment with liraglutide 3.0 mg, as adjunct to diet and exercise, resulted in significantly greater weight loss than diet and exercise alone in obese and overweight patients with at least one weight-related co-morbidity, including patients with T2DM and OSA. Liraglutide 3.0 mg met the 3 pre-specified mean and categorical weight-loss endpoints in each of the individual trials. In each trial, more than 35% of patients in the group assigned to liraglutide 3.0 mg achieved the 5% weight loss benchmark set forth in the FDA guidance (the proportion across trials was 46 to 78%),<sup>37</sup> and the proportion achieving the benchmark was more than twice that in the group assigned to diet and exercise alone (which ranged from 13.5 to 30% across trials). In the largest trial in the clinical



development program, trial 1839, as well as in the weight maintenance trial, 1923, and the phase 2 dose-finding trial, 1807, the difference in mean weight loss between the liraglutide 3.0 mg and placebo-treated groups was at least 5 percent and statistically significant. Among all the demographic sub-populations evaluated (categorized by sex, age, race/ethnicity, BMI and glycemic status), liraglutide 3.0 mg had greater efficacy for weight loss than diet and exercise alone. All the sub-populations achieved a minimum 5% weight loss from baseline and met the categorical weight loss criteria stipulated in the FDA weight management guidance.<sup>37</sup> Weight loss was maintained in each of the trials with a duration of at least 56 weeks, as long as patients remained on treatment with liraglutide 3.0 mg, and for up to 2 years based on completers of the 2-year extension of trial 1807.

Consistent with its known glucose-dependent effects, liraglutide 3.0 mg, as compared with diet and exercise alone, caused statistically significant and clinically meaningful improvements in glycemic control in trial 1922 (patients with T2DM), in terms of reductions in HbA<sub>1c</sub>, FPG and postprandial glycemia, greater numbers of patients achieving HbA<sub>1c</sub> targets, and reduced use of concomitant medications for the treatment of diabetes. As expected, similar though lesser improvements were seen in patients without T2DM in the other trials. Consequently, in patients with pre-diabetes at screening in trial 1839, a greater proportion of those treated with liraglutide 3.0 mg compared with placebo no longer had pre-diabetes after 56 weeks, and fewer of those without pre-diabetes at screening in the liraglutide group compared with the placebo group had developed pre-diabetes. These overall improvements in glycemic control with liraglutide 3.0 mg could be attributed to direct effects of the drug as well as weight loss dependent effects.

Liraglutide-associated weight loss was also associated with changes in cardiovascular risk markers such as reduction in waist circumference, systolic and diastolic blood pressure, improvements in triglycerides, LDL, VLDL, HDL and total cholesterol, free fatty acids and reduced use of concomitant medications for the treatment of hypertension or dyslipidemia, improvements in cardiovascular biomarkers such as hsCRP and PAI-1, and in the severity of OSA. The significant effects in trial 1839 were mirrored by significant effects or favorable trends in each of the other trials.

Finally, liraglutide 3.0 mg was associated with clinically meaningful improvements in quality of life, with statistically significant increases in the IWQoL-Lite total scores in each of the trials in which the questionnaire was used. The improvement in IWQoL-Lite scores was mainly driven by improvements in physical function. Significant increases in overall physical and mental health domains of the SF-36 questionnaire were also observed in trial 1839. Quality of life generally improved with weight loss and the effect was enhanced with the greater weight loss achieved with liraglutide 3.0 mg treatment.

The beneficial effects observed with liraglutide on secondary endpoints consistently were related to the amount of body weight lost. Accordingly, effects on many endpoints, notably lipids, glycemic control and quality of life, were greatest with liraglutide 3.0 mg as compared with lower doses, both

in patients with T2DM as well as in those without T2DM, supporting liraglutide 3.0 mg as the optimally effective dose.

## 6 Clinical Safety

### Summary

- Over 3,000 patients were exposed to liraglutide 3.0 mg and over 1,900 patients to placebo for up to one year in the weight management clinical development program which met the criteria for exposure in the FDA guidance.<sup>37</sup> Nine hundred (900) patients were exposed to liraglutide 3.0 mg for at least two years in an extension of trial 1839. The clinical development program is in addition to more than 3.3 million patient years of exposure worldwide with Victoza<sup>®</sup> for T2DM.
- Consistent with the pharmacodynamic effects of a GLP-1 receptor agonist, the most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders, particularly at the start of treatment.
- More patients reported gallbladder-related adverse events with liraglutide 3.0 mg (2.3%) than with placebo (0.9%). Gallstone disease occurred more frequently in patients who lost more than the mean weight loss for the liraglutide-treated cohort. The incidence of gallbladder-related SAE appeared to diminish over time based on reports in the ongoing extension of trial 1839 where presumably no further substantial weight loss is observed.
- The incidence of pancreatitis was low but higher in individuals treated with liraglutide than placebo (0.4% vs. <0.1%, respectively, for liraglutide 3.0 mg vs. placebo treated patients) but was consistent with that observed with liraglutide (Victoza<sup>®</sup>) in T2DM. The risk of pancreatitis appeared to be associated with increased risk of gallstone disease. Observed pancreatitis events were generally mild and uncomplicated, none was necrotizing or hemorrhagic. All patients recovered.
- Consistent with other GLP-1 receptor agonists, mean resting heart rate increased after initiation with liraglutide, peaked after approximately 6 weeks, and gradually declined thereafter. The increase was in line with that previously observed with Victoza<sup>®</sup> in T2DM. Prespecified MACE meta-analysis provided no evidence of an excess cardiovascular risk with liraglutide, including liraglutide 3.0 mg. The hazard ratios and 95% confidence interval were 0.40 [0.16; 1.01] for total liraglutide vs total comparator, and 0.33 [0.12; 0.90] for liraglutide 3.0 mg vs placebo, respectively.
- The overall risk of neoplasms and cancer in the weight management trials was low and balanced between treatment groups but with a numerical excess of infrequent cases of breast cancer/carcinoma in situ in female patients (0.59% vs 0.23%, odds ratio: 2.56 [0.71; 13.91]) and benign colon adenomas (0.52% vs 0.22%, 2.39 [0.78; 9.76]), mainly in male patients, treated with liraglutide 3.0 mg. Neither non-clinical, clinical trial nor post-marketing experience with liraglutide in T2DM, or any of the other marketed GLP-1 receptor agonists, have indicated similar imbalances.

- More pregnancies resulted in spontaneous abortions with liraglutide (25.6%) than with placebo (10.0%). A similar proportion of pregnant women gave birth to healthy children (46.2% and 35.0% of pregnancies for liraglutide and placebo, respectively). As with other weight loss medicines, the proposed labeling will include a pregnancy category X, informing prescribers that liraglutide 3.0 mg should not be used during pregnancy or by women who intend to become pregnant.
- There was no signal of specific hepatocellular function abnormalities, impairment of neuropsychiatric function, or other safety parameters.

## 6.1 Safety methodology

The safety evaluation is primarily based on pooled data up to 56 weeks from the placebo-controlled phase 2 and 3 clinical trials in the weight management program (trials 1807, 1839, 1923, 1922 and 3970: the weight management pool) ([Table 6–1](#)) with a cut-off date of July 2, 2013. These trials were conducted in an overweight and obese patient population (mean BMI across phase 3 trials:  $38.0 \pm 6.5 \text{ kg/m}^2$ ) expected to be representative of those intended to be treated with liraglutide 3.0 mg. Pooling of safety data across these 5 trials was considered appropriate due to the overall consistency in safety results seen in the individual trials, and in order to increase the likelihood of detecting potential treatment differences and smaller signals in specific safety areas with low numbers of events. In addition, the general safety data from the pooled phase 2 and phase 3 trials from up to 56 weeks has been supplemented by additional exposure data derived from the 120-Day Safety Update as described in [Section 6.1.1](#).

Additional supplementary adverse event data has been included from randomized, controlled phase 2 and 3 clinical trials across the type 2 diabetes mellitus (T2DM) development programs in which liraglutide, at doses up to 1.8 mg, was included as a treatment arm ([Table 6–1](#)). The baseline demographics, background diabetes treatments, and randomized treatment for the T2DM programs are provided in [Appendix Tables 6-1 to 6-3](#). Most T2DM trials used 2:1 randomization. Data from these trials are presented as supportive information for safety areas of interest. For the assessment of neoplasms, data will be included from all trials, including 3 trials that were either uncontrolled (all patients on liraglutide throughout the trial period) or included an uncontrolled trial extension where patients on comparator were shifted to liraglutide in the extension. The neoplasm rates are presented as ‘patient years at risk’ or PYR. PYR is calculated based on “time at risk” which means until the last record of the individual patient prior to database lock for each individual trial, including extension and observational follow-up periods. Rates include treatment-emergent and non-treatment-emergent events.

A primary pre-specified meta-analysis for the evaluation of Major Adverse Cardiovascular Events (MACE) was prepared for the weight management program. A supportive secondary meta-analysis of MACE based on data from all controlled phase 2 and 3 trials with liraglutide (weight

management or T2DM programs) was also prepared as part of the safety evaluation. MACE is discussed further in Section [6.3.4.6](#).

Novo Nordisk has an ongoing cardiovascular outcome trial (LEADER<sup>®</sup>) as a post-marketing requirement for liraglutide in T2DM. The trial is fully enrolled with 9,340 patients<sup>53</sup> and is scheduled to report in the first half of 2016. Further details of the cardiovascular outcome trial are presented in Section [6.3.4.7](#).

Post-marketing data for Victoza<sup>®</sup> (at doses up to liraglutide 1.8 mg in T2DM), including data from an ongoing claims database study, were utilized where additional information on liraglutide exposure was deemed relevant. The estimated number of patient years of exposure (PYE) from post-marketing experience as of June 30, 2014 is greater than 3.3 million patient years.

**Table 6–1 Overview of safety pools**

|   | Duration    | Trials Included                      | Patients Exposed to All Doses of Liraglutide | Patients Exposed to Placebo/Comparator |
|---|-------------|--------------------------------------|--|--|
| Liraglutide 3.0 mg Weight Management Pool (NDA)                         | 32–56 weeks | 1 Phase 2 Trial<br>4 Phase 3 Trials  | 3872 patients<br>3373 PYE <sup>2</sup>       | 1941 patients<br>1601 PYE              |
| Liraglutide in Type 2 Diabetes Mellitus Programs                        | 2–104 weeks | 24 Phase 2 and 3 Trials <sup>1</sup> | 7037 patients<br>5072 PYE                    | 3677 patients*<br>2445 PYE             |
| MACE Analysis (Weight Management and Type 2 Diabetes Mellitus Programs) | 2–104 weeks | 27 Phase 2 and 3 Trials              | 9383 patients<br>8312 PYE                    | 4784 patients<br>4040 PYE              |

<sup>1</sup> Includes data from controlled trials where liraglutide was included in at least one treatment arm.

<sup>2</sup> PYE: patient years of exposure

\* List of comparators used in the liraglutide in type 2 diabetes program is provided in [Appendix Table 6-3](#).

The safety evaluation is primarily based on the safety analysis set, which includes patients receiving at least one dose of the investigational product or comparators. Patients in the safety set contribute to the evaluation “as treated”.

In tables below, safety data from the weight management pool will be included from:

- main treatment period: includes treatment-emergent events belonging to the main treatment period of each trial. The main treatment period of trial 1807 is 52-weeks for this purpose. Treatment-emergent is defined as having onset up to 14 days after last treatment dose (except in the phase 2 dose-finding trial 1807, where treatment-emergent was defined as onset up to 7 days after last treatment dose). TEAEs also include AEs with onset before first dose but with an increase in severity during the treatment period.

- re-randomized period: includes treatment emergent events that occurred during the 12-week re-randomized period of trial 1839 (only patients without pre-diabetes at baseline were re-randomized). For all event types except MACE, pancreatitis and neoplasms, events in the re-randomized period are allocated to the actual treatment at the time of the event or to the last treatment received if event occurred in the 14-day post-treatment window. Patients who switched to placebo from liraglutide in the re-randomized period will be referred to as liraglutide/placebo patients. For MACE, events will be censored at 30 days after last drug date (i.e., events occurring within the first 30 days after switching to placebo will be counted as 'liraglutide'). For pancreatitis and neoplasms, to be conservative, any event occurring after re-randomization to placebo will be counted as 'liraglutide'. Event rates will be presented as events per 100 Patient Years at Risk [PYR], where risk time is defined as the time between first drug date and last contact.
- withdrawn patients: includes non-treatment emergent adverse events reported by patients more than 14 days (7 days for trial 1807) after treatment is discontinued permanently or if a patient is withdrawn during the treatment period (early discontinuation patients). In trials 1922 and 1839, patients who withdrew prematurely during the 1-year treatment period were to attend a follow-up visit at week 56 for measurement of bodyweight and reporting of AEs. Approximately 30% of early withdrawn patients from each treatment group attended this visit (liraglutide 3.0 mg: 238 of 790 patients; total liraglutide: 250 of 836 patients; placebo: 133 of 513 patients). Consistent with the conservative approach described above, all pancreatitis and neoplasm events reported by patients who had withdrawn from treatment prematurely but subsequently made contact to Novo Nordisk are included in the counts and rates presented in the pancreatitis and neoplasm sections.
- In trials 1839, 1922 and 1923, a 12-week follow-up period was included after the 56-week treatment period, to assess the effects of drug cessation on appetite, weight control, and possible withdrawal side-effects. In trials 1922 and 1923 patients were off-treatment during the follow-up period. Emphasis was put on the first two weeks after completing the 1-year treatment period in order to specifically address any rebound effects immediately upon drug discontinuation. Consistent with the conservative approach described above, all pancreatitis and neoplasms events reported by patients during off-treatment follow-up periods are included in the counts and rates presented in the pancreatitis and neoplasm sections.

### 6.1.1 120-Day Safety Update

A 120-Day Safety Update was submitted in April 2014 and included data as of November 11, 2013 from the ongoing extension of trial 1839. The extension was pre-planned and patients with pre-diabetes at randomization gave consent at enrolment; investigators and patients remained blinded to treatment. The report included updated information on deaths, SAEs, AEs leading to withdrawal, AEs subjected to prospective event adjudication, updated MACE meta-analysis with adjudicated MACEs from the ongoing trial 1839-ext and pregnancies. For AEs of special interest (deaths,

gallbladder SAE, pancreatitis, neoplasms, MACE, pregnancies), data from the 120-Day Safety Update will be presented. For a description of exposure in the 120-Day Safety Update, please refer to Section [6.1.4.2](#).

In subsequent presentation of data, “120-Day Safety Update” will be a combination of data from the NDA together with data from the 120-Day Safety Update.

### **6.1.2 Definition of adverse events**

An adverse event (AE) was defined as any undesirable medical event occurring to a patient in the clinical trial, whether or not related to the trial products.

A serious adverse event (SAE) was defined as an experience that at any dose resulted in any of the following outcomes: death, a life-threatening experience, an in-patient hospitalization or prolongation of existing hospitalization, 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 hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All hypoglycemic episodes were to be reported as AEs in the weight management trials. However, hypoglycemic episodes are presented separately from all other AEs as there were differences in the reporting of hypoglycemia for patients with or without T2DM. Details of how hypoglycemic episodes were identified and reported in the weight management trials are presented in Section [6.3.6](#).

Pregnancy and the intent to become pregnant were trial exclusion and withdrawal criteria in the liraglutide 3.0 weight management program ([Appendix Tables 1-3 and 1-4](#)). Accordingly, pregnancy was given particular attention in the clinical development program as described in Section [6.3.7](#).

#### **6.1.2.1 Medical events of special interest**

From previous experience with the clinical development of Victoza<sup>®</sup> (started in 1999), and safety issues identified during development or post-marketing of other anti-obesity agents, certain event types were given specific attention for safety and identified as medical events of special interest (MESI). MESIs were predefined in the protocol to ensure the collection of relevant and timely information for an in-depth evaluation of these events. MESIs are presented further in Section [6.3](#).

Novo Nordisk applied pre-defined MedDRA search criteria to the AE database to capture all events of potential relevance for the individual areas of medical interest. The search was conducted at adverse event preferred term (PT) level based on the individual PTs, high level terms (HLT), high level group terms (HLGT), system organ class (SOC) and standard MedDRA queries (SMQs) for

cardiovascular disorders, pancreatitis, gallbladder disorders, neoplasms, thyroid disease, acute renal failure, allergic reactions, injection site reactions, psychiatric disorders, medication errors, and suspected transmission of an infectious agent via a trial product. The MedDRA search criterion for these adverse event types is presented in [Appendix Section 5.2](#).

#### 6.1.2.2 Adjudication of medical events of special interest

Selected MESIs were subjected to blinded assessment by an external event adjudication committee (EAC) that performed ongoing adjudication, standardization and assessment of selected events to ensure consistency in the evaluation of the events. The EAC was composed of 3 individual subcommittees that evaluated the events according to their areas of expertise: cardiovascular events, pancreatitis events and events of neoplasms and thyroid disease requiring thyroidectomy.

The adjudication process was managed by an external, independent company (ICON Medical Imaging, Warrington, PA) who managed the collection of relevant source information from the clinical trial sites for adjudicated events and ensured that information was blinded with respect to treatment assignment and anonymized before forwarding it to the Event Adjudication Committee (EAC). AEs that were adjudicated by the EAC were processed through 5 different means:

- All investigator-identified MESIs were sent through ICON for adjudication by the EAC.
- AEs not identified as MESIs by the investigator but identified by Novo Nordisk through pre-defined “preferred term” query search on all reported AEs were sent to ICON, who pre-evaluated the events, and forwarded relevant events to the EAC for adjudication.
- During the review of source data by the EAC, the adjudicator in some cases identified events that had not been reported as an AE by the investigator. Novo Nordisk was notified and the investigator was asked to consider reporting the identified event as an AE.
- Events not already identified by the investigator with increased lipase/amylase and concomitantly reported abdominal pain were sent to ICON, who pre-evaluated the events for potential pancreatitis, and forwarded relevant events to the EAC for adjudication.
- A group of Central ECG readers (external, blinded to treatment) evaluated all scheduled ECGs from trials 1839, 1922, and 3970 for signs of ischemia, rhythm/conduction disorder and any other abnormalities not present at baseline and/or the prior scheduled ECG. If the central ECG reader identified a significant new abnormality indicating ischemia, the ECG was sent to the EAC for evaluation of acute coronary syndrome.

An overview schematic for the selection of medical events of special interest for adjudication is presented in [Appendix Figure 5-1](#).

Trials 1839, 1922, and 3970 included prospective adjudication. Prospective adjudication was not implemented in trial 1923, which was the first of the four phase 3 trials and close to completion at



the time prospective adjudication was implemented in the clinical development program. Therefore, events from trial 1923 were subject to *post hoc* adjudication following similar methodology and process as prospectively adjudicated events. The phase 2 dose-finding trial (trial 1807) was completed prior to the introduction of the adjudication process; however, all potential major adverse cardiovascular events (MACEs) and all fatal cases from trial 1807 were adjudicated *post hoc* as a pre-requisite for inclusion in the pre-planned pooled meta-analyses of MACEs across the liraglutide trials.

### 6.1.3 Recording of adverse events

All AEs either observed by the investigator or reported spontaneously by the patients were to be recorded by the investigator and evaluated. For each AE, the investigator was to classify the AE with respect to severity, relationship to trial product, outcome and action taken due to the AE.

Severity by Novo Nordisk standards was classified as: a) mild if there were no or transient symptoms, or no interference with the patient's daily activities; b) moderate if there were marked symptoms, or moderate interference with the patient's daily activities; or c) severe if there was considerable or unacceptable interference with the patient's daily activities.

### 6.1.4 Exposure

#### 6.1.4.1 Original NDA

Across the five phase 2 and 3 weight management clinical trials, 5,827 patients were randomized and 5,813 patients were exposed to treatment: 3,872 patients to liraglutide and 1,941 patients to placebo ([Table 6-2](#)). Total exposure for all liraglutide doses was 3,373 patient years of exposure (PYE), of which 2,974 PYE (88% of total liraglutide exposure) was with liraglutide 3.0 mg. The number of patients exposed and durations of exposure meet the FDA guidance. Liraglutide exposures at doses lower than 3.0 mg are presented in [Table 6-2](#).

**Table 6-2 Liraglutide exposure in the weight management pool**

|                          | Liraglutide |            |            |            |            | Placebo    |
|--------------------------|-------------|------------|------------|------------|------------|------------|
|                          | 1.2 mg      | 1.8 mg     | 2.4 mg     | 3.0 mg     | Total      |            |
| Number of patients       | 95          | 300        | 93         | 3384       | 3872       | 1941       |
| Total exposure (years)   | 73          | 256        | 70         | 2974       | 3373       | 1601       |
| Patient exposure (years) |             |            |            |            |            |            |
| Mean (SD)                | 0.77 (0.3)  | 0.85 (0.4) | 0.75 (0.3) | 0.88 (0.3) | 0.87 (0.3) | 0.82 (0.3) |
| Median                   | 1.00        | 1.05       | 0.99       | 1.07       | 1.07       | 1.06       |

SD: Standard Deviation.

Liraglutide exposure from the randomized, controlled phase 2 and 3 clinical trials across the T2DM development programs represents an additional 5072 PYE to liraglutide ([Table 6-1](#)).

An overview of exposure in terms of major demographic sub-populations defined by age, sex, BMI, race, and ethnicity, adequately represented the intended weight management target population and all were of sufficient size to allow for statistical analysis of treatment effect ([Appendix Table 1-5](#)). Patients in the age group 18 to 65 years accounted for most (93%) of the exposure to liraglutide 3.0 mg.

#### 6.1.4.2 120-Day Safety Update

A total of 1584 patients (liraglutide 3.0 mg, 1087 patients; placebo, 497 patients) with pre-diabetes at randomization completed the main part of trial 1839 and were eligible to enter into the extension ([Figure 5-4](#)). In the current set of 120-Day Safety Update data, exposure from the ongoing 1839 extension was estimated to be 1115 years for liraglutide 3.0 mg and 494 years for placebo. All patients in the extension of trial 1839 had been exposed to trial product for at least 12 months. A total of 906 patients (83%) with liraglutide 3.0 mg and 386 patients (78%) with placebo have had a total exposure of more than 24 months ([Table 6-3](#)).

**Table 6-3 Exposure by Duration of Treatment: Trial 1839 (through 120-Day Safety Update)**

|                            | ----- Liraglutide 3.0 mg ----- |        | ----- Placebo ----- |        |
|----------------------------|--------------------------------|--------|---------------------|--------|
|                            | N                              | %      | N                   | %      |
| Number of patients         | 1087                           |        | 497                 |        |
| Exposed at least 12 months | 1087                           | (100)  | 497                 | (100)  |
| Exposed at least 18 months | 999                            | (91.9) | 449                 | (90.3) |
| Exposed at least 24 months | 906                            | (83.3) | 386                 | (77.7) |

N: Number of patients, %: Percentages are based on total N.

#### 6.1.5 Patient disposition

The patient disposition in the individual weight management trials is presented in [Section 5.4.5](#). Patient disposition for the phase 3 trials is presented by treatment in [Table 5-8](#), and was comparable across trials. Approximately 70% of patients completed the phase 3 trials: 73% of the liraglutide-treated patients and 67% of the placebo-treated patients.

An overview of reasons for withdrawal in the weight management program is presented in [Table 6-4](#). More patients on liraglutide 3.0 mg than on placebo were withdrawn due to AEs (9.8% vs. 4.2%). However, the percentage of patients withdrawn because of AEs in the liraglutide 3.0 mg group was similar to that in the total liraglutide group, suggesting that there was no dose-dependent increase in the incidence of AE withdrawal for liraglutide treatment. The number of patients withdrawing because of “target dose not tolerated” in the liraglutide 3.0 mg group was not greater than the number of patients withdrawing from the total liraglutide group ([Table 6-4](#)).

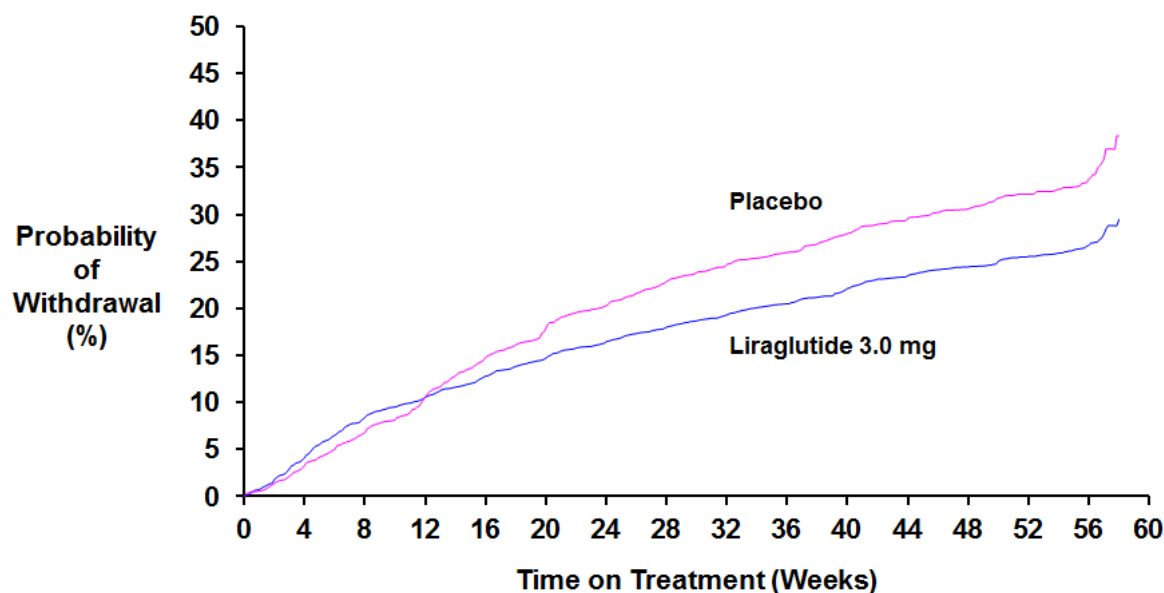
**Table 6–4 Patient Disposition: Phase 2 and 3 Trials (NDA)**

|   | Liraglutide 3.0 mg |         | Total Liraglutide |         | Placebo |         |
|---|--------------------|---------|-------------------|---------|---------|---------|
|   | N                  | (%)     | N                 | (%)     | N       | (%)     |
| Randomized  | 3395               | (100.0) | 3884              | (100.0) | 1943    | (100.0) |
| Exposed   | 3384               | (99.7)  | 3872              | (99.7)  | 1941    | (99.9)  |
| Full analysis set   | 3328               | (98.0)  | 3808              | (98.0)  | 1919    | (98.8)  |
| Safety analysis set   | 3384               | (99.7)  | 3872              | (99.7)  | 1941    | (99.9)  |
| Completer*  | 2471               | (72.8)  | 2809              | (72.3)  | 1291    | (66.4)  |
| Withdrawn   | 924                | (27.2)  | 1075              | (27.7)  | 652     | (33.6)  |
| Adverse event   | 324                | (9.5)   | 366               | (9.4)   | 80      | (4.1)   |
| Ineffective therapy   | 48                 | (1.4)   | 52                | (1.3)   | 88      | (4.5)   |
| Non-compliance with protocol  | 95                 | (2.8)   | 111               | (2.9)   | 64      | (3.3)   |
| Withdrawal criteria**   | 340                | (10.0)  | 371               | (9.6)   | 307     | (15.8)  |
| Withdrawn consent   | 296                | (8.7)   | 319               | (8.2)   | 284     | (14.6)  |
| Target dose not tolerated   | 3                  | (0.1)   | 6                 | (0.2)   | 0       | (0.0)   |
| Pregnancy or pregnancy intent   | 32                 | (0.9)   | 33                | (0.8)   | 14      | (0.7)   |
| Use of insulin, GLP-1RA or DPP4I <sup>1</sup>   | 0                  | (0.0)   | 2                 | (0.1)   | 2       | (0.1)   |
| Unacceptable hyperglycemia <sup>2</sup>   | 5                  | (0.1)   | 7                 | (0.2)   | 9       | (0.5)   |
| Unacceptable hypoglycemia <sup>2</sup>  | 0                  | (0.0)   | 0                 | (0.0)   | 0       | (0.0)   |
| Acute pancreatitis <sup>3</sup>   | 6                  | (0.2)   | 6                 | (0.2)   | 0       | (0.0)   |
| Psych disorder (acc. to INV/MHP opinion) <sup>3</sup>   | 1                  | (0.0)   | 1                 | (0.0)   | 2       | (0.1)   |
| Diagnosis of T2DM <sup>4</sup>  | 1                  | (0.0)   | 1                 | (0.0)   | 0       | (0.0)   |
| Other   | 107                | (3.2)   | 125               | (3.2)   | 101     | (5.2)   |
| Lost to follow-up   | 67                 | (2.0)   | 74                | (1.9)   | 59      | (3.0)   |
| Did not participate in the year-2 ext of Trial 1807   | 10                 | (0.3)   | 50                | (1.3)   | 12      | (0.6)   |
| Adverse event including target dose not tolerated, pancreatitis and psychiatric disorder <sup>5</sup> | 334                | (9.8)   | 379               | (9.8)   | 82      | (4.2)   |
| Withdrawn patients attending the nominal Week 56 end-of-trial visit                                   | 238                | (30.1)  | 250               | (29.9)  | 133     | (25.9)  |

N: Number of patients, %: Proportion of randomized patients, \*: A completer is defined as a patient who completed the treatment period in the individual trials, \*\*: A patient can have more than one withdrawal criterion and be counted more than once in the detailed withdrawal criteria. The table presents the primary reason for withdrawal registered in the CRF. Table is based on trials 1839 (56 week period), 1923 (56 week period), 1922 (56 week period), 3970 (32 weeks), 1807 (52-week period)

1) Trials 1839, 1922 and 3970; 2) trial 1922; 3) trials 1839, 1923, 1922, and 3970; 4) trial 1923; 5) includes specific withdrawal criteria related to AEs of special interest.

During the initial 12 weeks of the trials, there was higher withdrawal caused by AEs for patients treated with liraglutide (Section 6.2.3), largely caused by gastrointestinal AEs during this period. The withdrawal rate from week 12 onward was lower with liraglutide 3.0 mg than with placebo (Figure 6–1). Towards the end of the trials, there was an apparent increase in withdrawal after week 56. However, as most patients had completed the trials prior to week 56, according to protocol, this observation is the consequence of the small denominator after week 56.



**Figure 6–1 Time to discontinuation (weeks) in the weight management pool (NDA)**

## 6.2 Adverse event profile

### 6.2.1 Overview of adverse events

The proportion of patients reporting AEs and the event rate were higher with liraglutide 3.0 mg (91.6%, 681.2 events per 100 PYE) than with placebo (83.6%, 507.1 events per 100 PYE) ([Table 6–5](#)). SAEs were reported for 6.3% of the patients in the liraglutide 3.0 mg group and 4.6% of the patients in the placebo group. Deaths are further discussed in Section [6.2.2.1](#).

The proportions of patients with AEs not recovered or recovering as of the database lock for the individual trials were similar with liraglutide 3.0 mg and placebo. The AEs with an outcome of not recovered reported by the highest proportion of patients with liraglutide 3.0 mg included constipation (3.2% of patients), decreased appetite (1.9% of patients) and arthralgia (1.7% of patients).

**Table 6–5 Treatment emergent adverse events in the weight management pool (NDA)**

|                           | Liraglutide 3.0 mg |        |       |       | Placebo |        |      |       |
|---------------------------|--------------------|--------|-------|-------|---------|--------|------|-------|
|                           | N                  | (%)    | E     | R     | N       | (%)    | E    | R     |
| Number of patients        | 3384               |        |       |       | 1941    |        |      |       |
| Years of exposure         | 2974.3             |        |       |       | 1600.9  |        |      |       |
| Adverse events (AE)       | 3101               | (91.6) | 20260 | 681.2 | 1622    | (83.6) | 8119 | 507.1 |
| SAEs                      | 213                | (6.3)  | 277   | 9.3   | 89      | (4.6)  | 113  | 7.1   |
| Severity                  |                    |        |       |       |         |        |      |       |
| Severe                    | 420                | (12.4) | 627   | 21.1  | 168     | (8.7)  | 233  | 14.6  |
| Moderate                  | 1903               | (56.2) | 5405  | 181.7 | 902     | (46.5) | 2293 | 143.2 |
| Mild                      | 2863               | (84.6) | 14225 | 478.3 | 1472    | (75.8) | 5590 | 349.2 |
| Missing                   | 3                  | (<0.1) | 3     | 0.1   | 2       | (0.1)  | 3    | 0.2   |
| Outcome                   |                    |        |       |       |         |        |      |       |
| Recovered                 | 3027               | (89.5) | 17967 | 604.1 | 1551    | (79.9) | 6767 | 422.7 |
| Recovering                | 137                | (4.0)  | 162   | 5.4   | 82      | (4.2)  | 106  | 6.6   |
| Recovered with sequelae   | 6                  | (0.2)  | 7     | 0.2   | 1       | (<0.1) | 1    | <0.1  |
| Not recovered             | 1137               | (33.6) | 1995  | 67.1  | 630     | (32.5) | 1132 | 70.7  |
| Fatal                     | 1                  | (<0.1) | 2     | <0.1  | 3       | (0.2)  | 3    | 0.2   |
| Unknown                   | 81                 | (2.4)  | 127   | 4.3   | 54      | (2.8)  | 110  | 6.9   |
| AEs leading to withdrawal | 331                | (9.8)  | 500   | 16.8  | 83      | (4.3)  | 116  | 7.2   |

N: Number of patients, %: Percentages are based on total N, E: Number of events, R: Event rate per 100 years of exposure

Treatment emergent adverse events in the main treatment period of each of the individual trials.

Consistent with the pharmacodynamic effects of a GLP-1 receptor agonist, the most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders ([Table 6–6](#)). In addition, decreased appetite, fatigue, and dizziness occurred more frequently with liraglutide than placebo ([Table 6–6](#)) and were often co-reported with gastrointestinal events.

**Table 6–6 Most frequent ( $\geq 5\%$ ) adverse events (preferred terms) in the weight management pool (NDA)**

|                                   | Liraglutide 3.0 mg<br>(N=3384) |      | Placebo<br>(N=1941) |      |
|-----------------------------------|--------------------------------|------|---------------------|------|
|                                   | %                              | R    | %                   | R    |
| Nausea                            | 39.3                           | 65.4 | 13.8                | 20.9 |
| Diarrhea                          | 20.9                           | 34.7 | 9.9                 | 14.9 |
| Constipation                      | 19.4                           | 26.3 | 8.5                 | 11.5 |
| Nasopharyngitis                   | 17.5                           | 27.6 | 19.2                | 30.8 |
| Vomiting                          | 15.7                           | 26.4 | 3.9                 | 5.6  |
| Headache                          | 13.6                           | 21.9 | 12.6                | 21.1 |
| Decreased appetite                | 10.0                           | 12.0 | 2.3                 | 2.9  |
| Dyspepsia                         | 9.6                            | 13.2 | 2.7                 | 3.6  |
| Upper respiratory tract infection | 9.0                            | 12.4 | 9.8                 | 14.8 |
| Fatigue                           | 7.5                            | 9.6  | 4.6                 | 6.1  |
| Back pain                         | 7.1                            | 10.3 | 8.2                 | 11.7 |
| Dizziness                         | 6.9                            | 10.0 | 5.0                 | 6.8  |
| Influenza                         | 6.1                            | 8.4  | 6.3                 | 9.2  |
| Injection hematoma                | 5.5                            | 7.2  | 7.3                 | 10.1 |
| Abdominal pain                    | 5.4                            | 7.6  | 3.1                 | 4.4  |
| Lipase increased                  | 5.3                            | 6.7  | 2.2                 | 3.0  |
| Arthralgia                        | 5.2                            | 6.6  | 5.9                 | 7.9  |
| Abdominal pain upper              | 5.1                            | 7.2  | 2.7                 | 3.8  |
| Sinusitis                         | 4.9                            | 6.2  | 6.4                 | 9.8  |

N: Total number of patients; %: Percentage of patients experiencing at least one event; R: event rate per 100 PYE.  
Please note that AEs of hypoglycemia are not included in this table.

AEs of hypoglycemia were commonly reported in patients with T2DM, especially in those patients taking concomitant sulfonylureas. Due to the differences in how these events were collected and classified in patients with or without T2DM, information about hypoglycemia is presented separately by population and not included in the pooled AE summaries (see Section [6.3.6](#) below).

## 6.2.2 Deaths and other serious adverse events

### 6.2.2.1 Deaths

As of 11 November 2013 (cut-off for 120-Day Safety Update), 6 deaths occurred in the weight management program, three in the liraglutide group and three in the placebo group, despite approximately twice as many patients exposed to liraglutide compared to placebo. Four (4) deaths occurred during the main treatment periods, 1 during follow-up, and 1 in the ongoing 1839 extension ([Table 6–7](#)). The reported fatal events do not differ with respect to cause from what would be expected for the patient population enrolled in these clinical trials, in terms of age, co-morbidities and medical history.



**Table 6–7 Patients with fatal events: all weight management trials (through 120-Day Safety Update)**

| Treatment                 | Age/Sex        | Trial                   | Days of Exposure at Onset | Event Adjudication Committee Cause of Death |
|---------------------------|----------------|-------------------------|---------------------------|---|
| <i>Liraglutide 1.8 mg</i> | 53 years/male  | 1922 (follow-up period) | 391                       | Cardiovascular death                        |
| <i>Liraglutide 3.0 mg</i> | 50 years/male  | 1839                    | 235                       | Cardiovascular death                        |
|                           | 65 years/ male | 1839 (extension period) | 578                       | Cardiovascular death                        |
| <i>Placebo</i>            | 58 years/male  | 1923                    | 136                       | Cardiovascular death                        |
|                           | 51 years/male  | 1839                    | 114                       | Cardiovascular death                        |
|                           | 59 years/male  | 1839                    | 111                       | Non-cardiovascular death                    |

**6.2.2.2 Most frequent serious adverse events**

In the weight management pool, the proportion and rate of patients reporting SAEs was low overall, but was higher in the liraglutide 3.0 mg group (6.3%, 9.3 events per 100 PYE) than in the placebo group (4.6%, 7.1 events per 100 PYE) ([Table 6–5](#)). No dose-response relationship among patients exposed to liraglutide doses 1.2, 1.8, 2.4 and 3.0 mg (in trial 1807 and 1922) was apparent, suggesting no increased risk of SAEs with liraglutide 3.0 mg as compared with lower doses. Of these SAEs, ‘hepatobiliary disorders’ were reported more frequently with liraglutide 3.0 mg than with placebo. The most frequently reported treatment-emergent SAEs with liraglutide 3.0 mg were ‘cholelithiasis’ and ‘cholecystitis acute’ and ‘osteoarthritis’ ([Table 6–8](#)). More details on MESI are provided in [Section 6.3](#).

**Table 6–8 Most frequent treatment emergent SAEs (≥0.2% of patients): weight management pool (NDA)**

|                                 | Liraglutide 3.0 mg |      |      | Placebo |     |     |
|---------------------------------|--------------------|------|------|---------|-----|-----|
|                                 | N                  | %    | R    | N       | %   | R   |
| Cholelithiasis                  | 27                 | 0.8  | 0.9  | 5       | 0.3 | 0.3 |
| Cholecystitis acute             | 14                 | 0.4  | 0.5  | 0       | 0   | 0   |
| Osteoarthritis                  | 7                  | 0.2  | 0.3  | 0       | 0   | 0   |
| Cellulitis                      | 1                  | <0.1 | <0.1 | 4       | 0.2 | 0.2 |
| Chest pain                      | 0                  | 0    | 0    | 4       | 0.2 | 0.2 |
| Gastroesophageal reflux disease | 0                  | 0    | 0    | 4       | 0.2 | 0.2 |

N: number of patients; %: Percentage of patients, R: event rate per 100 patient years of exposure.

In the 120-Day Safety Update, the proportion of patients with SAEs and the rates of SAEs were comparable between the ongoing extension of 1839 and the main part of trial 1839.

### 6.2.3 Adverse events leading to withdrawal of treatment

In the weight management pool, the proportion of patients withdrawing from the trial due to AEs was higher with liraglutide 3.0 mg (9.8%) than with placebo (4.3%) (Table 6–9). As shown in Figure 6–2, the difference between groups was seen only in the initial 8 weeks of treatment, after which AE-related withdrawal rates were similar. As expected with a GLP-1 receptor agonist, the higher proportion of AE withdrawals with liraglutide was mainly attributable to more withdrawals related to gastrointestinal disorders in this group (e.g., nausea, vomiting, diarrhea) occurring during the initiation/titration period (Table 6–9 and Figure 6–3); this pattern was also seen across the individual trials. AEs leading to withdrawal in other system organ classes were of relatively low frequency (<1%), including protocol-specified withdrawals for acute pancreatitis (0.2% for liraglutide 3.0 mg; none for placebo) and psychiatric disorders (<0.1% for liraglutide 3.0 mg; 0.1% for placebo). No patients with T2DM were withdrawn due to unacceptable hypoglycemia during the T2DM trial (1922).

**Table 6–9 Most frequent (≥1%) TEAEs (preferred terms) leading to withdrawal: weight management pool (NDA)**

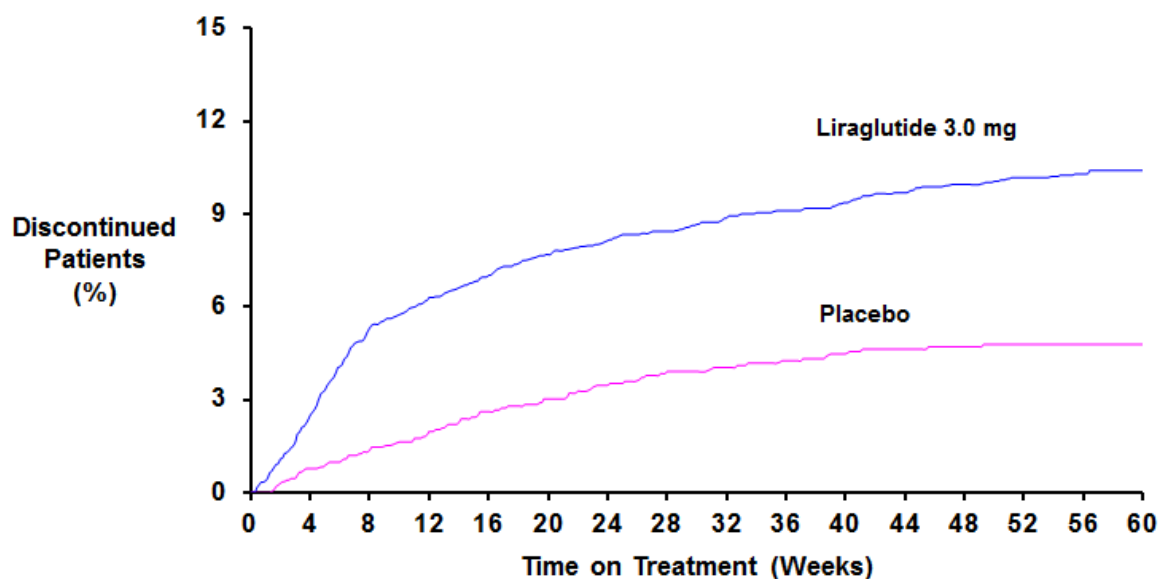
|                                      | Liraglutide 3.0 mg |       |     |      | Placebo |        |     |      |
|--------------------------------------|--------------------|-------|-----|------|---------|--------|-----|------|
|                                      | N                  | (%)   | E   | R    | N       | (%)    | E   | R    |
| Number of patients                   | 3384               |       |     |      | 1941    |        |     |      |
| Years of exposure                    | 2974.3             |       |     |      | 1600.9  |        |     |      |
| Adverse events leading to withdrawal | 331                | (9.8) | 500 | 16.8 | 83      | (4.3)  | 116 | 7.2  |
| Nausea                               | 98                 | (2.9) | 98  | 3.3  | 4       | (0.2)  | 4   | 0.2  |
| Vomiting                             | 58                 | (1.7) | 58  | 2.0  | 1       | (<0.1) | 1   | <0.1 |
| Diarrhea                             | 49                 | (1.4) | 51  | 1.7  | 0       | (0.0)  | 0   | 0.0  |

N: Number of patients, %: Percentages are based on total N, E: Number of events; R: Event rate per 100 years of exposure.

Treatment emergent adverse events in the main treatment period of each of the individual trials.

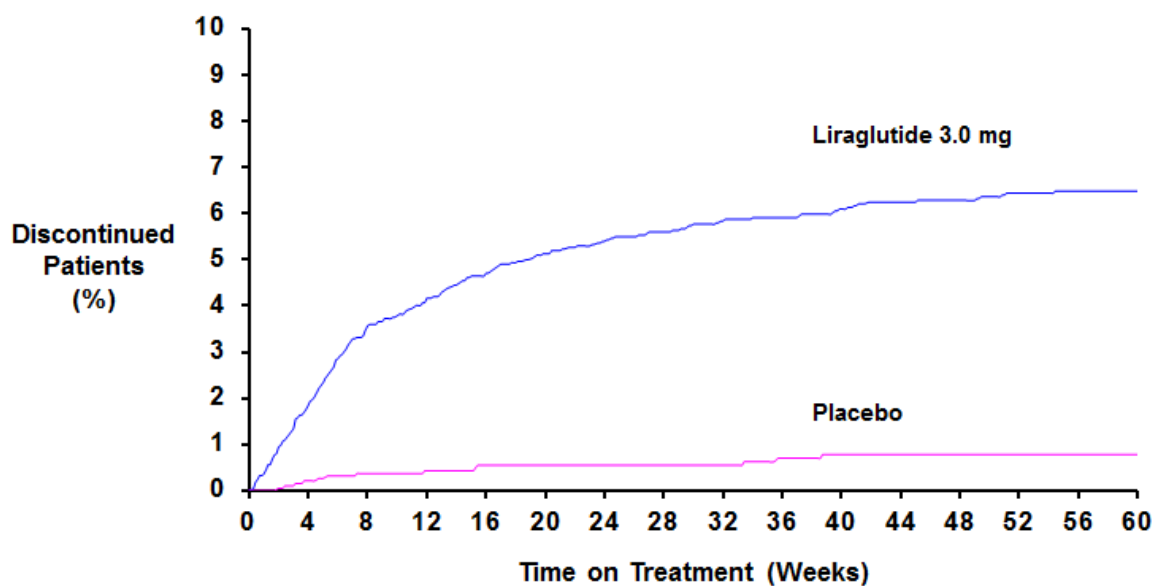
Based on the 120-Day Safety Update, the proportion of patients withdrawn due to AEs in the extension of trial 1839 were low (liraglutide 3.0 mg: 23 patients [2.1%]; placebo: 7 patients [1.4%]) compared to the main part of trial 1839 (liraglutide 3.0 mg 9.8%; placebo 3.8%), and reasons for withdrawal similar.





Duration of trials 3970 and 1807 (52-week period) was 32 weeks and 52 weeks, respectively. Includes withdrawal criteria for pancreatitis and psychiatric disorders.

**Figure 6–2 Time to discontinuation (weeks) due to adverse events: weight management pool (NDA)**



Duration of trials 3970 and 1807-ext was 32 and 52 weeks, respectively.

**Figure 6–3 Time to discontinuation due to 'gastrointestinal disorders' (SOC): weight management pool (NDA)**

## 6.2.4 Adverse Events in sub-populations

The potential impact of various demographic parameters (intrinsic factors) on the AE profile of liraglutide 3.0 mg for weight management was investigated based on pooled data from the phase 2 and 3 clinical trials in the weight management development program. Intrinsic factors included: baseline sex, age, race, ethnicity, region, BMI, glycemic status, lower and highest ALT/AST quartiles, renal function (estimated creatinine clearance), Edmonton Obesity Staging System (EOSS) category, time on treatment and weight loss at end of trial (based on LOCF). Furthermore, *post hoc* analyses of AEs, SAEs and AEs leading to withdrawal were also made by baseline bodyweight quartile and sex, to account for lower mean body weight and higher plasma exposure to liraglutide in females (Section [4.3.1](#)), as compared with males.

Overall, the proportions of patients with AEs, SAEs, and the proportions of patients withdrawing due to AEs were similar between men and women with liraglutide 3.0 mg, while fewer women than men in the placebo group experienced SAEs and AEs leading to withdrawal. In both treatment groups, more women than men reported more mild, moderate and severe AEs. No trends in AE reporting were seen in the proportions of patients with AEs with lower (or higher) body weight in either men or women. The AE pattern was also generally similar, with minor differences across individual types of AE.

Further analyses investigated the relationship between plasma concentration of liraglutide (referred to as ‘exposure’, based on model-derived AUC, Section [4.3.1](#)) in the entire dose range tested in phase 2 and 3 trials in the weight management program and the occurrence of nausea, vomiting (1.2-3.0 mg) and hypoglycemia (only patients with T2DM, 1.8 mg-3.0 mg). These analyses indicated a relationship between plasma exposure and ‘any’ nausea, and a less clear relationship for vomiting with no clear relationship for moderate and severe events, and none for hypoglycemia. Multivariate analyses accounting for trial, baseline body weight and sex suggested that part of the relationship with exposure could be explained by sex. Further, the relationship was stronger in the trials which included multiple doses (trials 1807, 1922), suggesting that the relationship is stronger at the lower doses, and levels off at higher doses.

The other intrinsic factors investigated did not lead to clinically meaningful differences between the treatment groups.

## 6.3 Medical events of special interest

The identification and handling of medical events of special interest is presented in Section [6.1.2.1](#).

### 6.3.1 Gallbladder-related AEs

#### 6.3.1.1 Background

Gallstones are common in the general population; 10% to 20% of Americans will develop gallstones at some time.<sup>125</sup> The majority (up to 80%) of people with gallstones are asymptomatic

and will never experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis.<sup>126</sup>

Multiple case-control studies, comparing patients with gallstones versus those without, have shown that gallstone formation is multifactorial. Some features, such as ethnicity, genetics, advancing age and female sex cannot be modified, whereas others (e.g., diet, physical activity, rapid weight loss and obesity) are modifiable.<sup>42</sup> Women are almost twice as likely as men to form gallstones; however, the difference between men and women diminishes after women go through menopause.<sup>42</sup> Female sex hormones are major contributors to the gender differences with parity, oral contraceptive use, and estrogen replacement therapy being established risk factors for cholesterol gallstone formation.<sup>127-129</sup>

Obesity, particularly central obesity, is a well-established risk factor for gallstone disease.<sup>42,43,130,131</sup> At least 25% of morbidly obese individuals undergoing bariatric surgery have evidence of gallstone disease.<sup>44,45</sup> The age-adjusted relative risk is up to 4 times greater in obese women as compared to obese men<sup>45</sup>; the 2-year incidences of cholelithiasis, cholecystitis, and cholecystectomy in the obese control (i.e., non-operated) group of the longitudinal SOS Intervention Study were 1.2%, 0.7%, and 0.7% (males) and 4.5%, 2.5%, and 2.3% (females), respectively.<sup>45</sup>

Low calorie diets and/or bariatric surgery with rapid weight loss are associated with gallstone development in 30 to 71% of individuals.<sup>43</sup> Weight loss-associated gallstones are typically asymptomatic; only 7% to 16% develop symptoms, best predicted by a post-operative weight loss exceeding 25% of the body weight.<sup>44-46</sup> Proposed mechanisms underlying gallstone formation during weight reduction include bile stasis due to reduced caloric intake, increased biliary cholesterol saturation secondary to increased cholesterol mobilization, and increased nucleation due to changes in bile arachidonate and glycoprotein concentrations.<sup>132,133</sup> Even less extreme weight fluctuations create a risk for stone formation,<sup>47</sup> as does a history of dieting.<sup>48</sup>

Little is known about acute or sustained GLP-1 receptor activation on gallbladder motility in humans. A recent publication examined gallbladder emptying in fasting healthy individuals without a previous history of gallbladder dysfunction in a randomized, double-blind crossover study, with acute single-dose administration of exenatide 10 µg or placebo, with or without cholecystokinin infusion to stimulate gallbladder emptying. Exenatide significantly reduced gallbladder emptying, with no change in the diameter of the pancreatic or bile ducts.<sup>134</sup> The reduction was of lesser magnitude than that reported with exogenous infusion of somatostatin, a potent inhibitor of gallbladder motility, when somatostatin was infused at doses mimicking endogenous postprandial concentrations.<sup>135</sup> It is unknown whether exenatide mediates the effect directly, via stimulation of the GLP-1 receptor, or indirectly. No such study has been conducted with liraglutide. A mechanistic study on the effect of liraglutide on gallbladder emptying is proposed in Section [7.5](#).

While GLP-1 receptor agonists including liraglutide have not been directly associated with increased risk of gallbladder-related AEs in clinical use for T2DM, an increased risk of gallstone

formation, induced by weight loss, has been proposed<sup>136</sup> as a potential mediator of rare cases of acute pancreatitis cases reported in patients with T2DM using GLP-1 receptor agonists.

### 6.3.1.2 Gallbladder-related AEs in the weight management program

The proportion of patients reporting gallbladder-related AEs was higher with liraglutide 3.0 mg (2.3%, 91 events) than with placebo (0.9%, 20 events) (Table 6–10). The imbalance was mainly driven by reports of cholelithiasis and cholecystitis ('cholelithiasis': 1.5% vs. 0.5%; 'cholecystitis acute': 0.4% vs. <0.1%; 'cholecystitis': 0.2% vs. <0.1%, respectively, for liraglutide 3.0 mg vs. placebo). This was also reflected by a higher proportion of patients with gallbladder-related SAEs with liraglutide 3.0 mg (1.2%) than with placebo (0.3%). None of these events were fatal. The MedDRA preferred terms used to pool gallbladder-related AEs are presented in Appendix Section 5.2.

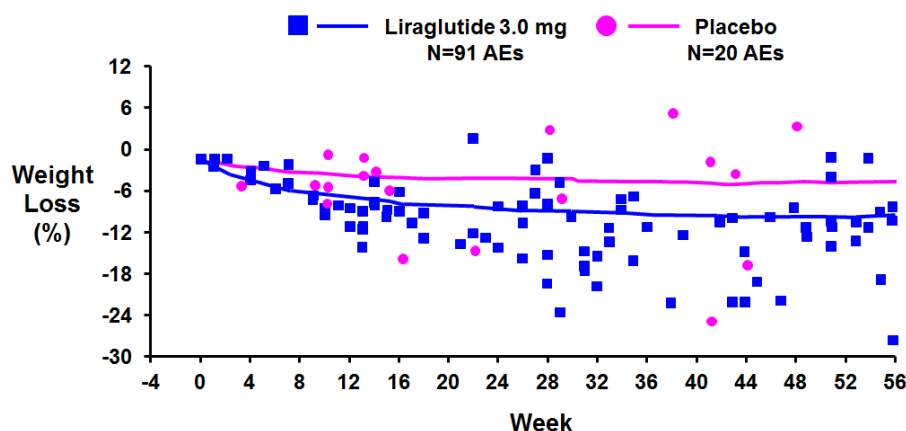
**Table 6–10 Gallbladder-related AEs identified by MedDRA search: weight management pool (NDA)**

|                                      | Liraglutide 3.0 mg |        |    |        | Placebo |        |    |      |
|--------------------------------------|--------------------|--------|----|--------|---------|--------|----|------|
|                                      | N                  | (%)    | E  | R      | N       | (%)    | E  | R    |
| Number of patients                   | 3384               |        |    |        | 1941    |        |    |      |
| Years of exposure                    | 2974.3             |        |    |        | 1600.9  |        |    |      |
| Total                                | 79                 | (2.3)  | 91 | 3.1    | 17      | (0.9)  | 20 | 1.2  |
| Gastrointestinal disorders           | 2                  | (<0.1) | 2  | (<0.1) | 0       | (0.0)  | 0  | 0.0  |
| Gastrointestinal signs and symptoms  | 2                  | (<0.1) | 2  | (<0.1) | 0       | (0.0)  | 0  | 0.0  |
| Abnormal feces                       | 1                  | (<0.1) | 1  | (<0.1) | 0       | (0.0)  | 0  | 0.0  |
| Feces pale                           | 1                  | (<0.1) | 1  | (<0.1) | 0       | (0.0)  | 0  | 0.0  |
| Hepatobiliary disorders              | 74                 | (2.2)  | 85 | 2.9    | 16      | (0.8)  | 18 | 1.1  |
| Gallbladder disorders                | 70                 | (2.1)  | 78 | 2.6    | 13      | (0.7)  | 15 | 0.9  |
| Cholelithiasis                       | 51                 | (1.5)  | 54 | 1.8    | 10      | (0.5)  | 11 | 0.7  |
| Cholecystitis acute                  | 14                 | (0.4)  | 14 | 0.5    | 2       | (0.1)  | 2  | 0.1  |
| Cholecystitis                        | 7                  | (0.2)  | 7  | 0.2    | 1       | (<0.1) | 1  | <0.1 |
| Gallbladder disorder                 | 2                  | (<0.1) | 2  | <0.1   | 0       | (0.0)  | 0  | 0.0  |
| Cholecystitis chronic                | 1                  | (<0.1) | 1  | <0.1   | 1       | (<0.1) | 1  | <0.1 |
| Bile duct disorders                  | 6                  | (0.2)  | 6  | (0.2)  | 3       | (0.2)  | 3  | 0.2  |
| Biliary colic                        | 3                  | (<0.1) | 3  | (0.1)  | 3       | (0.2)  | 3  | 0.2  |
| Bile duct stone                      | 2                  | (<0.1) | 2  | <0.1   | 0       | (0.0)  | 0  | 0.0  |
| Bile duct obstruction                | 1                  | (<0.1) | 1  | <0.1   | 0       | (0.0)  | 0  | 0.0  |
| Hepatic and hepatobiliary disorders  | 1                  | (<0.1) | 1  | <0.1   | 0       | (0.0)  | 0  | 0.0  |
| Hyperbilirubinemia                   | 1                  | (<0.1) | 1  | <0.1   | 0       | (0.0)  | 0  | 0.0  |
| Investigations                       | 4                  | (0.1)  | 4  | 0.1    | 2       | (0.1)  | 2  | 0.1  |
| Enzyme investigations NEC            | 3                  | (<0.1) | 3  | 0.1    | 1       | (<0.1) | 1  | <0.1 |
| Blood alkaline phosphatase increased | 3                  | (<0.1) | 3  | 0.1    | 1       | (<0.1) | 1  | <0.1 |
| Hepatobiliary investigations         | 1                  | (<0.1) | 1  | <0.1   | 1       | (<0.1) | 1  | <0.1 |
| Blood bilirubin increased            | 1                  | (<0.1) | 1  | <0.1   | 1       | (<0.1) | 1  | <0.1 |

N: Number of patients, %: Percentages are based on total N, E: Number of events; R: Event rate per 100 years of exposure

Treatment emergent adverse events in the main treatment period of each of the individual trials.

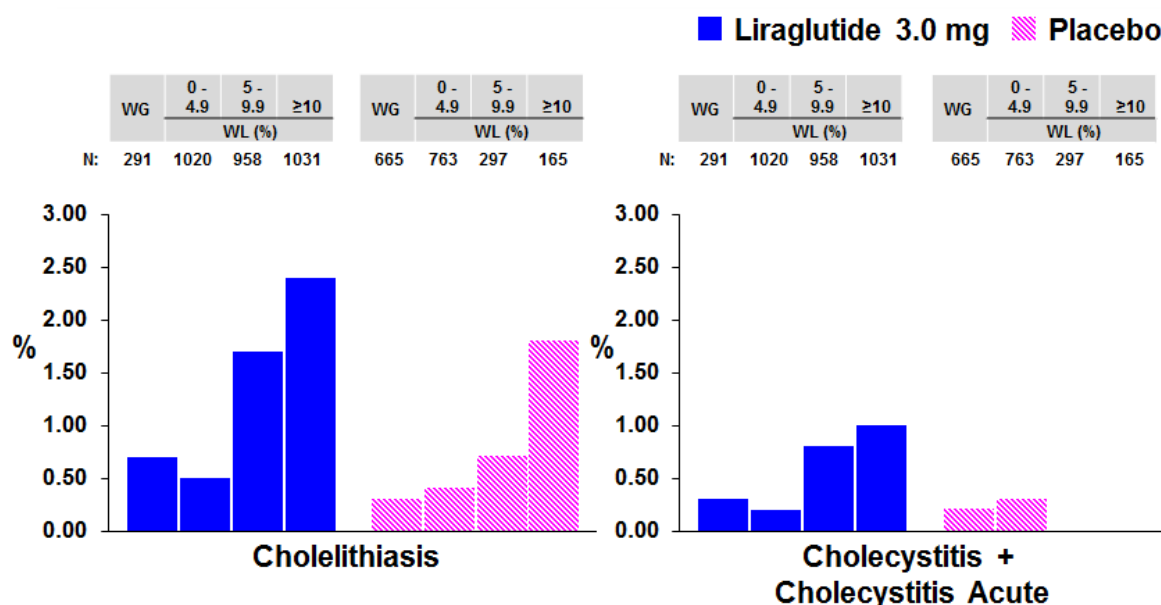
As shown in [Figure 6–4](#), gallbladder-related AEs occurred throughout the treatment period with both liraglutide 3.0 mg and placebo. The lines in [Figure 6–4](#) represent the mean weight loss by liraglutide- and placebo-treated patients in the pooled analysis; each gallbladder event is plotted by time of event and the weight loss experienced by the patient at the time of the event. For liraglutide 3.0 mg treated patients, gallstone disease occurred more frequently in patients who lost more than the mean weight loss for the liraglutide-treated cohort. This was not as clear for the placebo group.



Note that patients are randomized 2:1 to liraglutide and placebo.

**Figure 6–4 Weight loss at the time of onset of treatment-emergent gallbladder-related AEs: weight management pool (NDA)**

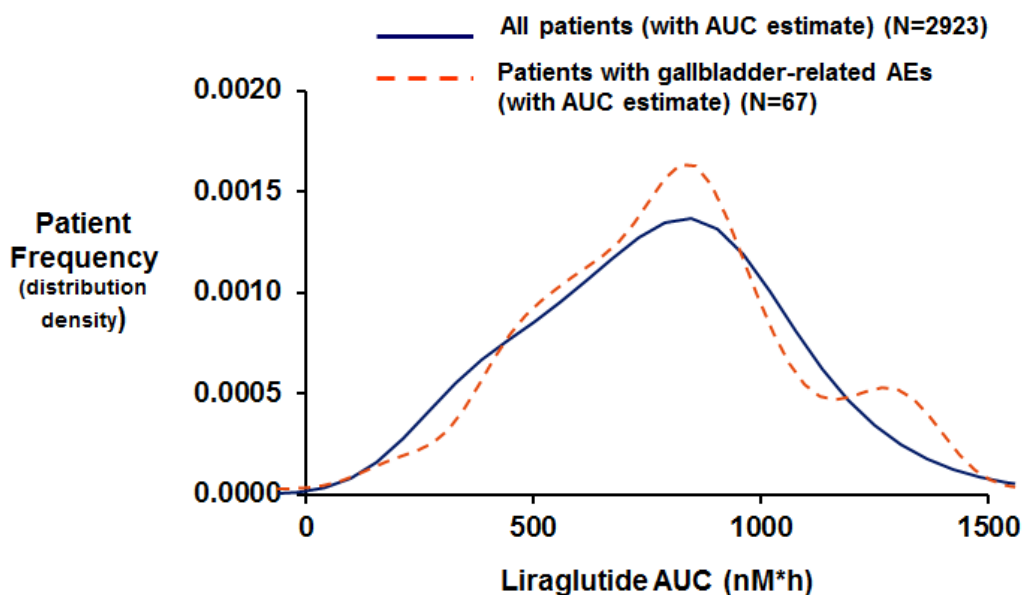
As predicted, the majority of events in those treated with either liraglutide 3.0 or placebo occurred in females (who generally also lost more weight than did males) and in those with a weight loss  $\geq 5\%$  ([Figure 6–5](#)). Because the increased incidence of gallbladder-related AEs with liraglutide was consistently observed across weight-loss categories, factors in addition to weight loss appear to be involved.



N number of patients contributing to analysis; % percentages are based on total N; WG, weight gain; WL, weight loss. Events captured by preferred terms 'cholelithiasis', 'cholecystitis' and 'cholecystitis acute'.

**Figure 6–5 Percentage of patients with cholelithiasis and cholecystitis by weight change category: weight management pool (NDA)**

No indication of a dose-response relationship in the occurrence of gallbladder-related AEs was found based on the two trials which included lower doses of liraglutide (trial 1807, a phase 2 trial with liraglutide doses 1.2, 1.8, 2.4 and 3.0 mg; and trial 1922, a T2DM trial with both liraglutide 1.8 and 3.0 mg). Moreover, consistent with this observation, patients with gallbladder adverse events were not observed to have higher liraglutide exposures compared to the trial population as a whole ([Figure 6–6](#)). The curves demonstrate that the distribution of plasma liraglutide exposures for patients with events was the same as for those without events.

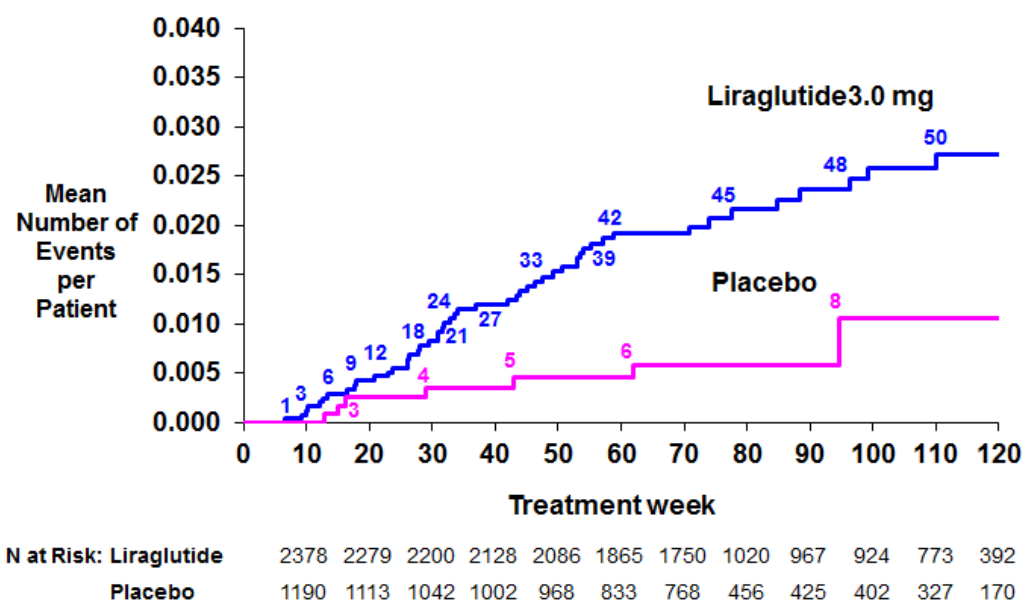


**Figure 6–6 Distribution of liraglutide exposure based on model-derived AUC in patients with or without gallbladder-related AEs: Trials 1839 and 1922 (NDA)**

Approximately 70% (53/79 patients in the liraglutide 3.0 mg group and 12/17 patients in the placebo group) of patients reporting events of gallbladder-related adverse events underwent a cholecystectomy, mostly as elective surgery. The majority of patients recovered (often after cholecystectomy) and continued on unchanged randomized treatment, or had liraglutide re-introduced after surgery.

Cholelithiasis was simultaneously reported for 3 (2 with liraglutide, 1 with placebo) of the 13 EAC-confirmed acute pancreatitis events (12 with liraglutide, 1 with placebo), and cholelithiasis may have contributed to the occurrence of pancreatitis in those patients ([Table 6–11](#)). Based on the pattern of liver function tests ( $\text{ALT} \geq 3\text{ULN}$ ) at the time of diagnosis of pancreatitis, 3 additional cases of EAC-confirmed cases of pancreatitis may have been precipitated by gallstones (see [Section 6.3.2.2](#)).

The incidence of gallbladder-related SAE appeared to diminish over time based on reports in the ongoing extension of trial 1839, included with the 120-Day safety update, where presumably no further substantial weight loss is observed. In the main trial period of trial 1839, gallbladder-related SAEs were reported by 1.5% of patients on liraglutide 3.0 mg (1.9 events per 100 PYE) and 0.4% on placebo (0.5 events per 100 PYE). In the 1839 extension, the corresponding numbers were 0.9% (0.9 events per 100 PYE) and 0.2% (0.4 events per 100 PYE), respectively ([Figure 6–7](#)).



Includes treatment emergent and non-treatment emergent events from 1839 main, re-randomized and extension periods up to cut-off for 120-day safety update. Events are allocated as per original treatment randomization; risk time defined as from first drug date to last contact. Numbers in plot represent cumulative gallbladder-related SAEs at that time point.

**Figure 6-7 Mean cumulative events over time plot of all gallbladder-related SAEs after randomization: Trial 1839 (through 120-Day Safety Update)**

### 6.3.1.3 Experience with liraglutide in type 2 diabetes programs

The same pre-defined MedDRA search was applied to the pooled data obtained from all controlled trials with liraglutide for T2DM. The search identified 64 treatment-emergent events in 55 patients treated with liraglutide at doses up to 1.8 mg (0.8%, 1.3 events per 100 PYE) and 31 treatment-emergent events in 28 patients treated with comparator (0.8%, 1.3 events per 100 PYE); thus no difference between groups was observed. The most frequent event was 'cholelithiasis' reported by similar proportions and rates across the two groups (liraglutide: 19 patients (0.3%) with 19 events; 0.4 events per 100 PYE, comparator: 14 patients (0.4%) with 14 events; 0.6 events per 100 PYE).

### 6.3.1.4 Non-clinical gallbladder findings

The chronic effects of supra-therapeutic concentrations of liraglutide on various organs and tissues, including the gallbladder, have been studied as part of the regulatory non-clinical toxicity and carcinogenicity program of liraglutide for T2DM (Victoza®). A small non dose-dependent imbalance in gallbladder findings was observed in mice after life-time administration. There were no findings in monkeys. See Section [3.4.2](#) for non-clinical gallbladder findings.



### 6.3.1.5 Conclusions for gallbladder safety in the weight management program

In summary, although infrequent, gallbladder-related AEs (mainly ‘cholelithiasis’ and ‘cholecystitis’) were observed at a higher frequency with liraglutide in the weight management trials. A similar signal was not seen in the T2DM trials, likely attributed to differences in population (more women, higher BMI) and greater weight loss in the weight management trials.

Novo Nordisk acknowledges the observed imbalance in these events compared to placebo in the weight management population and believes that this signal is due in part to the increased weight loss achieved with liraglutide. A weight-loss independent drug-class related effect cannot be excluded. Novo Nordisk believes that the risk identified can be appropriately managed through proposed labeling (see Section 7).

## 6.3.2 Pancreatitis

### 6.3.2.1 Background

Obesity, in particular abdominal obesity, has been associated with increased risk of acute pancreatitis<sup>137</sup>, and was found to be an independent risk factor for development of pancreatitis-related complications and mortality in most,<sup>138</sup> but not all studies.<sup>137</sup> No such relationship with obesity exists for chronic pancreatitis.<sup>139</sup> Compared to a non-obese reference population, obese patients had an increased prevalence of pancreatitis (cross-sectional SOS Registry Study);<sup>45</sup> among men, the figures were 1.4% versus 0.2%. The corresponding figures in women were 1.9% and 0.5%, respectively (odds ratio 4.5).<sup>45</sup> The same study also reported 2-year incidence of pancreatitis for obese individuals opting or not opting for gastric bypass surgery.<sup>45</sup> The 2-year incidence in the non-operated controls was low, 0.2% for males and 0.4% for females. T2DM, a common co-morbidity of obese individuals, independently increases the risk of acute pancreatitis by 50%, compared to controls without T2DM.<sup>140</sup> The incidence of acute pancreatitis in individuals with T2DM ranges between 0.5–4.2 events per 1,000 PYE.<sup>141-145</sup>

A small number of pancreatitis cases have been reported in clinical trials with GLP-1 receptor agonists (including liraglutide) and DPP-4 inhibitors in patients with T2DM, with a numerical imbalance against the GLP-1 based therapy. A substantial number of cases have been observed through spontaneous reports. Database studies, including ‘insurance claims’ databases have shown inconsistent results, varying from no increased risk to increased risk of hospitalization.<sup>141,146-149</sup>

Currently ongoing cardiovascular outcome trials with GLP-1 based therapies also collect information on pancreas safety, and the first of these, SAVOR-TIMI 53 and EXAMINE, recently reported similar rates of pancreatitis and no increase in pancreatic cancer with saxagliptin compared to placebo.<sup>150,151</sup> All GLP-1 based therapies carry label warnings concerning pancreatitis.

Patients with a history of idiopathic acute pancreatitis or chronic pancreatitis were excluded from the phase 3 trials in the liraglutide 3.0 weight management program. During the trials, all suspected drugs were to be discontinued in case of a suspicion of acute pancreatitis and the patient withdrawn

from the trial if the diagnosis was confirmed. Across the five phase 2 and 3 trials, the diagnostic criteria for acute pancreatitis required that at least 2 of the following 3 criteria were met: 1) characteristic abdominal pain, 2) amylase and/or lipase above 3×ULN and/or 3) characteristic findings on imaging of the pancreas (ultrasound, CT, magnetic resonance imaging [MRI]<sup>152</sup>).

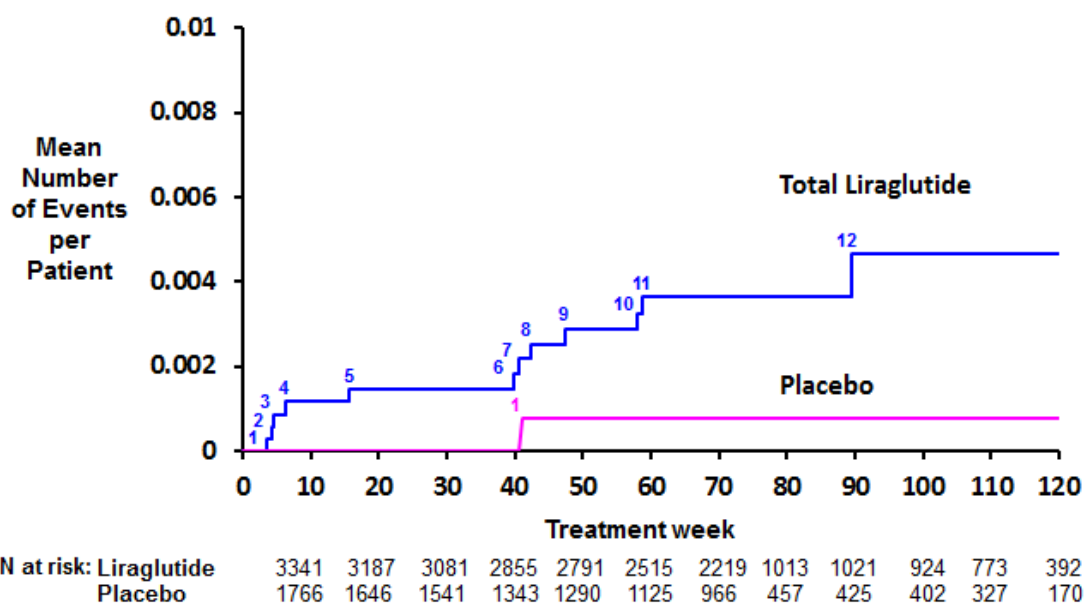
Novo Nordisk took additional measures to identify potential events of pancreatitis not already identified by study investigators. During conduct of trials 1839, 1922 and 3970, Novo Nordisk performed ongoing blinded searches in the clinical AE database for potential events of pancreatitis not already identified by investigators, including AEs of increased lipase/amylase with concomitant reporting of AEs of abdominal pain (occurring within a time window of +/- 30 days of the elevated lipase/amylase). All potential cases of pancreatitis were independently adjudicated in the liraglutide weight management program. An overview of the event adjudication process is presented in [Appendix Figure 5-1](#). All events with preferred term ‘pancreatitis acute’ or ‘pancreatitis’ were confirmed by the EAC as acute pancreatitis, whereas the more unspecific terms (e.g., lipase or amylase increased, abdominal pain), when reported in isolation, were typically not confirmed.

#### 6.3.2.2 Pancreatitis in the weight management program

There were a total of 13 EAC-confirmed cases of pancreatitis (12 cases in the liraglutide 3.0 mg group [0.4% of patients; 0.26 events per 100 Patient Years at Risk [PYR]] and 1 case in the placebo group [<0.1% of patients; <0.1 events per 100 PYR] by the cut-off for the 120-Day Safety Update; 2 of the cases reported for liraglutide 3.0 mg treated patients occurred in the 1839 extension and 3 cases after discontinuation of liraglutide treatment. All of the liraglutide events occurred at the 3.0 mg dose, in trial 1839. All events were confirmed as ‘acute pancreatitis’, none as ‘chronic pancreatitis’.

In the phase 2 dose-finding trial, trial 1807, which did not include adjudication (neither prospectively or *post hoc*), the MedDRA search captured 1 additional event of ‘pancreatitis acute’ reported in the liraglutide 3.0 mg group. This ‘acute pancreatitis’ event occurred after 299 days of treatment and coincided with a diagnosis of cholelithiasis.

An overview of the 13 EAC-confirmed pancreatitis events in the weight management pool is presented in [Table 6–11](#). Events of acute pancreatitis occurred sporadically throughout the duration of the trials ([Figure 6–8](#)). Three occurred after more than 1 year of treatment, and 3 after discontinuation of liraglutide treatment; one of these occurred 12 days after switching to placebo after 392 days of liraglutide 3.0 mg exposure, two 74 and 124 days after last dose of liraglutide 3.0 mg exposure, respectively.



Output is based on 1839 including the re-randomization period and the 120-Day Safety Update. 1922 and 1923 including the 12-week follow-up period and 3970. Patients are allocated according to treatment in the main treatment period. Risk time is defined as the time between first drug date and last contact as non-treatment emergent events are included. Numbers in plot represent cumulative pancreatitis events at that time point.

**Figure 6-8 Mean cumulative events of EAC confirmed pancreatitis over time: phase 3 trials (through 120-Day Safety Update)**

Imaging results were available for 12 of the 13 EAC-confirmed events of acute pancreatitis, as well as for the non-adjudicated event from trial 1807. In 7 of the 13 EAC-confirmed events, the EAC indicated that positive imaging contributed to the diagnosis; for the remaining 5 cases imaging was described as 'normal' and the diagnosis was based on co-reporting of abdominal pain and elevated pancreatic enzymes.

Of the patients with EAC-confirmed events, 3 had evidence of gallstones (imaging, symptoms) at the time of the pancreatitis event (2 liraglutide 3.0 mg treated patients and 1 placebo patient). One of the liraglutide 3.0 mg treated patients had been withdrawn from the trial due to cholelithiasis after 170 days and later had confirmed acute pancreatitis 124 days after the last drug dosing date. All of the events of pancreatitis associated with documented gallstones were concomitant with elevated liver function tests ([Table 6-11](#)), and all three events occurred >90 days after randomization. Three additional cases of pancreatitis without imaging evidence of gallstones had concomitant elevation of liver function tests (>3xULN) at the time of diagnosis of acute pancreatitis, supporting a diagnosis of gallstone pancreatitis.<sup>49</sup>

The EAC was not requested to classify events according to severity. Based on sponsor's review of the case narratives, none of the confirmed cases qualified as being severe (defined as having

persistent organ failure), but three of the cases, all treated with liraglutide, would likely have been classified as moderately severe (defined by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure) according to the revised Atlanta criteria.<sup>152</sup> For the majority of cases, the duration was short (2–15 days), and all patients recovered.

**Table 6–11 EAC-confirmed pancreatitis in phase 3 trials (through 120-Day Safety Update)**

| Treatment            | Preferred term        | Exposure (days)* | Age/Sex/<br>BMI | Diagnostic criteria fulfilled                  | Severity<br>(Atlanta criteria**) | Gallstone<br>(Y/N) | Elevated<br>ALT (Y/N)   |
|----------------------|-----------------------|------------------|-----------------|--|----------------------------------|--------------------|-------------------------|
| Liraglutide 3.0 mg   | Pancreatitis acute    | 24               | 32/F/38.9       | Abdominal pain, enzymes                        | Mild                             | N                  | N                       |
|                      | Pancreatitis acute    | 29               | 51/M/32.7       | Abdominal pain, enzymes,<br>(imaging not done) | Mild                             | N                  | N                       |
|                      | Pancreatitis acute    | 31               | 52/M/62.9       | Abdominal pain, enzymes                        | Mild                             | N                  | Y ALT 4X ULN            |
|                      | Pancreatitis acute    | 43               | 58/M/34.7       | Abdominal pain, imaging                        | Mild                             | N                  | N                       |
|                      | Lipase increased      | 277              | 51/F/48.6       | Abdominal pain, enzymes                        | Mild                             | N                  | N                       |
|                      | Pancreatitis          | 283              | 40/F/41.7       | Abdominal pain, enzymes, imaging               | Moderately severe                | Y                  | Y ALT 8X ULN            |
|                      | Pancreatitis acute    | 330              | 40/M/54.0       | Abdominal pain, imaging                        | Moderately severe                | N                  | Y                       |
|                      | Gastroenteritis       | 410              | 62/F/38.7       | Abdominal pain, enzymes                        | Mild                             | N                  | N                       |
|                      | Pancreatitis          | 626              | 48/F/45.1       | Abdominal pain, imaging                        | Mild                             | N                  | N                       |
| Liraglutide/Placebo# | Pancreatitis acute    | 392              | 41/F/36.2       | Abdominal pain, enzymes                        | Mild                             | N                  | Y ALT 5X ULN            |
| Placebo              | Pancreatic disorder   | 287              | 55/F/35.5       | Abdominal pain, imaging                        | Mild                             | Y                  | Y ALT 2.5X ULN          |
|                      | Pancreatitis          | 35 <sup>1</sup>  | 64/M/38.1       | Abdominal pain, enzymes, imaging               | Mild                             | N                  | Y ALT 3X ULN            |
| Liraglutide 3.0 mg   | Pancreatic pseudocyst | 170 <sup>2</sup> | 41/F/42.9       | Abdominal pain, enzymes, imaging               | Moderately severe                | Y                  | Unknown,<br>AST 24X ULN |

\*Exposure during trial for events with onset after trial drug stop; \*\*Evaluated by Novo Nordisk

# Event on day 404, 12 days after last dose of liraglutide.

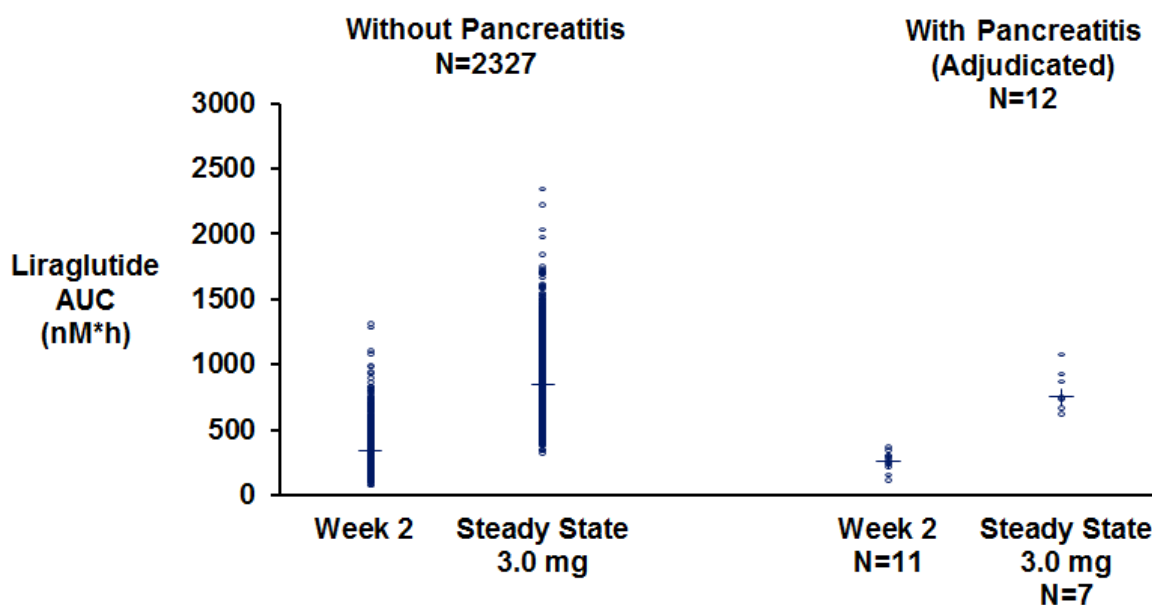
1: Event occurred 74 days after last drug dose. 2: Event occurred 124 days after last drug dose.

M: Male; F: Female; BMI: Body Mass Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal range

All patients recovered.

Except for the ~50% of the liraglutide patients diagnosed with an event of acute pancreatitis who also had coincident gallstones on imaging and/or the presence of ALT levels 3 or more times the upper limit of normal, there do not appear to be any patient characteristics that can serve as potential predictors of pancreatitis. Specifically, elevated amylase and/or lipase had low positive predictive value (<1% for lipase  $\geq 3$  ULN, no amylase values  $\geq 3$  ULN) (Section [6.3.2.5](#))

Liraglutide plasma exposure was similar in liraglutide-treated patients with and without confirmed pancreatitis at week 2 (population pharmacokinetic sampling time point during dose escalation) and at steady state (after which plasma exposure is constant), supporting absence of an adverse exposure-response relationship in the 1.2-3.0 mg dose range in the weight management trials ([Figure 6-9](#)). Further, a random distribution of pancreatitis events across doses in the T2DM program also does not support a clear dose-response relationship (See Section [6.3.1.3](#)).



Includes treatment-emergent and non-treatment emergent cases with population PK measurements, steady state exposure (3.0 mg) based on PK sample weeks 12/16/28.

**Figure 6-9 Liraglutide exposure based on model-derived AUC in patients with and without EAC-confirmed pancreatitis: Trial 1839 (through 120-Day Safety Update)**

### 6.3.2.3 Experience with liraglutide in type 2 diabetes programs

The rates of pancreatitis in the T2DM liraglutide programs and the relative imbalance to comparator were similar to those in the weight management pool (0.2 events per 100 PYE for liraglutide, and <0.1 events per 100 PYE for comparator or placebo). Events occurred at 0.6-1.8 mg doses, according to relative exposure at these doses in the pooled T2DM trials ([Table 6-12](#)).

**Table 6–12 Pancreatitis events identified by MedDRA search (preferred terms) in the type 2 diabetes programs (NDA)**

|                        | ----- Total Liraglutide ----- |        |   |      | ----- Total Comparator ----- |        |   |      |
|------------------------|-------------------------------|--------|---|------|------------------------------|--------|---|------|
|                        | (N=7037)                      |        |   |      | (N=3677)                     |        |   |      |
|                        | N                             | (%)    | E | R    | N                            | (%)    | E | R    |
| Total number of events | 9                             | (0.1)  | 9 | 0.2  | 2                            | (<0.1) | 2 | <0.1 |
| Pancreatitis           | 3                             | (<0.1) | 3 | <0.1 | 1                            | (<0.1) | 1 | <0.1 |
| Pancreatitis chronic   | 3                             | (<0.1) | 3 | <0.1 | 0                            | (0.0)  | 0 | 0    |
| Pancreatitis acute     | 2                             | (<0.1) | 2 | <0.1 | 1                            | (<0.1) | 1 | <0.1 |
| Edematous pancreatitis | 1                             | (<0.1) | 1 | <0.1 | 0                            | (0.0)  | 0 | 0    |

N: Number of patients, %: Percentages are based on total N, E: Number of events; R: Event rate per 100 years of exposure

When comparing rates across development programs, it should be noted that pancreatitis was not adjudicated in the T2DM programs, and both average exposure to treatment and the follow-up were different from the weight management trials. There was an overall high consistency between investigator-reported events of pancreatitis and EAC diagnosis of pancreatitis in the weight management trials.

As a component of the post-marketing commitment for Victoza<sup>®</sup>, Novo Nordisk is conducting a prospective ongoing pharmacovigilance study utilizing a medical claims database in which pancreatitis is one of the medical events of interest. Individuals are propensity-score matched to those taking other commonly utilized diabetes drugs to account for identifiable confounders. As of the most recent annual report for this study, there is no evidence of a significant increase in the relative risk of pancreatitis for liraglutide (Victoza<sup>®</sup>) compared to exenatide, metformin, sulfonylureas, DPP4 inhibitors, or pioglitazone ([Table 6–13](#)).

**Table 6–13 Acute Pancreatitis Diagnoses from Medical Claims Database**

|                                     | Liraglutide<br>N | Comparator<br>N | Relative Risk to<br>Liraglutide | [95 % CI] |
|-------------------------------------|------------------|-----------------|---------------------------------|-----------|
| Pioglitazone                        | 15,718           | 15,721          | 0.9                             | [0.7-1.2] |
| Metformin                           | 20,143           | 20,135          | 1.0                             | [0.8-1.2] |
| Sulphonylurea (glipizide/glyburide) | 20,588           | 20,596          | 1.0                             | [0.8-1.2] |
| DPP-4 inhibitors*                   | 17,976           | 17,974          | 1.0                             | [0.8-1.3] |
| Exenatide                           | 7,728            | 7,733           | 0.9                             | [0.6-1.3] |

Treatment Initiators from 01 Feb 2010 to 31 Dec 2012 with follow-up through 31 Mar 2013

Represents >25,000 PYE liraglutide initiators; propensity score–based matching with comparators

CI: confidence interval; DPP-4: dipeptidyl peptidase-4; \*DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin).

### 6.3.2.4 Non-clinical pancreas safety findings

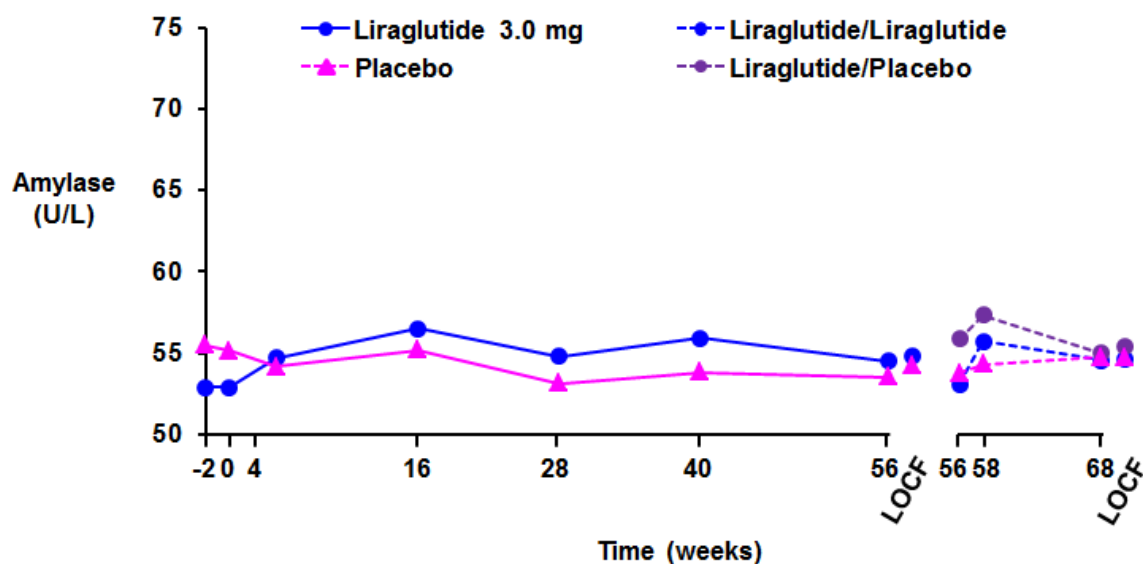
There were no treatment-related findings in non-clinical studies (see Section [3.4.1](#)).

### 6.3.2.5 Elevated lipase or amylase

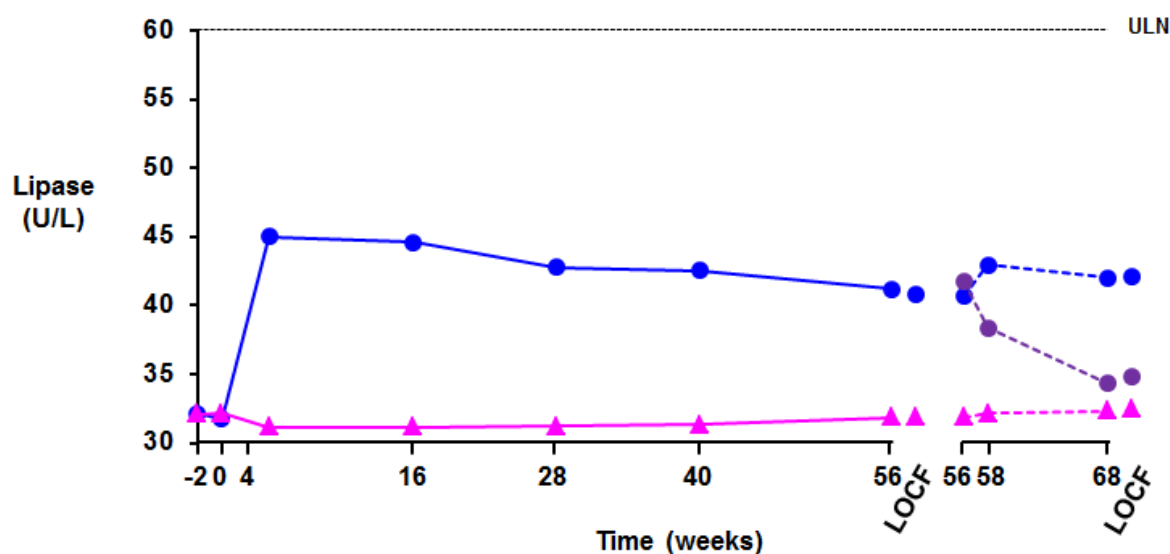
Following post-marketing reports of hemorrhagic and necrotizing pancreatitis with exenatide (Byetta<sup>®</sup>) and other GLP-1 receptor agonists and DPP-4 inhibitors, regulatory authorities requested pharmaceutical companies developing GLP-1 based therapies to routinely monitor pancreatic enzymes (amylase and lipase) activity in their clinical trials, as potential biomarkers for pancreatitis. Serum amylase and lipase activities were assessed at regular intervals (screening, randomization, approximately once every 3 months during treatment, end-of-treatment, and at follow-up) in all of the phase 3 trials in the weight management program.

Baseline serum amylase activity was similar with liraglutide 3.0 mg (52.4 U/L, geometric mean) and placebo (53.4 U/L, geometric mean), and increased slightly in both groups during the first 3 months of treatment (within the normal range), followed by a gradual decline until the end of treatment (1 year); mean amylase activity with liraglutide 3.0 mg was higher than placebo throughout the treatment period (56.4 U/L and 53.4 U/L, respectively, at end of treatment). Baseline serum lipase activity was similar with liraglutide 3.0 mg (32.8 U/L, geometric mean) and placebo (33.0 U/L). With liraglutide 3.0 mg, mean serum lipase activity increased (within the normal range) during the first 3 months of treatment and then gradually declined until the end of treatment (1 year) but remained above the baseline level (43.4 U/L at end of treatment); no change was observed with placebo (33.3 U/L at end of treatment). There was no indication of a dose-response. Mean serum amylase and lipase returned to baseline after treatment with liraglutide was discontinued as seen in trial 1839 for patients switching from liraglutide 3.0 mg to placebo in the re-randomized period ([Figure 6–10](#)).





NDA; Trial 1839; geometric mean; upper limit of normal (ULN): 112 U/L; LOCF: last observation carried forward



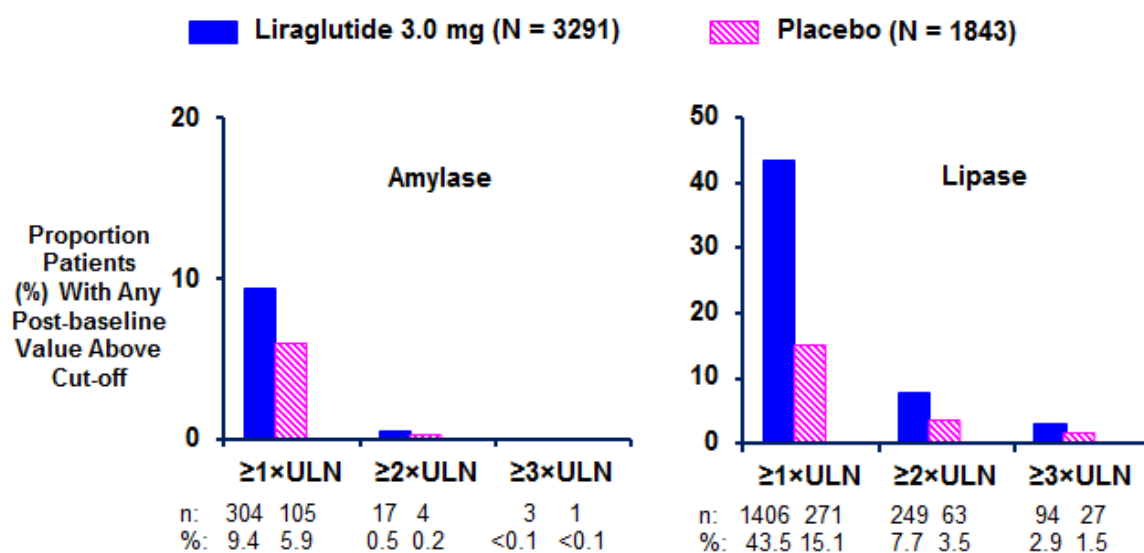
NDA; Trial 1839; geometric mean; upper limit of normal (ULN): 60 U/L; LOCF: last observation carried forward

**Figure 6–10 Amylase and lipase activity decreases for patients switching from liraglutide 3.0 mg to placebo in the re-randomized period: trial 1839 (NDA)**

Few patients experienced pancreatic enzyme activity levels  $\geq 3 \times \text{ULN}$  (Figure 6–11), and most elevations were incidental (i.e., occurred once or twice during treatment) and were not accompanied by signs or symptoms of pancreatitis. The positive predictive value of isolated elevations of lipase

and/or amylase for the diagnosis of pancreatitis was very low (<1% for lipase  $\geq 3$  ULN, no amylase values  $\geq 3$  ULN).

While the underlying mechanism remains elusive and the clinical implications (if any) yet unknown,<sup>153,154</sup> the reversibility of pancreatic enzyme activity upon treatment discontinuation indicates that progressive or irreversible damage to the pancreas is not likely to be occurring. This is also supported by lack of histopathological changes in the pancreas in the non-clinical data. A similar treatment effect has been observed with other GLP-1 receptor agonists, suggestive of a class effect.<sup>50,155</sup>



**Figure 6-11 Percentage of patients with amylase or lipase elevations greater than 1x , 2x, or 3x the upper limit of normal at any time during treatment: phase 3 trials (NDA)**

### 6.3.2.6 Conclusions for pancreatic safety in the weight management program

In conclusion, there was a higher incidence of EAC-confirmed pancreatitis in individuals treated with liraglutide 3.0 mg than placebo in the weight management pool. This imbalance is consistent with that observed with liraglutide (Victoza<sup>®</sup>) in T2DM. Observed pancreatitis events were generally uncomplicated, none was necrotizing or hemorrhagic. All patients recovered. There was no indication of an exposure-response relationship, and no increased risk of pancreatitis with prolonged exposure. No 'common denominator' was identified to either explain or predict event onset, although gallstones were implicated in some of the cases based on imaging and/or elevated liver enzymes at diagnosis. There was no uniform mode of presentation, with respect to time to onset, symptoms or weight loss prior to onset. The positive predictive value of elevated pancreatic enzymes was very low, suggesting that screening patients for lipase and amylase before initiating liraglutide treatment is not warranted.

A recent FDA and EMA assessment using outcomes studies as well as animal models concluded that a causal relationship between incretin-based therapies and pancreatitis or pancreatic cancer is “inconsistent with the current data.”<sup>156</sup> In the weight management pool, there were no events of exocrine pancreas cancer. However, a higher incidence of acute pancreatitis was observed in individuals treated with liraglutide 3.0 mg. Accordingly, pancreatitis will be included in the labeling and will be monitored through the risk management plan as it is being monitored for the Victoza<sup>®</sup> diabetes indication.

### **6.3.3 Hepatic Safety**

#### **6.3.3.1 Background**

While GLP-1 receptor agonists, including liraglutide, have not been directly associated with increased risk of hepatobiliary AEs in clinical use for T2DM, laboratory assessments for hepatic safety have been routinely performed in the liraglutide T2DM development program and in the phase 2 and 3 trials of the weight management pool.

#### **6.3.3.2 Liver function tests in the weight management program**

Potential drug-induced liver injury was evaluated based on Hy’s law defined as an increase in alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN) and an increase in total bilirubin >2 times the ULN without elevated alkaline phosphatase (AP). No patients in the weight management pool fulfilled Hy’s law.

Overall, mean levels of ALT, AP, and aspartate aminotransferase (AST) during the treatment period (up to 1 year) decreased from baseline with liraglutide 3.0 mg and were reduced by approximately 17%, 7% and 8%, respectively, at the end of treatment. Reductions were also observed in the small number of patients with significantly elevated values at baseline (ALT and AST > 3 times the ULN, AP > 2 times the ULN, total bilirubin > 1.5 times the ULN). The proportions of patients who experienced elevations of ALT or AST >3 times the ULN, AP >2.5 times the ULN, or of total bilirubin >1.5 times the ULN were low and similar between liraglutide 3.0 mg and placebo treatment groups ([Table 6–14](#)).

Medical review of all cases of ALT elevations >10 times the ULN revealed that all cases had accompanying confounding factors such as suspected gallstone formation/passage or cholecystitis. In all cases, the increases in ALT were transient and all patients continued the trial drug and experienced normalization of liver parameters before trial finalization.

**Table 6–14 Patients with elevated hepatic enzyme levels during the treatment period: weight management pool**

|                                  | <b>Liraglutide 3.0 mg<br/>N (%)</b> | <b>Placebo<br/>N (%)</b> |
|----------------------------------|-------------------------------------|--------------------------|
| Total number of patients         | 3384                                | 1941                     |
| ALT (alanine aminotransferase)   |                                     |                          |
| 3xULN                            | 36 (1.1)                            | 20 (1.0)                 |
| 5xULN                            | 9 (0.3)                             | 4 (0.2)                  |
| 10xULN                           | 5 (0.1)                             | 1 (0.1)                  |
| 20xULN                           | 2 (0.1)                             | 0 (0.0)                  |
| AST (aspartate aminotransferase) |                                     |                          |
| 3xULN                            | 18 (0.5)                            | 12 (0.6)                 |
| 5xULN                            | 8 (0.2)                             | 4 (0.2)                  |
| 10xULN                           | 3 (0.1)                             | 2 (0.1)                  |
| 20xULN                           | 1 (0.0)                             | 0 (0.0)                  |
| AP (alkaline phosphatase)        |                                     |                          |
| 2.5xULN                          | 3 (0.1)                             | 3 (0.2)                  |
| 5xULN                            | 1 (0.0)                             | 0 (0.0)                  |
| 20xULN                           | 0 (0.0)                             | 0 (0.0)                  |
| Total bilirubin                  |                                     |                          |
| 1.5xULN                          | 20 (0.6)                            | 13 (0.7)                 |
| 3xULN                            | 0 (0.0)                             | 1 (0.1)                  |
| 10xULN                           | 0 (0.0)                             | 0 (0.0)                  |

ULN=upper limit of normal, %=percentage of patients based on the total number of patients

### 6.3.3.3 Experience with liraglutide in type 2 diabetes programs

As in the weight management pool, no patients fulfilled Hy's Law with respect to liver function abnormalities. The number of patients with ALT or AST >3 times the ULN during treatment were also low and similar between liraglutide (doses up to 1.8 mg) and total comparator (ALT: 0.5% of patients in both groups; AST: 0.4% of patients with liraglutide and 0.3% of patients with placebo). The prevalence of Hepatobiliary Disorders (SOC) was low and similar in both liraglutide and total comparator groups (1.7% vs. 1.6% of patients, respectively). No cases of autoimmune hepatitis have been reported in the liraglutide T2DM development program.

### 6.3.3.4 Post-marketing data

A case of Victoza-related autoimmune hepatitis was recently reported<sup>157</sup> and is summarized below. The case concerned a 29-year-old Hispanic female patient with T2DM and vitiligo who had been treated with Victoza® for 4 months (previously treated with exenatide twice daily) prior to the diagnosis of marker-negative autoimmune hepatitis. The patient presented at the hospital with 10 days of nausea and vomiting and laboratory tests showed high elevations of AST (991 U/L) and ALT (1123 U/L) and normal total bilirubin and AP. Liraglutide was discontinued a few days after symptoms first appeared. Subsequent liver biopsies revealed acute hepatitis and hepatic necrosis.

After examination for viral, autoimmune and metabolic etiologies proved unrevealing, the patient was treated with corticosteroids and an immunosuppressive agent (immuran) for presumed marker-negative drug-induced hepatitis. After 6 months of therapy, the patient had not recovered (AST and ALT levels declined but did not return to the reference range) but continued to receive prednisone and immuran.

A number of confounding factors potentially contributing to the event were present, including pre-existing autoimmune condition (vitiglio), female gender, young age and exposure to a medication with a known risk for drug-induced hepatotoxicity/hepatitis and hypersensitivity reaction (ciprofloxacin).<sup>158</sup> Ciprofloxacin was identified after the case report had been published. Furthermore, there were no liver function test results to confirm when the hepatic abnormalities began. Also, improvement after discontinuation of Victoza<sup>®</sup> was confounded by the corticosteroid treatment.

#### **6.3.3.5 Non-clinical data**

The chronic effects of supra-therapeutic concentrations of liraglutide on various organs and tissues have been studied as part of the regulatory non-clinical toxicity and carcinogenicity program of liraglutide for T2DM (Victoza<sup>®</sup>). No indication for hepatotoxicity has been observed with liraglutide in mice, rats or monkeys. The small imbalance in murine gallbladder findings is described in Section [3.4.2](#).

#### **6.3.3.6 Conclusion for hepatic safety in the weight management program**

There was no signal of specific hepatocellular function abnormalities with liraglutide in either the weight management or the T2DM development programs. Overall, mean levels of ALT, AP, and aspartate aminotransferase (AST) during the treatment period (up to 1 year) decreased from baseline with liraglutide 3.0 mg and were reduced by approximately 17%, 7% and 8%, respectively, at the end of treatment. Furthermore, no indication for liraglutide-related hepatotoxicity has been identified in non-clinical studies. In the post-marketing case of autoimmune hepatitis attributed to treatment with Victoza<sup>®</sup>, the case was confounded by several risk factors and should therefore be interpreted with caution.

### **6.3.4 Cardiovascular safety**

#### **6.3.4.1 Background**

Obesity is a well-known risk factor for cardiovascular (CV) disease. The incidence of hypertension, coronary artery disease, congestive heart failure, venous thrombosis and stroke increases with increasing BMI.<sup>159-161</sup> Furthermore, CV mortality has been shown in most epidemiological studies to be positively correlated with increasing BMI.<sup>162</sup> Weight loss in turn is associated with improvements in CV risk markers (waist circumference, blood pressure, lipid profile, inflammatory markers, glucose homeostasis, sleep apnea severity) and use of concomitant medication to control

blood pressure and dyslipidemia. However, there are no studies that have conclusively demonstrated that mortality and morbidity are decreased when obese patients lose weight.<sup>163</sup>

CV safety has traditionally been a focus area for weight management drugs. Stimulation of sympathetic activity is the principal mechanism of action of several anti-obesity drugs approved by the FDA during the past 50 years. These drugs have the potential to increase blood pressure, heart rate, or both, thereby contributing directly to increased CV risk, possibly offsetting the clinical benefits of weight reduction. This along with the previously documented adverse cardiac effects of valvulopathy and pulmonary hypertension seen with fenfluramine (another sympathomimetic agent) has raised concerns about the CV safety of all new anti-obesity drugs.

An increase in resting heart rate of 2–3 beats/min, with simultaneous reduction in systolic blood pressure, has been observed with liraglutide,<sup>15</sup> as well as other GLP-1 receptor agonists.<sup>50,51</sup> The underlying mechanism remains to be determined but preliminary data indicates the presence of GLP-1 receptors on myocytes of the sino-atrial node (pacemaker of the heart) in nonhuman primates and humans.<sup>52</sup> The presence of GLP-1 receptors in the heart's pacemaker increases the likelihood of the resting heart rate increase being mediated by a direct chronotropic effect of liraglutide.

Non-clinical studies have demonstrated multiple cardio-protective actions of GLP-1 receptor agonists, and short-term studies of GLP-1 receptor agonists in human patients with heart disease have not revealed evidence for adverse effects on cardiac function.<sup>164</sup> Consistently, retrospective meta-analyses of MACEs across clinical development programs with GLP-1 receptor agonists in T2DM (randomized clinical trials of at least 24 weeks duration) did not indicate an increased CV risk.<sup>165</sup> Results of multiple ongoing CV outcomes trials (including LEADER<sup>®</sup> with liraglutide in T2DM) will ultimately define the long-term risk of GLP-1 receptor agonists.

#### **6.3.4.2 Methodology for Heart Rate Measurements**

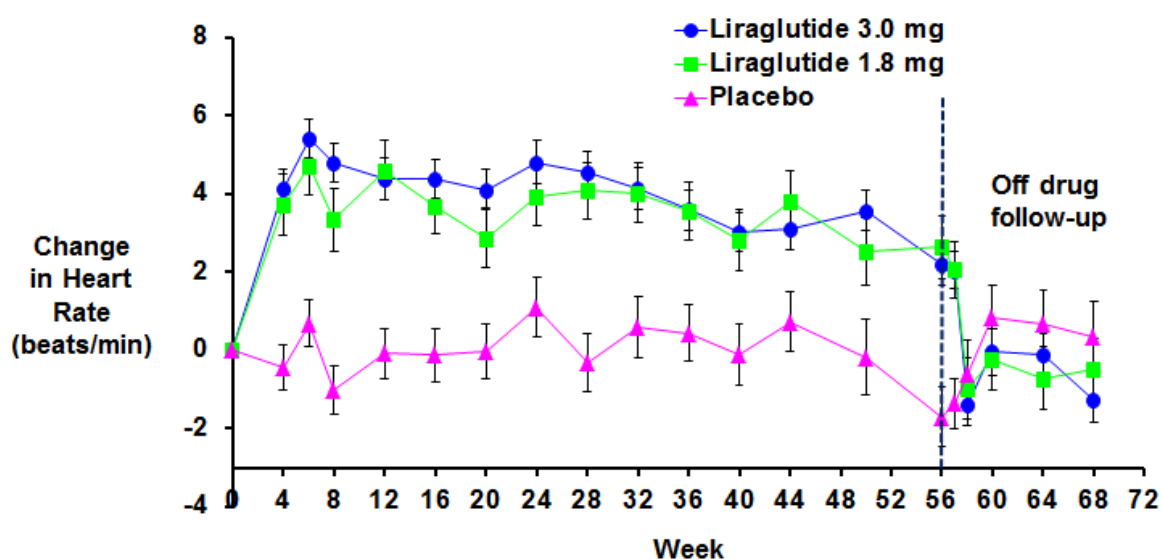
Resting heart rate was measured according to local clinical practice, with the patient sitting after having rested in a chair for 5 minutes. Resting heart rate was recorded at the majority of visits in the treatment periods of the phase 2 and 3 trials, approximately once monthly.

In three of the phase 3 trials, mean heart rate obtained from machine-read ECGs at screening and at end-of-treatment evaluated by central readers was used to confirm the recordings from the clinic. ECGs were also taken mid-trial in trials 1922 and 1839. In trial 3970 in patients with obstructive sleep apnea, nocturnal heart rate was derived from the ECG data collected during the overnight polysomnography (PSG) assessments at visits 2 (week –1), 7 (week 12) and 12 (week 32).

The effects of liraglutide on heart rate were investigated by 24-hour continuous heart rate monitoring in the mechanistic clinical pharmacology trial (trial 3630) in obese non-diabetic patients.

### 6.3.4.3 Resting heart rate during study visits

Mean resting heart rate increased after treatment initiation with liraglutide, peaked after approximately 6 weeks, and gradually declined thereafter ([Figure 6–12](#)). Mean resting heart rate remained above baseline at end-of-treatment, and returned to baseline values upon treatment discontinuation. With placebo, fluctuations were seen throughout the treatment period and at end-of-treatment the mean resting heart rate value was similar to the baseline value (0.2 beats/min increase, week 56 LOCF pooled data). In pooled phase 2 and phase 3 trials, the estimated treatment difference between liraglutide 3.0 mg and placebo in mean resting heart rate at end-of-treatment was 2.49 beats/min ( $p < 0.0001$ , ANCOVA), with consistent effects seen across trials.

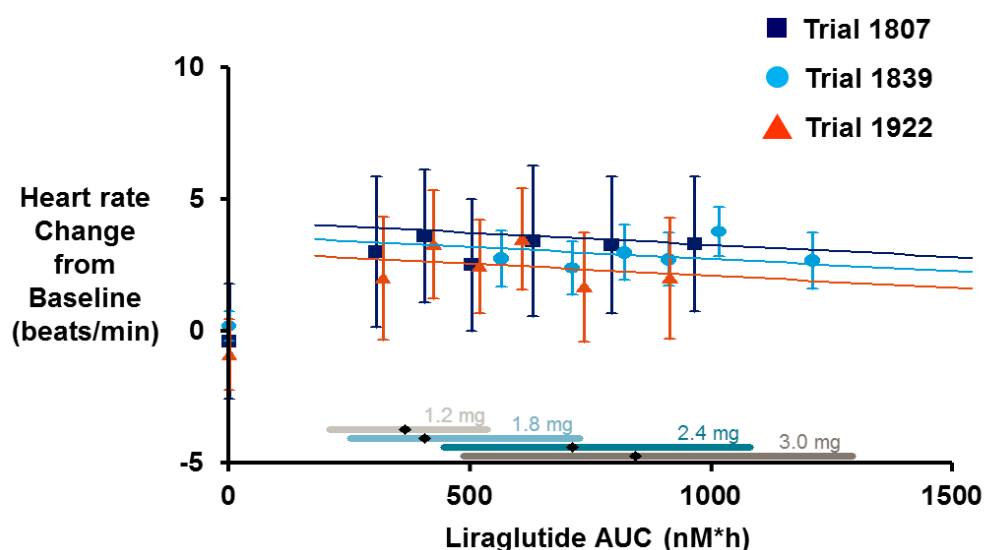


Liraglutide 3.0 mg: 422 patients, liraglutide 1.8 mg: 210 patients, placebo: 212 patients. Mean (+/- standard error)

**Figure 6–12 Resting heart rate (change from baseline): Trial 1922 (T2DM) (NDA)**

No dose-response relationship was observed between liraglutide 1.8 and 3.0 mg in trial 1922 (patients with T2DM) ([Figure 6–12](#)) or across the 4 investigated doses in the dose-finding trial (1.2-3.0 mg, patients without T2DM,  $p=0.40$ ; [Table 5–4](#)). Moreover, no exposure-response was noted based on plasma liraglutide exposures and change in resting heart rate at end of main trial period for the 3 trials which included population pharmacokinetic sampling ([Figure 6–13](#)) (see Section [4.3.1](#)).





Slope not significant ( $p \sim 0.18$ )

Lines represent the results of a multivariate regression analysis of the individual data

Heart rate change from baseline: Mean values with 95% CI versus exposure (in 6 AUC quantiles). Placebo is indicated on the figure as AUC=0.

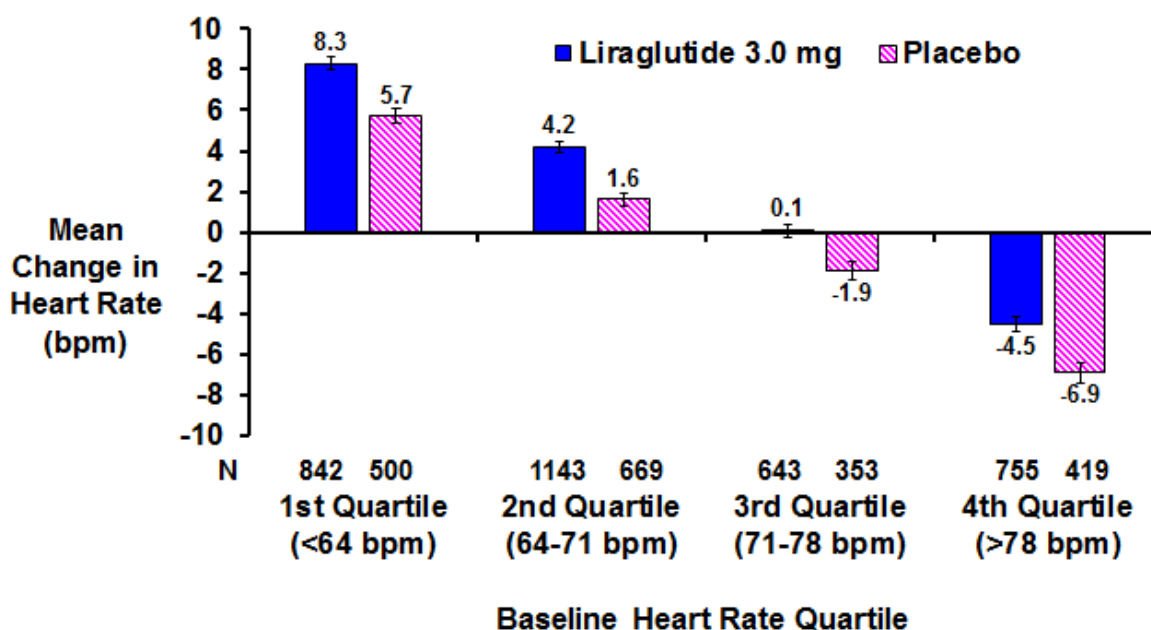
Horizontal lines with diamonds represent median and 90% exposure ranges

**Figure 6-13 Resting heart rate change from baseline: Exposure-Response Relationship in patients with and without T2DM (based on model-derived AUC): Trial 1807, 1839, 1922**

The pooled ECG-based resting heart rate results showed a similar treatment effect with liraglutide 3.0 mg, confirming the reliability of the clinic-based resting heart rate recordings.

Also, the impact of missing data on the results was investigated by evaluating the overall pattern of the mean response in resting heart rate of patients who withdrew prior to end-of-treatment compared to the mean response for patients who completed the treatment period. No consistent difference could be observed between patients completing or withdrawing from trial, confirming the robustness of the results and the absence of selection bias in the analysis.

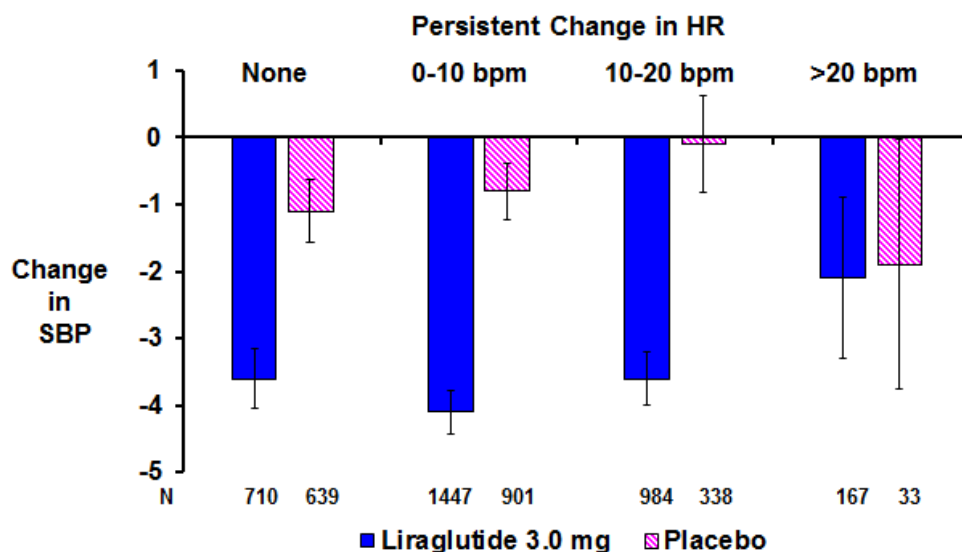
The mean change from baseline in resting heart rate depended on the baseline heart rate quartile in both treatment groups. When examined based on cohorts defined by baseline resting heart rate there was an absolute increase (liraglutide 3.0 mg: +8.3 beats/min, placebo: +5.7 beats/min) in mean heart rate in the lowest baseline heart rate quartile (<64 beats/min) and an absolute decrease in mean heart rate (liraglutide 3.0 mg: -4.5 beats/min, placebo: -6.9 beats/min) in the highest baseline quartile (>78 beats/min). The treatment difference between liraglutide 3.0 mg and placebo was similar (i.e., with a 2–3 beats/min increase in resting heart rate for liraglutide 3.0 mg compared to placebo) across baseline heart rate quartiles ([Figure 6-14](#)).



bpm: beats per minute; LOCF at end of trial +/- SE; N: number of patients in subgroup;

**Figure 6–14 Heart rate change varied by baseline heart rate quartile**

The mean increase in resting heart rate observed with liraglutide 3.0 mg was also similar (2–3 beats/min increase at end-of-treatment) across baseline quartiles of systolic blood pressure, and for patients with or without reported hypertension at baseline, for patients with or without a history of CV disease (defined by the SMQs ‘Ischemic heart disease’, ‘Cardiac failure’, and ‘Central nervous system hemorrhages and cerebrovascular conditions’ and ‘Embolus and thrombotic events’) as well as across all demographic sub-populations. A decrease in systolic BP was observed for all categories of heart rate increase ([Figure 6–15](#)).

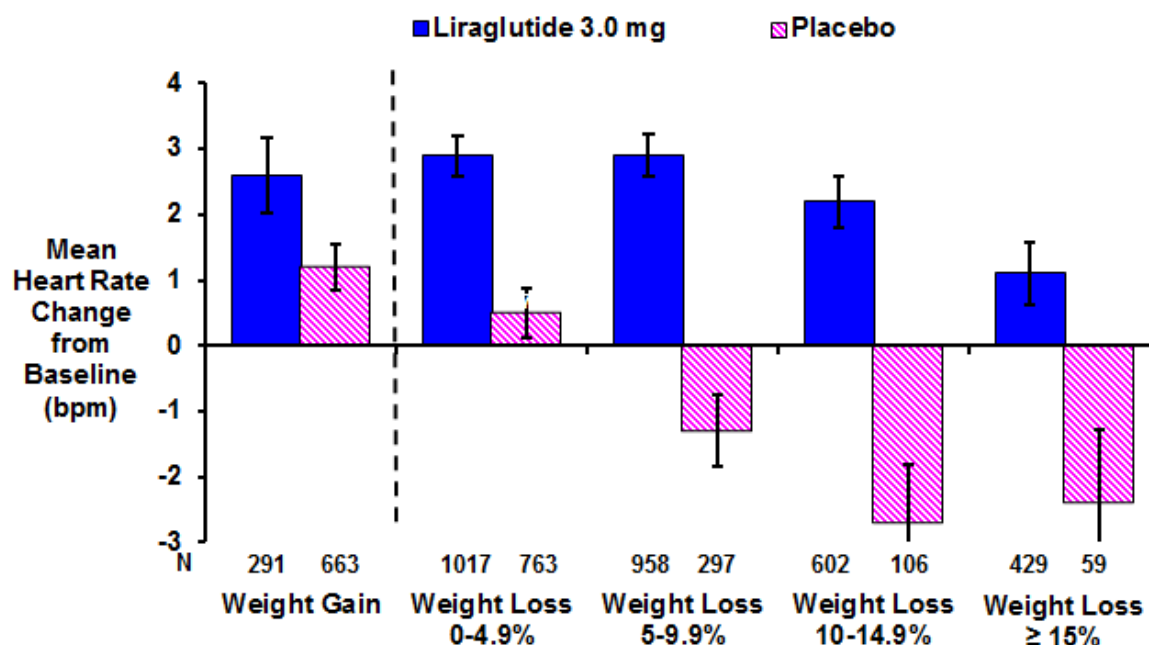


Persistent increase is defined as an increase at 2 or more consecutive visits. Mean change  $\pm$  SE (LOCF), N: number of patients in subgroup; SBP: systolic blood pressure; HR: heart rate

**Figure 6–15 Mean changes in systolic blood pressure at end of treatment by persistent change heart rate category**

Weight loss generally is associated with a decrease in heart rate.<sup>166</sup> This pattern was maintained in the overall weight management population although at each category of weight (gain or loss), heart rate was higher with liraglutide than with placebo ([Figure 6–16](#)).

A persistent increase (defined as an increase at  $\geq 2$  consecutive visits) of resting heart rate  $>20$  beats/min was reported for 4.9% of the liraglutide 3.0 mg-treated patients and for 1.7% of the placebo-treated patients ([Table 6–15](#)).



Mean change from baseline until end of trial (LOCF, SE), N, number of patients in subgroup.

**Figure 6–16 Change in heart rate by magnitude of weight loss at the end of the trial: weight management pool (NDA)**

**Table 6–15 Persistent changes from baseline in resting heart rate (beats/min): weight management program (NDA)**

|   | ----- Liraglutide 3.0 mg ----- |        | ----- Placebo ----- |        |
|---|--------------------------------|--------|---------------------|--------|
|   | N                              | (%)    | N                   | (%)    |
| Number of patients                                      | 3384                           |        | 1941                |        |
| change in heart rate > 10 bpm at ≥ 2 consecutive visits | 1151                           | (34.0) | 371                 | (19.1) |
| > 5 changes in heart rate > 10 bpm                      | 594                            | (17.6) | 126                 | (6.5)  |
| > 10 changes in heart rate > 10 bpm                     | 187                            | (5.5)  | 21                  | (1.1)  |
| change in heart rate > 10 bpm at all visits             | 62                             | (1.8)  | 12                  | (0.6)  |
| change in heart rate > 20 bpm at ≥ 2 consecutive visits | 167                            | (4.9)  | 33                  | (1.7)  |
| > 5 changes in heart rate > 20 bpm                      | 46                             | (1.4)  | 5                   | (0.3)  |
| > 10 changes in heart rate > 20 bpm                     | 11                             | (0.3)  | 1                   | (<0.1) |
| change in heart rate > 20 bpm at all visits             | 4                              | (0.1)  | 1                   | (<0.1) |

N: Number of patients fulfilling criteria, bpm: Beats per minute

Similarly, a persistent ( $\geq 2$  consecutive visits) post-baseline resting heart rate of  $> 90$  beats/min was reported for 7.3% of the liraglutide 3.0 mg-treated patients and for 4.0% of the placebo-treated patients ([Table 6–16](#)).

**Table 6–16 Persistent maximal heart rate at any time during the trial: weight management program (NDA)**

|   | Liraglutide 3.0 mg |            | Placebo |            |
|---|--------------------|------------|---------|------------|
|   | N                  | (%)        | N       | (%)        |
| Number of patients                                    | 3384               |            | 1941    |            |
| heart rate $> 90$ bpm at $\geq 2$ consecutive visits  | 248                | (7.3)      | 77      | (4.0)      |
| $> 5$ heart rate assessments $> 90$ bpm               | 99                 | (2.9)      | 18      | (0.9)      |
| $> 10$ heart rate assessments $> 90$ bpm              | 24                 | (0.7)      | 2       | (0.1)      |
| heart rate $> 90$ bpm at all visits                   | 11                 | (0.3)      | 3       | (0.2)      |
| heart rate $> 100$ bpm at $\geq 2$ consecutive visits | 31                 | (0.9)      | 5       | (0.3)      |
| $> 5$ heart rate assessments $> 100$ bpm              | 7                  | (0.2)      | 1       | ( $<0.1$ ) |
| $> 10$ heart rate assessments $> 100$ bpm             | 2                  | ( $<0.1$ ) | 0       | (0.0)      |
| heart rate $> 100$ bpm at all visits                  | 1                  | ( $<0.1$ ) | 2       | (0.1)      |

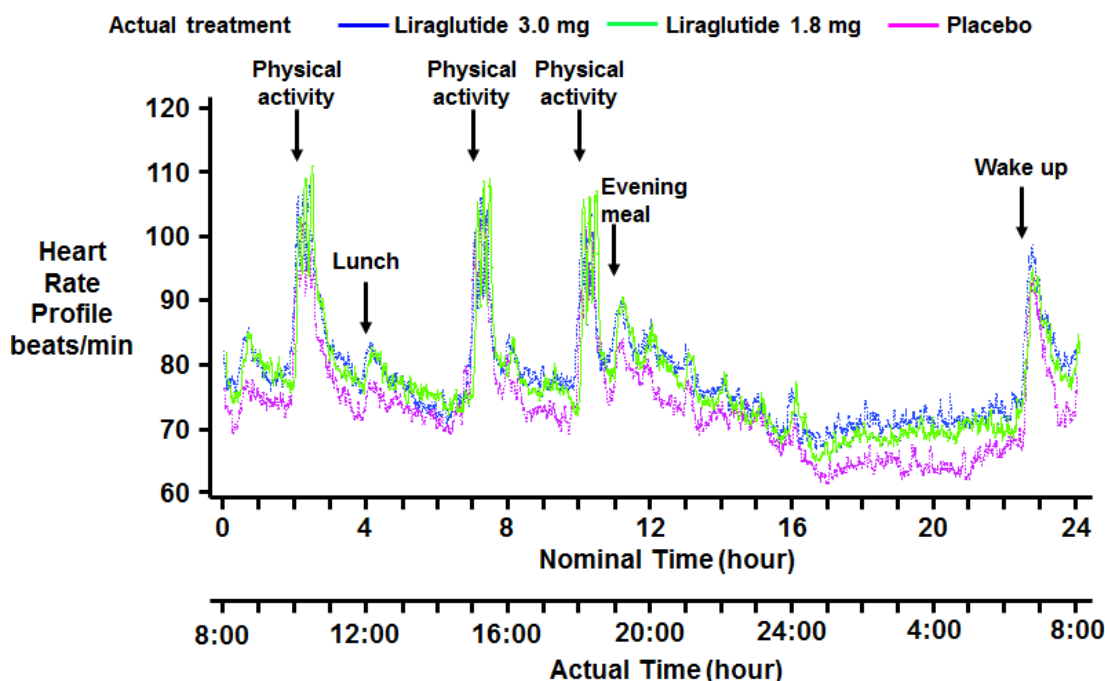
N: Number of patients fulfilling criteria, bpm: Beats per minute

Analyses of categorical increases in resting heart rate (incidental, persistent) were also investigated by baseline heart rate quartile. As expected, more patients in the highest baseline quartile ( $>78$  beats/min) had incidental and persistent resting heart rate of  $\geq 80$  beats/min and  $\geq 90$  beats/min in both groups, and more so with liraglutide 3.0 mg. The likelihood of having incidental or persistent increase in resting heart rate of  $> 20$  beats/min was greater in the lower baseline quartiles. Very few patients in the highest baseline quartile ( $>78$  beats/min) had end-of-treatment resting heart rate increase of  $>20$  beats/min or persistent increase  $> 20$  beats/min (0.3% and 0.7% with liraglutide 3.0 mg and placebo, respectively). Likewise, very few patients ( $<1\%$  in both groups) with a baseline resting heart rate in the 3 lowest quartiles ( $\leq 78$  beats/min) had end-of-treatment resting heart rate of 100 beats/min.

#### 6.3.4.4 Diurnal variation of heart rate

To further understand the increase in heart rate with liraglutide treatment, the effects of liraglutide on heart rate were investigated by 24-hour continuous heart rate monitoring in the mechanistic clinical pharmacology trial (trial 3630) in obese non-diabetic patients (liraglutide 3.0 mg: 32 patients, liraglutide 1.8 mg: 30 patients, placebo: 32 patients). As seen from [Figure 6–17](#), both placebo and liraglutide-treated patients exhibited a normal physiological circadian heart rate profile. Liraglutide treatment (3.0 mg and 1.8 mg) resulted in an increased mean heart rate throughout the 24-hour period; the increase was more pronounced during night time than during day time. There were no differences between liraglutide doses (3.0 and 1.8 mg), except during sleep at the time of

the lowest physical activity where the increase in heart rate was greatest with liraglutide 3.0 mg (treatment difference to liraglutide 1.8 mg was 1.9 beats/min).



Liraglutide 3.0 mg: 32 patients, liraglutide 1.8 mg: 30 patients, placebo: 32 patients.

**Figure 6-17 Mean 24-hour Heart Rate Profiles: Clinical Pharmacology Trial 3630**

These results are in alignment with results obtained in trial 3970 (in obese patients with moderate or severe obstructive sleep apnea), which showed a decrease in heart rate during the night in both treatment groups, but less so with liraglutide 3.0 mg than placebo.

The mechanism underlying the increase in resting heart rate is not currently understood but does not appear to involve increased activation of the sympathetic nervous system. This was supported by results from the clinical pharmacology trial 3630, where liraglutide treatment did not significantly change 24-hour energy expenditure, and no treatment differences were observed for urinary adrenalin excretion, while a significant decrease in urinary noradrenalin excretion (~11%) was observed. The presence of GLP-1 receptors on the sino-atrial node suggests a direct chronotropic effect of treatment.<sup>52</sup>

The increase in heart rate noted with liraglutide in the weight management pool is consistent with data from the T2DM development program for liraglutide and for other GLP-1 receptor agonists. No particular patient sub-population could be identified to be at higher risk for elevated heart rate other than those with the lowest baseline heart rate. The differences between liraglutide and placebo were consistent across all sub-populations of patients. The implications of the increase in heart rate

remain unclear but have been further investigated by assessing episodes of arrhythmia and MACE events as the most relevant clinical outcomes. Few cases of EAC-confirmed heart failure occurred in the weight management pool; 1 with placebo and 1 with liraglutide 3.0 mg.

#### 6.3.4.5 Cardiac Arrhythmia

Liraglutide at doses up to 1.8 mg does not produce QTc prolongation and no exposure-response relationship is observed between  $\Delta$ QTc and liraglutide exposure. As agreed with the FDA, these findings can be extrapolated to the obese patients in the weight management pool based on substantial overlap between exposures in the QTc trial in obese/overweight individuals treated with 3.0 mg (Section [4.2.4](#)).

A predefined MedDRA search was performed among all AEs to identify and summarize all events potentially related to cardiac arrhythmia ([Appendix Section 5.2](#)). The proportion of patients with events and the rates of these events were similar with liraglutide 3.0 mg (3.3%, 4.4 event per 100 PYE) and placebo (3.0%, 4.0 event per 100 PYE). ‘Palpitations’, ‘syncope’ and ‘tachycardia’ were the most frequent events in both groups; all were reported by less than 1% of patients in both groups ([Table 6–17](#)). The remaining events occurred at even lower frequency in both groups. A similar picture was observed across the individual trials and lower doses of liraglutide. Likewise, analyses of centrally-read ECGs did not reveal imbalances for conduction/rhythm disorder.

‘Tachycardia’ was reported by a higher proportion of patients with liraglutide 3.0 mg (0.6%) than with placebo (0.1%). All ‘tachycardia’ events but one (in a patient treated with liraglutide 3.0 mg) were non-serious, and no patients were withdrawn due to ‘tachycardia’ in either group. The SAE of ‘tachycardia’ was reported in a patient who had undergone embolectomy (reported as an SAE) approximately 4 weeks earlier. Further investigation of treatment effect on event rates across sub-populations (sex, age, baseline use of beta blockers and weight loss categories) revealed no significant trends.



**Table 6–17 Treatment-emergent events of cardiac arrhythmia identified by MedDRA search (reported by  $\geq 0.1\%$  of patients in either group): weight management program (NDA)**

|                                     | Liraglutide 3.0 mg<br>(N=3384) |      |    |      | Placebo<br>(N=1941) |     |    |     |
|-------------------------------------|--------------------------------|------|----|------|---------------------|-----|----|-----|
|                                     | N                              | %    | E  | R    | N                   | %   | E  | R   |
| Palpitations                        | 25                             | 0.7  | 28 | 0.9  | 18                  | 0.9 | 22 | 1.4 |
| Syncope                             | 21                             | 0.6  | 23 | 0.8  | 9                   | 0.5 | 9  | 0.6 |
| Tachycardia                         | 19                             | 0.6  | 19 | 0.6  | 2                   | 0.1 | 2  | 0.1 |
| Atrial fibrillation                 | 9                              | 0.3  | 10 | 0.3  | 5                   | 0.3 | 5  | 0.3 |
| Atrioventricular block first degree | 6                              | 0.2  | 7  | 0.2  | 0                   | 0.0 | 0  | 0.0 |
| Arrhythmia                          | 5                              | 0.1  | 5  | 0.2  | 3                   | 0.2 | 3  | 0.2 |
| Heart rate increased                | 5                              | 0.1  | 5  | 0.2  | 2                   | 0.1 | 2  | 0.1 |
| Ventricular extrasystoles           | 5                              | 0.1  | 5  | 0.2  | 2                   | 0.1 | 3  | 0.2 |
| Bundle branch block right           | 4                              | 0.1  | 4  | 0.1  | 0                   | 0.0 | 0  | 0.0 |
| Supraventricular extrasystoles      | 4                              | 0.1  | 4  | 0.1  | 0                   | 0.0 | 0  | 0.0 |
| Electrocardiogram abnormal          | 3                              | <0.1 | 3  | 0.1  | 3                   | 0.2 | 3  | 0.2 |
| Sinus bradycardia                   | 2                              | <0.1 | 2  | <0.1 | 3                   | 0.2 | 3  | 0.2 |
| Sinus tachycardia                   | 1                              | <0.1 | 1  | <0.1 | 3                   | 0.2 | 3  | 0.2 |
| Bradycardia                         | 1                              | <0.1 | 1  | <0.1 | 2                   | 0.1 | 2  | 0.1 |
| Extrasystoles                       | 1                              | <0.1 | 1  | <0.1 | 2                   | 0.1 | 2  | 0.1 |

N: Total number of patients; %: Percentage of patients experiencing at least one event; E: number of events; R: event rate per 100 PYE.

#### 6.3.4.6 Major Adverse Cardiovascular Events

Major Adverse Cardiovascular Events (MACE) were defined and classified according to the FDA guidance for assessment of CV risk issued for drugs to be used for treatment of T2DM and comprise non-fatal MI, non-fatal stroke and cardiovascular death ([Table 6–18](#)). In the integrated analyses of MACE events, events of MACE were considered treatment-emergent if reported no later than 30 days after last treatment.

A pre-specified meta-analysis was defined for the weight management pool to investigate the effect of treatment with liraglutide (all doses), compared to a pooled comparator group (placebo and active comparator), on cardiovascular safety. The primary endpoint of time from first drug date to first occurrence of MACE was analyzed using a Cox proportional hazards model stratified by trial with treatment as explanatory variable. Patients not experiencing an event in the treatment period or within 30 days after last dose were censored at last treatment date plus 30 days. The population for this analysis was the on-treatment analysis population. A number of sensitivity analyses were performed in order to evaluate the robustness of the primary analysis, these included liraglutide 3.0 mg dose vs. placebo, censoring at end of treatment (time of last dose), including off-drug follow-up periods, and Mantel-Haenszel asymptotic method stratified by trial. The analyses were repeated based on all data available up to the cut-off for the 120-Day Safety Update and were consistent with the analysis conducted for the NDA but only the latter data (120-Day Safety Update) will be presented below.

Overall, the number of EAC-confirmed events was low as expected for the population enrolled in the weight management pool. The event rate was lower with liraglutide 3.0 mg (0.18%, 0.16 events per 100 PYE) than with placebo (0.52%, 0.43 events per 100 PYE), and consistent across the 3 components of the composite endpoint ([Table 6–18](#)).

**Table 6–18 Adjudicated MACE in weight management pool for the on-treatment analysis population (through 120-Day Safety Update)**

|                      | Liraglutide 3.0 mg |       |      |      | Total Liraglutide |       |      |      | Comparator |       |      |     |
|----------------------|--------------------|-------|------|------|-------------------|-------|------|------|------------|-------|------|-----|
|                      | N                  | (%)   | E    | R    | N                 | (%)   | E    | R    | N          | (%)   | E    | R   |
| Number of patients   |                    |       | 3384 |      |                   |       | 3872 |      |            |       | 2036 |     |
| EAC Confirmed Events | 6                  | (0.2) | 7    | 0.2  | 9                 | (0.2) | 10   | 0.2  | 10         | (0.5) | 10   | 0.4 |
| Non-fatal Myocardial | 3                  | (0.1) | 3    | 0.1  | 5                 | (0.1) | 5    | 0.1  | 5          | (0.3) | 5    | 0.2 |
| Non-fatal Stroke     | 2                  | (0.1) | 2    | <0.1 | 3                 | (0.1) | 3    | 0.1  | 3          | (0.2) | 3    | 0.1 |
| Cardiovascular Death | 2                  | (0.1) | 2    | <0.1 | 2                 | (0.1) | 2    | <0.1 | 2          | (0.1) | 2    | 0.1 |

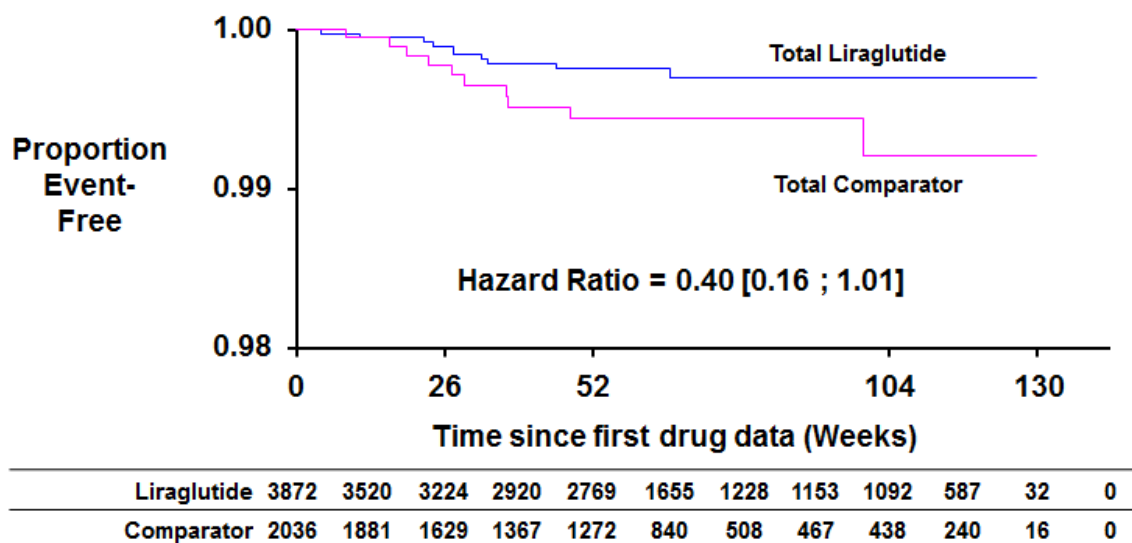
EAC: (external) Event adjudication committee, MACE: Major cardiovascular event, N: Number of patients, %:

Percentage of patients, E: Number of events, R: Event rate per 100 years of exposure

Cardiovascular death includes 1 case adjudicated as unknown cause of death.

A Kaplan Meier analysis of time to first MACE event demonstrates the low event rate and shows that the total liraglutide group trended toward a lower probability of MACE than comparator (primary analysis) throughout the observation period ([Figure 6–18](#)).

The MACE analysis (primary and key sensitivity analyses) provided the following hazard ratios and 95% confidence intervals: 0.40 [0.16; 1.01] for total liraglutide *versus* total comparator (primary analysis, number of events = 19), and 0.33 [0.12; 0.90] for liraglutide 3.0 mg *versus* placebo (sensitivity analysis, number of events = 16).



Events are 3-component MACE; on-treatment analysis population  
Weight management pool (pooled phase 2 and 3 trials)

**Figure 6–18 Kaplan-Meier plot of time to first MACE in weight management analysis (through 120-Day Safety Update)**

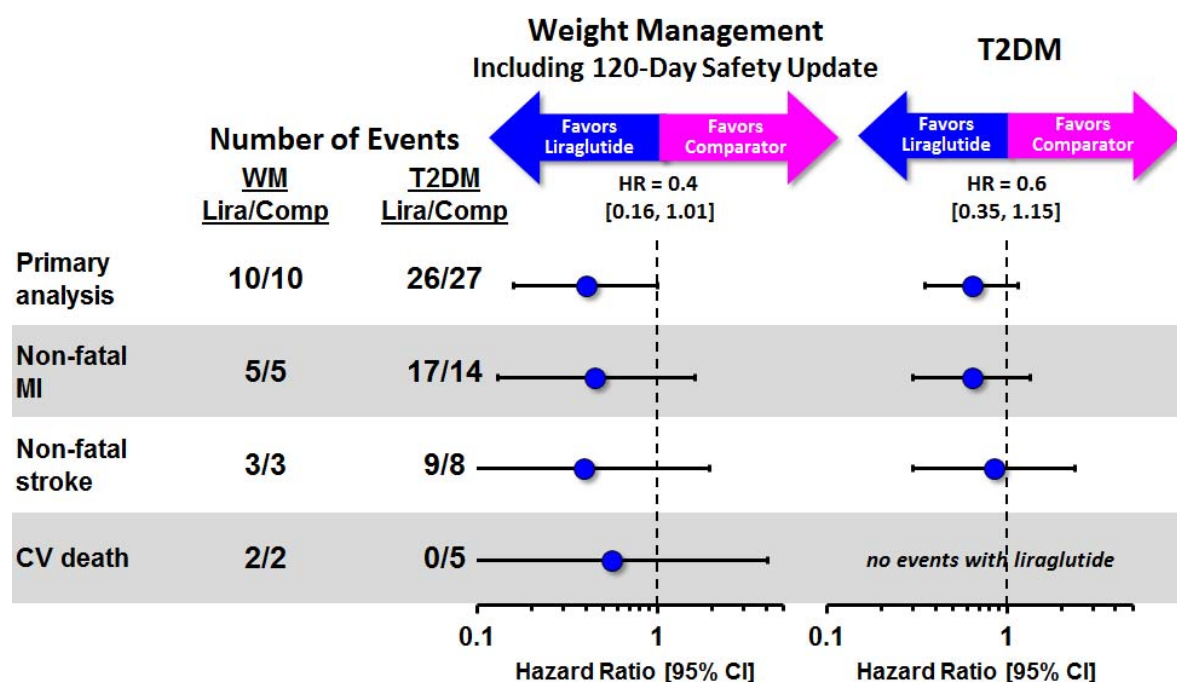
To further support the primary analysis and confirm the robustness of the results, a pre-specified pooled analysis of all (27) controlled phase 2 and 3 trials with liraglutide in the weight management and T2DM clinical development programs was conducted (see [Table 6–1](#)). Pooling of MACE was considered appropriate based on the overlap in phenotypic characteristics of the populations, as well as consistency in the direction of treatment estimates of the hazard ratios across populations (weight management, T2DM) and dose (0.9 mg to 3.0 mg).

For this analysis, *post hoc* adjudication using all available source information was conducted for all trials that did not prospectively identify and adjudicate MACE. This included all trials with liraglutide in T2DM as well as the dose finding trial 1807 in the weight management program. Events were identified by the following 5 SMQs for the MedDRA 15.1 preferred terms: ‘Myocardial infarction’, ‘Other ischemic heart disease’, ‘Ischemic cerebrovascular conditions’, ‘Hemorrhagic cerebrovascular conditions’, and ‘Conditions associated with central nervous system hemorrhages and cerebrovascular accidents’, and further classified as non-fatal myocardial infarction or non-fatal stroke according to the criteria described in the event adjudication charter. Adjudication of all serious and non-serious adverse events was performed by the blinded external independent committee. All deaths were adjudicated and categorized as either ‘CV death’, ‘non-CV death’ or ‘death due to unknown cause’. All events were further categorized according to the likelihood of being a MACE, and all events deemed ‘definitely’ or ‘likely’ MACE, as well as all

‘deaths due to unknown cause’ were considered as confirmed MACE. Confirmed events were included in the meta-analysis.

Consistent with the primary analysis for the weight management trials, the primary endpoint in the combined weight management and T2DM meta-analysis was analyzed using a Cox proportional hazards model stratified by trial with treatment as explanatory variable for trials in the development programs. The population for this analysis was the on-treatment analysis population and included events through the cut-off for the weight management NDA. The hazard ratio and 95% confidence interval was 0.56 [0.34; 0.93] (total liraglutide vs. total comparator, number of events=70) for the combined analysis of EAC confirmed MACE from all trials within the weight management and T2DM clinical development programs.

Figure 6–19 illustrates the consistency between programs as well as across individual components of the composite MACE endpoint. The hazard ratio and confidence intervals for the primary analysis and each of the individual components are given for each development program separately.



WM, weight management; MI, myocardial infarction; CV, cardiovascular; HR, hazard ratio; “Lira” includes all doses of liraglutide; “Comp” includes all comparators. The events in WM program occurred through 120 DSU, while the events in the T2DM programs occurred through WM NDA cut-off.

**Figure 6–19 MACE analysis in weight management (through 120-Day Safety Update) and T2DM programs (NDA)**

In conclusion, the results of the MACE meta-analysis provide no evidence of an excess cardiovascular risk with liraglutide, including liraglutide 3.0 mg. This is consistent with previous MACE meta-analyses of randomized clinical trials of at least 24 weeks duration with GLP-1 receptor agonists in patients with T2DM.<sup>165,167,168</sup>

#### **6.3.4.7 Experience with liraglutide in the type 2 diabetes programs**

No cardiovascular signal was observed during the development program for liraglutide 1.8 mg for T2DM.

As a post-marketing requirement for liraglutide in type 2 diabetes, Novo Nordisk is conducting the LEADER<sup>®</sup> trial, an ongoing cardiovascular outcome trial. LEADER<sup>®</sup> enrolled two distinct populations of high-risk patients either with or without prior cardiovascular disease (CVD): (1) 7,592 patients with prior CVD who were  $\geq 50$  years of age and had one or more of the following cardiovascular co-morbidities: concomitant CVD, cerebrovascular disease, peripheral vascular disease, chronic renal failure, or chronic heart failure; (2) 1,748 patients without prior CVD who were  $\geq 60$  years of age at screening and had one or more cardiovascular risk factors. The mean age of patients was  $64.3 \pm 7.2$  years, 64.3% were men, and mean body mass index was  $32.5 \pm 6.3$  kg/m<sup>2</sup>.<sup>53</sup>

The primary objective of LEADER<sup>®</sup> is to assess the effect of treatment with liraglutide 1.8 mg plus standard of care compared to placebo plus standard of care (for at least 3.5 years and up to 5 years) on the incidence of MACE, as defined by the primary endpoint of cardiovascular death, non-fatal myocardial infarction or stroke, in adult patients with T2DM. The trial is fully enrolled with 9,340 patients and is scheduled to report in 2016.

Novo Nordisk believes that the results of this trial will further add to our understanding of risk for the 3.0 mg dose of liraglutide. A significant number of patients in LEADER<sup>®</sup> are overweight or obese (>7,500 patients with BMI  $>27$  kg/m<sup>2</sup>, >5,500 patients with BMI  $>30$  kg/m<sup>2</sup>), and all have T2DM and high cardiovascular risk.

#### **6.3.4.8 Conclusions for cardiovascular safety in the weight management program**

Consistent with the pharmacology of the GLP-1 receptor agonist class and the non-clinical and clinical data observed with liraglutide, no signals or notable imbalances between liraglutide 3.0 mg and placebo were noted in cardiovascular AEs across the 5 weight management trials. An increase in resting heart rate has previously been reported with liraglutide and other GLP-1 receptor agonists, and this finding was replicated in the weight management pool. The increase in heart rate was not dose dependent within the clinical dose range used in the weight management trials. The clinical significance of the increase in resting heart rate remains to be determined. In the weight management trials, the resting heart rate increase was accompanied by decreases in both systolic and diastolic blood pressure and improvements in other cardio-metabolic risk factors, and was not associated with an increased risk of MACE or other clinically significant adverse outcomes. Nevertheless, the heart rate increase will be noted in product labeling. Long-term cardiovascular

outcome trials with GLP-1 receptor agonists in patients with T2DM are currently ongoing, including LEADER<sup>®</sup> (liraglutide 1.8 mg) that will provide data on the CV-risk profile of liraglutide in a population of patients at higher risk than the obesity population studied in phase 3.

### 6.3.5 Neoplasm

#### 6.3.5.1 Background

Obesity has been recognized to be associated with an increased risk of various neoplasms. These include cancers of the esophagus, pancreas, colon and rectum, breast (after menopause), endometrium, kidney, thyroid, and gallbladder.<sup>169</sup> Various mechanisms have been suggested to explain the association of obesity with increased risk of certain cancers. These include: 1) excess estrogen production in women in fat tissue (high levels are associated with risk of breast, endometrial and other cancers); 2) high circulating levels of insulin and insulin-like growth factor-1 (IGF-1) which have been suggested to promote the development of certain tumors; and 3) adipokines.<sup>170</sup> A recent meta-analysis reported an association between weight loss and the reduction in risk of obesity-related cancers, particularly in women.<sup>171</sup>

Neither liraglutide nor any of the other approved GLP-1 receptor agonists are mutagenic or genotoxic.<sup>15,172,173</sup> In the non-clinical safety studies with liraglutide, no treatment-related tumors have been found except for thyroid C-cell tumors and skin fibrosarcomas (3.4.3). The relevance of these rodent findings to humans is considered to be low. There are currently no long-term clinical studies of sufficient size and duration to permit conclusions regarding cancer risk in humans.<sup>174</sup> However, based on available clinical and non-clinical data, there is no indication that GLP-1 receptor agonists are associated with an increased risk of cancer.

Because of the rodent findings, marketed GLP-1 receptor agonists (liraglutide, exenatide, albiglutide) are contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia type 2 (MEN2).

In post-marketing reports, liraglutide (at doses up to 1.8 mg) has not been associated with increased incidence of cancer in more than 3.3 million patient years of clinical use or based on pharmacoepidemiology and case-series registry data.

#### 6.3.5.2 Methodology

Neoplasms were defined as MESI in the liraglutide weight management program and events were identified and subjected to external, blinded, independent adjudication as described in [Appendix Figure 5-1](#) and Section [6.1.2.2](#).

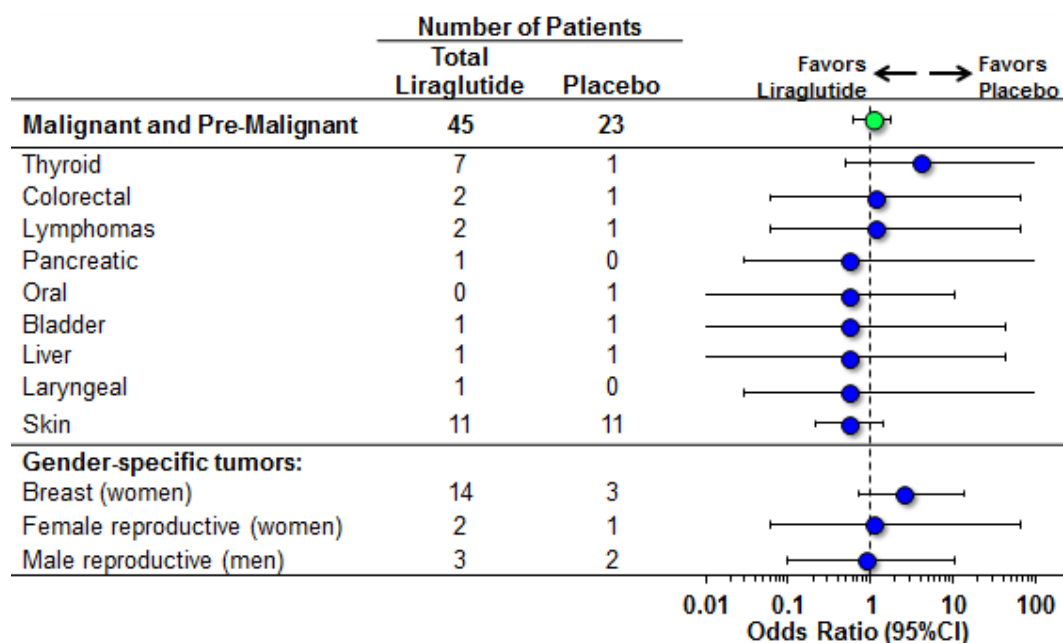
Neoplasm events were evaluated by the EAC with regard to confirmation of the diagnosis, malignancy status, staging of malignant neoplasms, and tissue/organ class of origin. Thyroid disorders requiring thyroidectomy were subject to adjudication with respect to whether the event was a thyroid neoplasm and the type of neoplasm, malignancy status, and the stage of the neoplasm



in case the thyroid neoplasm could be classified as medullary microcarcinoma (carcinoma *in situ*) or a MTC. Adjudication was based on review of the pathology report and any other relevant source documents.

### 6.3.5.3 Overview of neoplasms in the weight management program

There was no overall increased risk of EAC-confirmed neoplasms (malignant, malignant and pre-malignant combined, benign) in the weight management pool, based on all events reported by patients currently and previously treated with liraglutide (and placebo) through the 120-Day Safety Update. The estimated exact odds ratios [95% CI] for total liraglutide vs. placebo were 1.00 [0.56; 1.85] for 'malignant neoplasms', 0.96 [0.57; 1.68] for 'malignant and pre-malignant neoplasms combined' (Figure 6–20), and 1.31 [0.72; 2.49] for 'benign neoplasms', respectively. The overall incidence of adjudicated malignant and pre-malignant neoplasms was low and similar between total liraglutide, liraglutide 3.0 mg and placebo; for malignant neoplasms: 0.84 events per 100 PYR, 0.88 events per 100 PYR, and 0.96 events per 100 PYR, respectively, and for pre-malignant neoplasms: 0.15 events per 100 PYR, 0.15 events per 100 PYR, and 0.35 PYR respectively, through the 120-Day Safety Update.



All malignant and pre-malignant events occurred with liraglutide 3.0 mg

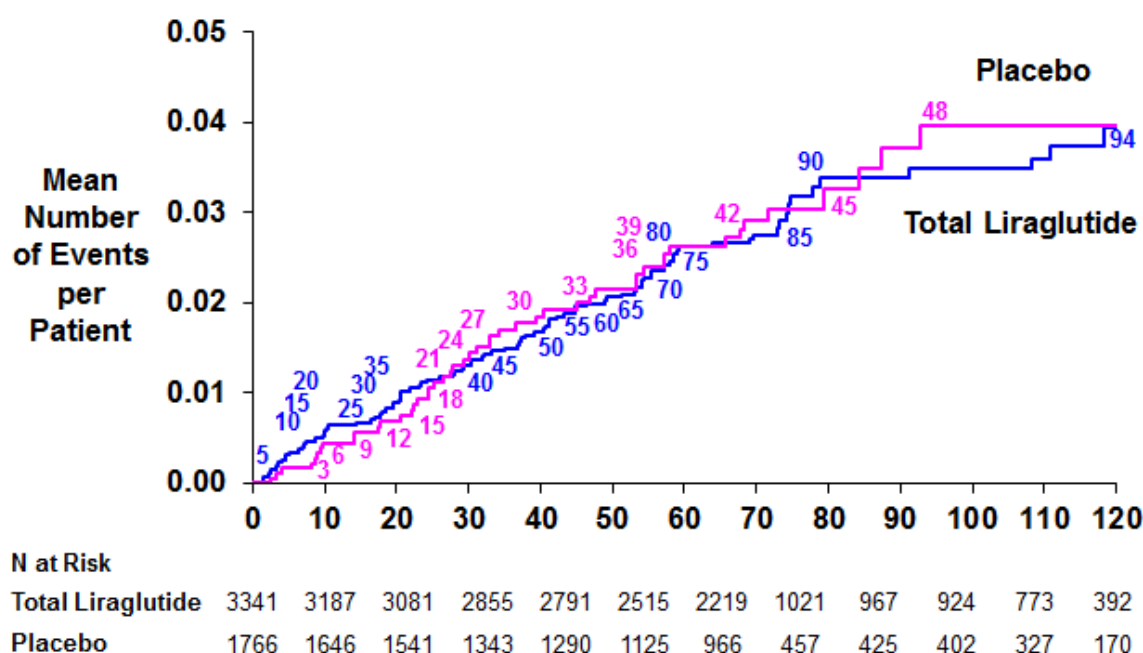
Treatment-emergent and non-treatment emergent events included

Upper 95% CI limit for thyroid extends to 177 and to infinity for pancreatic and laryngeal. Lower 95% CI limit for oral, bladder, and liver extends to infinity.

**Figure 6–20 EAC-confirmed malignant and pre-malignant neoplasms (combined) in phase 3 trials (through 120-Day Safety Update)**

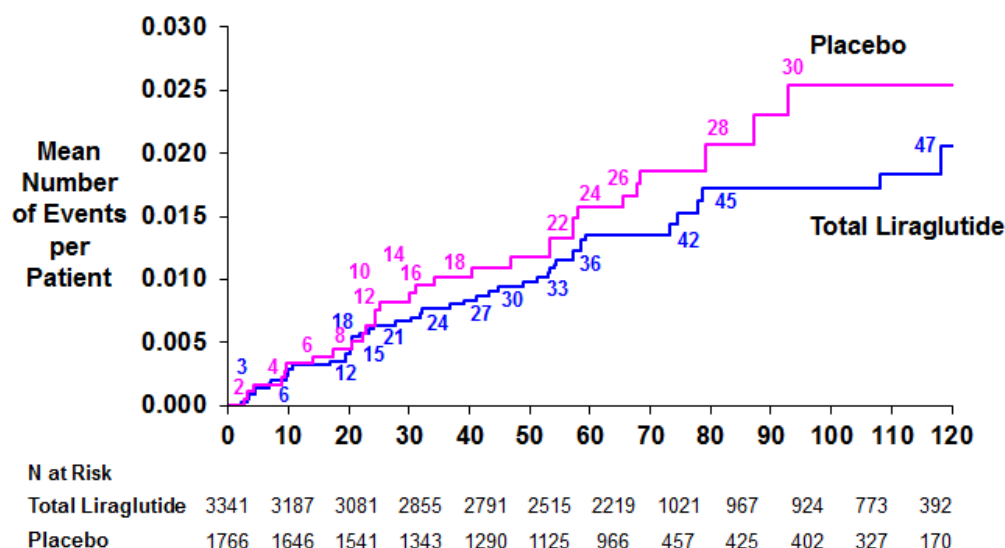


In both treatment groups, the majority of EAC-confirmed neoplasms were captured during the main treatment periods (0-56 weeks), as illustrated by [Figure 6–21](#) for all neoplasms (malignant, pre-malignant and benign neoplasms combined), and by [Figure 6–22](#) for all malignant and pre-malignant neoplasms combined. There was no indication of an increasing rate with prolonged exposure. This was also true when considering the events from trial 1839 alone, the only trial in which patients were exposed to liraglutide 3.0 mg for more than a year ([Figure 6–23](#), all malignant and pre-malignant neoplasms).



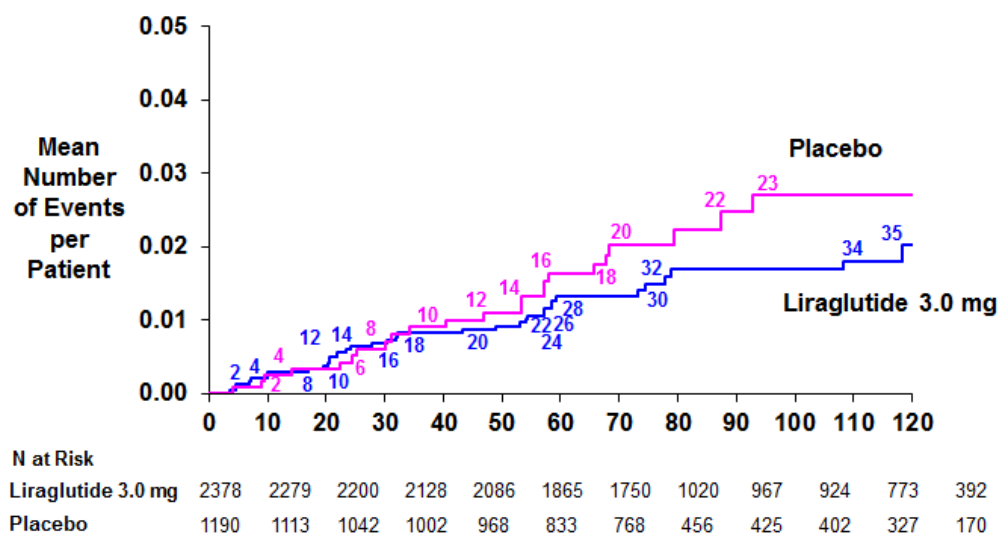
Output based on 1839 including re-randomized period and 120-Day safety update, 1922 and 1923 including 12 weeks follow-up period, and 3970. Patients are allocated according to treatment in the main treatment period. Risk time is defined as the time between first drug date and last contact as non-treatment emergent events are included. Numbers in plot represent cumulative neoplasms at that time point.

**Figure 6–21 Mean cumulative events of EAC-confirmed neoplasms over time: phase 3 trials (through 120-Day Safety Update)**



Output based on 1839 including re-randomized period and 120-Day safety update, 1922 and 1923 including 12 weeks follow-up period, and 3970. Patients are allocated according to treatment in the main treatment period. Risk time is defined as the time between first drug date and last contact as non-treatment emergent events are included. Numbers in plot represent cumulative neoplasms at that time point. All liraglutide events occurred with the liraglutide 3.0 mg dose.

**Figure 6-22 Mean cumulative events of EAC-confirmed malignant and pre-malignant neoplasms over time: phase 3 trials (through 120-Day Safety Update)**



Output based on 1839 including re-randomized period and 120-Day safety update. Patients are allocated according to treatment in the main treatment period. Risk time is defined as the time between first drug date and last contact as non-treatment emergent events are included. Numbers in plot represent cumulative neoplasms at that time point.

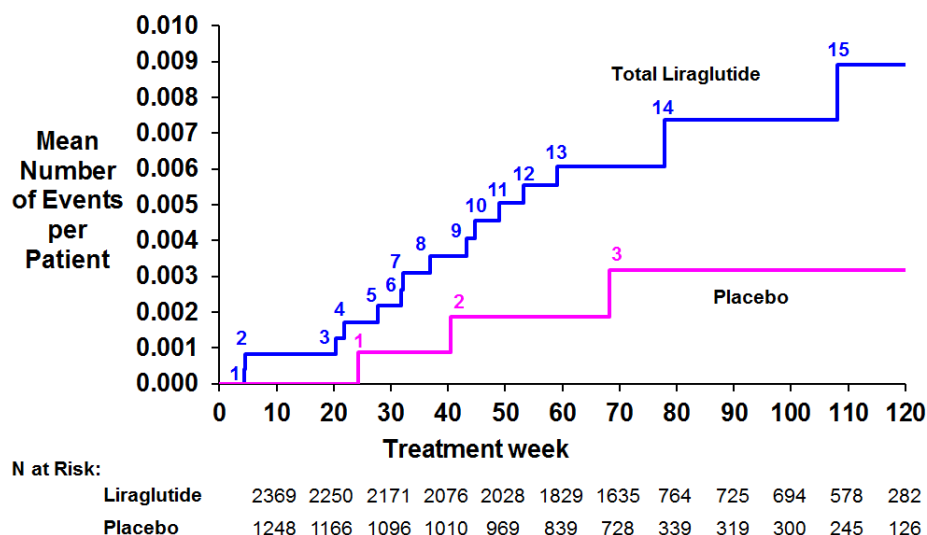
**Figure 6-23 Mean cumulative events of EAC-confirmed malignant and pre-malignant neoplasms over time: Trial 1839 (through 120-Day Safety Update)**

Based on an overall low number of events, breast cancer (malignant) and breast carcinoma *in situ* (pre-malignant) occurred more frequently in women treated with liraglutide 3.0 mg compared with placebo (Section 6.3.5.4). In addition, the incidence of benign colorectal neoplasms appeared higher with liraglutide 3.0 mg than with placebo (Section 6.3.5.7). Selected types of neoplasms, including breast and colorectal neoplasms, are described in further detail below.

#### 6.3.5.4 Breast neoplasms

Breast cancer (malignant, invasive) and breast carcinoma *in situ* (pre-malignant) occurred more frequently in women treated with liraglutide as compared with placebo. All malignant and pre-malignant neoplasm events with liraglutide occurred at the liraglutide 3.0 mg dose, consistent with its relative contribution to overall liraglutide exposure. In total, 12 invasive (malignant) cancers in 11 women (0.46% of women, one of whom developed bilateral breast cancer at age 37; 0.36 events per 100 PYR) were reported with liraglutide 3.0 mg and 2 invasive cancers in 2 women (0.15% of women, 0.12 events per 100 PYR) with placebo (exact odds ratio [95% CI]: 3.01 [0.66; 28.03]). One of the invasive breast cancer events occurring with liraglutide was a metastatic recurrence of a previous node positive, triple negative (estrogen receptor, progesterone receptor and HER2 negative) breast cancer diagnosed in 2009, prior to liraglutide exposure. Four cases of ductal carcinoma *in situ* were reported – three with liraglutide 3.0 mg (0.13% of women, 0.09 events per 100 PYR) and one with placebo (0.08% of women, 0.06 events per 100 PYR). In total, 14 women on liraglutide 3.0 mg developed malignant or pre-malignant breast neoplasms (0.59%) vs. 3 women on placebo (0.23%), an excess absolute risk of 0.36% percentage point with an odds ratio not statistically significantly different from 1 (exact odds ratio 2.56 [0.71; 13.91]). The incidence of invasive breast cancer in the liraglutide 3.0 mg group appears to be comparable to that of the background population, which ranges from 1.02 events per 1000 PYE to 2.67 events per 1000 PYE in obese pre-menopausal women<sup>175-179</sup>, and between 2.40 events per 1000 PYE to 7.04 events per 1000 PYE in obese post-menopausal women,<sup>175-177,179-182</sup> assuming that at least two-thirds of the women diagnosed with breast cancer in the liraglutide group were post-menopausal based on their age ( $\geq 50$  years) at randomization. Over a third of the females with breast cancer had relevant medical history (previous breast neoplasm or cancer, family history of breast cancer or history of hormone replacement therapy).

Relative to exposure (total PYR), the majority of the events occurred within the first 12 months of treatment, which does not indicate increased incidence with longer-term exposure (Figure 6–24).



Output based on 1839 including re-randomized period and 120-Day safety update, 1922 and 1923 including 12 weeks follow-up period, and 3970. Patients are allocated according to treatment in the main treatment period. Risk time is defined as the time between first drug date and last contact as non-treatment emergent events are included. Numbers in plot represent cumulative breast neoplasms at that time point. All liraglutide events occurred with the liraglutide 3.0 mg dose.

**Figure 6–24 Mean cumulative events of EAC-confirmed malignant and pre-malignant breast neoplasms in women over time: phase 3 trials (through 120-Day Safety Update)**

[Table 6–19](#) provides information relating to age at diagnosis of a breast neoplasm, interval between study entry and breast neoplasm diagnosis, whether the neoplasm was screen detected (vs. not), tumor grade and stage (TNM, AJCC/EAC) and hormone receptor status.

In women receiving liraglutide, invasive neoplasms were diagnosed between 30 and 756 days post-randomization (in 7 women during the first year and in 4 women after the first year). Eight of the 11 women were over 50 years at diagnosis. Approximately one-half of the tumors were screen detected and all had an infiltrating ductal component. As noted above, one of the events was a metastatic recurrence (occurring 313 days after liraglutide was begun) of a previously diagnosed node positive, triple negative breast cancer. Tumor size ranged from T1 to T3. The majority (8 of 10 cancers with known grade) were Grade II to III and the majority (7 of 9 non-metastatic cases with known stage) had nodal involvement. All tumors with known HER2 status were HER2 negative; the majority (6 of 8 non-metastatic cases with known hormone receptor status) were estrogen receptor (ER) or progesterone receptor (PgR) positive. In the placebo group, the two malignant breast neoplasms were diagnosed at 282 (age 40) and 477 (age 62) days. The first of these cases (diagnosed at 282 days) received neoadjuvant chemotherapy for a breast cancer with ‘known nodal involvement’ (post neoadjuvant chemotherapy pathologic staging was T1bN0); the other case was staged as T2N0. Both were hormone receptor positive, HER2 negative.

The characteristics of these invasive cancers (mainly Stage 2/3, Grade 2/3, node positive, hormone receptor positive) are consistent with those expected in a population of obese women who may not have participated regularly in a breast cancer screening program (mammography, breast physical examination).<sup>55,56</sup> Obese women are more likely to present with cancers that are larger, higher grade and have involved axillary nodes.<sup>183</sup> In postmenopausal women, obesity has been associated with increased risk of hormone receptor positive breast cancers.<sup>184</sup>

A recent report investigating tumor volume doubling times (TVDT) according to breast cancer subtype identified a mean TVDT for any type of breast cancer of approximately 193±141 days. TVDT for ER positive tumors was estimated to be 241±166 days, for HER2 positive tumors 162±60 days and for triple negative tumors 103±43 days.<sup>54</sup> Given this understanding of tumor growth, the size/stage of the reported breast cancers, and the short interval between randomization and breast cancer diagnosis, it appears likely that the majority of the invasive cancers reported in both liraglutide and placebo arms had been present (but undiagnosed) prior to study entry.

**Table 6–19 EAC-confirmed malignant and pre-malignant breast neoplasms in women: phase 3 trials (through the 120-Day Safety Update)**

| Treatment               | Diagnosis Study Day | Age/BMI | Trial | Screen Detected | Grade | Stage           |          |          |   | E/P/HER 2 Status | Weight Loss, % |
|-------------------------|---------------------|---------|-------|-----------------|-------|-----------------|----------|----------|---|------------------|----------------|
|                         |                     |         |       |                 |       | T               | N        | M        | AJCC <sup>1</sup> /EAC                          |                  |                |
| Malignant Neoplasms     |                     |         |       |                 |       |                 |          |          |   |                  |                |
| Liraglutide 3.0 mg      | 30                  | 51/53.2 | 1839  | Y               | 2     | pT2             | pN1a     | M0       | IIB/Stage 3: advanced                           | +/+/-            | -6.4           |
|                         | 142/224             | 60/29.6 | 1839  | N               | 2     | pT1c            | pN1      | M0       | IIA/Stage 1: localized                          | +/+/-            | -10.0          |
|                         | 193                 | 43/37.0 | 1839  | N               | 3     | cT3             | pN1      | M0       | IIIA/Stage 3:advanced                           | -/-/-            | -8.0           |
|                         | 222                 | 62/51.0 | 1839  | Y               | 2     | pT1c            | pN1a     |          | IIA/Stage 2: locally advanced                   | Unk              | -12.0          |
|                         | 258                 | 47/36.5 | 1923  | N               | 1     | T1mic           | N1       | M0       | IIA/Stage 1:localized                           | +/+/-            | -11.2          |
|                         | 313                 | 67/28.2 | 1922  | N               | 2-3   | T2 (2009)<br>T2 | N1<br>N1 | M0<br>M1 | Initial Stage 2<br>Stage IV recurrence on study | -/-/-            | -15.0          |
|                         | 342                 | 55/32.9 | 1839  | Y               | 3     | T1c             | N0       | M0       | I/Stage 1: localized                            | -/-/-            | -12.2          |
|                         | 373                 | 37/29.9 | 1923  | N               | Unk   |                 | Unk      |          | Unk <sup>2</sup>                                | Unk              | -11.1          |
|                         | 413                 | 57/36.3 | 1839  | Y               | 2     | pT1c            | pN1a     |          | IIA/Stage 3: advanced                           | +/+/-            | -30.0          |
|                         | 545                 | 53/36.6 | 1839  | Y               | 1     | pT1a            | pN0      | M0       | I/Stage 1: localized                            | +/+/-            | *              |
|                         | 756                 | 58/38.2 | 1839  | Y               | 2     | pT1c            | N1       |          | IIA/Stage 2: locally advanced                   | +/+/-            | *              |
| Placebo                 | 282                 | 40/34.3 | 1839  | Y               | 2     | T2              | pN1      | M0       | IIB/Stage 3: advanced node positive             | +/+/-            | +0.5           |
|                         | 477                 | 62/39.6 | 1839  | Unk             | 2     | pT2             | pN0      | pMX      | IIA/Stage 1:localized                           | +/+/-            | -4.8           |
| Pre-malignant Neoplasms |                     |         |       |                 |       |                 |          |          |   |                  |                |
| Liraglutide 3.0 mg      | 31                  | 54/44.2 | 1839  | Y               | 3     | pTis            | Nx       | Mx       | 0/Stage 0: <i>in situ</i>                       | ++/Unk           | -2.6           |
|                         | 152                 | 47/31.6 | 1839  | Y               | 3     | Tis             | Nx       | Mx       | 0/Stage 0: <i>in situ</i>                       | ++/Unk           | -7.6           |
|                         | 302                 | 59/44.5 | 1839  | Y               | 2     | pTis            | Nx       | Mx       | 0/Stage 0: <i>in situ</i>                       | +/-Unk           | -9.4           |
| Placebo                 | 169                 | 49/41.2 | 1839  | Y               | 2     | pTis            | Nx       | Mx       | 0/Stage 0: <i>in situ</i>                       | ++/Unk           | +1.4           |

\*Weight loss from 120-Day Safety Update not yet available; EAC: Event Adjudication Committee; E/P/HER 2: estrogen/progesterone/human epidermal growth factor receptor 2; Unk: unknown; BMI: Body Mass Index; <sup>1</sup>: AJCC: American Joint Committee on Cancer<sup>185</sup>; <sup>2</sup> Reported as bilateral breast cancer, unable to assess stage without lymph node information

One additional event of 'breast cancer' (treatment emergent, not-adjudicated) was reported with liraglutide 1.8/2.4 mg in year 2 (day 465) of the phase 2 trial 1807

Four cases of premalignant breast neoplasms (ductal carcinoma *in situ* - DCIS) were reported (at ages 47 to 59) – three with liraglutide and one with placebo. All were screen detected and diagnosed within the first year after study entry; all were hormone receptor positive. Without knowledge of previous screening histories, it is difficult to interpret the relationship of these CIS cases to initiation of liraglutide versus placebo; however, their characteristics are typical of screen-detected DCIS.

Liraglutide-treated women with events of breast neoplasms generally experienced greater than the average weight loss for the liraglutide-treated cohort ([Table 6–19](#)), and it raises the possibility that weight loss may have led to enhanced detection of breast neoplasms in this group of women. Obesity has been associated with reduced compliance with mammographic screening and screening breast examination compared to normal weight women.<sup>55,56</sup> Although information is unavailable on the effects of weight loss on compliance with mammographic screening and breast examination, extrapolation of these data suggest it is possible that weight loss could be associated with enhanced frequency of mammographic screening and physical examinations.

It is important to recognize that information on breast cancer risk factors and breast cancer screening practices was not generally available for study participants (some information was available in clinical records for women who were diagnosed with breast neoplasms). Furthermore, baseline mammograms and clinical breast examinations were not required, nor was there a study requirement for regular mammography or clinical breast exam in the full study population. Thus, there was no systematic approach to detection of breast cancer. Because of this, it is possible that some participants had undiagnosed breast cancers at study entry. It is also possible that breast screening activities differed in the two study arms post-randomization, with the potential for more frequent screening in those on liraglutide who lost large amounts of weight (as discussed above).

### **Breast neoplasms in the T2DM programs**

Neoplasms in the T2DM programs were not adjudicated, and it should be noted that the term ‘neoplasm’ does not imply malignancy. Neoplasms were assessed based on data from all completed phase 2 and 3 clinical trials (as of July 2013) in T2DM programs in which one or more liraglutide treatment arms, irrespective of the dose, was used. Most T2DM trials employed a 2:1 randomization, and 3 trials were either uncontrolled (all patients on liraglutide throughout the trial period) or included an uncontrolled trial extension where patients on comparator were shifted to liraglutide in the extension (liraglutide: 8344 patients (6747.6 PYR), comparator: 3671 patients (2525.3 PYR)). PYR or ‘patient years at risk’ is calculated based on “time at risk” which means until the last record of the individual patient prior to database lock for each individual trial, including extension and observational follow-up periods. Rates include treatment-emergent and non-treatment-emergent events.

Malignant breast neoplasms were infrequent (based on the high-level group term ‘breast neoplasms malignant and unspecified (incl nipple)’). For total liraglutide, the rate was 0.19% of women (7



women with 7 events, [0.23 events per 100 PYR]) versus the rate for total comparator 0.06% of women (1 woman with 1 event, [0.09 events per 100 PYR]) ([Appendix, Table 6-4](#)).

### Non-clinical data

Non-clinical data do not support a causal relationship between GLP-1 (liraglutide specifically) and breast cancer. No signal was identified in mice, rats, or monkeys. GLP-1 receptors were not detected in human breast carcinomas and only weak receptor expression was found in small milk ducts and lobuli of normal breast tissue.<sup>58</sup> There is no published literature indicating increased risk of breast cancer with GLP-1 receptor agonists. In fact, in the single publication identified, the GLP-1 receptor agonist exendin-4 was shown to inhibit *in vivo* growth of human cancer cells in a mouse model, while not affecting the growth of non-tumorous mammary cells.<sup>59</sup>

### Conclusions for breast neoplasms

The numeric excess of malignant breast neoplasms in females randomized to liraglutide 3.0 mg represents a signal that is not supported by non-clinical data or post-marketing surveillance for liraglutide. GLP-1 is not a mutagen and its specific receptor does not appear to be expressed in human breast cancers.<sup>58</sup> Furthermore, GLP-1 (and liraglutide) does not cross-react with other peptide hormone receptors. While there are potential indirect mechanisms by which GLP-1 could act as a progression factor for pre-existing neoplasms, available data do not lend support to such an effect. In the weight management program, liraglutide 3.0 mg decreased both fasting insulin levels and the area under the insulin concentration time curve following a standardized meal, and it is therefore difficult to implicate hyperinsulinemia as a potential mechanism.

Based on the low number of events, the short interval between study entry and diagnosis of breast cancer with involvement of axillary lymph nodes in most cases, and no indication of an increased risk based on the substantial clinical experience with GLP-1 receptor agonists in T2DM, it seems likely that the event imbalance observed in the weight management pool is not causally related to liraglutide, but rather a chance finding or resulting from enhanced ascertainment in women who lost more weight. Nevertheless, the noted imbalance will be addressed by including this information in the product labeling and by performing additional studies in the post-marketing period (see [Section 7](#)).

#### 6.3.5.5 Pancreatic cancer

##### Background

A series of studies suggested a potential risk for an association between incretin therapy and both pancreatic exocrine (pancreatic ductal adenocarcinomas) and pancreatic islet cell (glucagonomas) neoplasms.<sup>186-188</sup> Findings from these studies have been questioned by several independent investigators.<sup>184-186,189</sup> After extensive review of all non-clinical and clinical trial data, FDA and EMA have jointly published a commentary that concludes that current data do not support the findings in the controversial manuscripts published by a group of academic investigators. They

conclude that current labeling is appropriate for what is currently known about risks of pancreatic disease, including pancreatic cancer for which no signal has been identified.<sup>156,189</sup>

### **Pancreatic cancer in the weight management program**

In the weight management trials, there were no reports of exocrine pancreas cancer. A single patient was diagnosed with multiple endocrine neoplasia type 1 (MEN1) during treatment with liraglutide 3.0 mg (based on EAC-confirmed events of malignant neuroendocrine pancreas neoplasm and benign parathyroid adenoma); this patient had been under investigation for the disorder prior to trial enrolment (please refer to [Appendix Table 5-1](#) for more details regarding this event).

### **Pancreatic cancer in the T2DM programs with liraglutide**

Neoplasms in the T2DM programs were not adjudicated, and it should be noted that the term ‘neoplasm’ does not imply malignancy. Neoplasms were assessed based on data from all completed phase 2 and 3 clinical trials (as of July 2013) in T2DM programs in which one or more liraglutide treatment arms, irrespective of the dose, was used. Most T2DM trials employed a 2:1 randomization, and 3 trials were either uncontrolled (all patients on liraglutide throughout the trial period) or included an uncontrolled trial extension where patients on comparator were shifted to liraglutide in the extension (liraglutide: 8344 patients, 6747.6 PYR, comparator: 3671 patients, 2525.3 PYR). PYR or ‘patient years at risk’ is calculated based on “time at risk” which means until the last record of the individual patient prior to database lock for each individual trial, including extension and observational follow-up periods. Rates include treatment-emergent and non-treatment-emergent events.

The rate of pancreatic cancer (based on preferred terms ‘adenocarcinoma pancreas’, ‘pancreatic carcinoma’, ‘pancreatic carcinoma stage IV’, and ‘pancreatic carcinoma metastatic’) for total liraglutide was 0.04% (3 events in 3 patients, [0.04 events per 100 PYR]) versus the rate for total comparator 0.03% (1 event in 1 patient, [0.04 events per 100 PYR]) ([Appendix, Table 6-5](#)). Based on comparison of more than 25,000 initiators of Victoza<sup>®</sup> with a matched cohort of initiators of other antidiabetic agents between 01 Feb 2010 and 31 March 2013 in the medical claims database, the relative risk for pancreatic cancer was  $\leq 1$  in the liraglutide group.

#### **6.3.5.6 Thyroid cancer, including elevated blood calcitonin**

##### **Background**

Medullary thyroid carcinoma (MTC), an extremely rare form of cancer in humans,<sup>190,191</sup> was a focus of discussion in the original regulatory review of liraglutide for the treatment of T2DM and a number of Post Marketing Requirements (PMR) have been completed (non-clinical) or are underway (pharmacoepidemiology and case series registry). As described in Section [3.4.3](#), liraglutide caused dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) in 2-year carcinogenicity studies in mice and rats.<sup>15,84</sup> Similar

findings have been observed in rodents with other GLP-1 receptor agonists.<sup>172,173</sup> The relevance of these findings to humans is uncertain but considered to be low based on considerable species differences. Primates including humans have many fewer C-cells, few GLP-1 receptors, and no evidence of activation of these receptors. Additionally, there is no signal from the liraglutide clinical development programs or the ongoing post-marketing surveillance program for Victoza<sup>®</sup>. Nevertheless, thyroid disease, thyroid neoplasms in particular, was a safety area of interest for the liraglutide 3.0 mg weight management program.

### Thyroid neoplasms in the weight management program

The overall incidence of thyroid cancers (i.e., malignant neoplasms) in the weight management trials was low, with no apparent differences between liraglutide 3.0 mg (4 patients (0.12%) with 4 events, 0.09 events per 100 PYR) and placebo (1 patient (0.05%) with 1 event, 0.04 events per 100 PYR) through the 120-Day Safety Update based on the small number of events. All but one event were of papillary or follicular origin. One MTC case occurred in a placebo patient shortly after randomization. In addition, three patients on liraglutide 3.0 mg reported 3 events of pre-malignant thyroid neoplasms (papillary microcarcinoma) (0.09%, 0.07 events per 100 PYR). All 3 were incidental findings, detected during work-up for either elevated calcitonin or nodular goiter. Detailed descriptions of all EAC-confirmed thyroid neoplasms are provided in [Appendix Table 5-2](#).

### Thyroid neoplasms in T2DM programs with liraglutide

Neoplasms in the T2DM programs were not adjudicated, and it should be noted that the term ‘neoplasm’ does not imply malignancy. Neoplasms were assessed based on data from all completed phase 2 and 3 clinical trials (as of July 2013) in T2DM programs in which one or more liraglutide treatment arms, irrespective of the dose, was used. Most T2DM trials employed a 2:1 randomization, and 3 trials were either uncontrolled (all patients on liraglutide throughout the trial period) or included an uncontrolled trial extension where patients on comparator were shifted to liraglutide in the extension (liraglutide: 8344 patients, 6747.6 PYR, comparator: 3671 patients, 2525.3 PYR). PYR or ‘patient years at risk’ is calculated based on “time at risk” which means until the last record of the individual patient prior to database lock for each individual trial, including extension and observational follow-up periods. Rates include treatment-emergent and non-treatment-emergent events.

The rate of ‘thyroid cancer’ for total liraglutide was 0.11% (9 events in 9 patients, [0.13 events per 100 PYR]) versus the rate for total comparator 0.05% (2 events in 2 patients, [0.08 events per 100 PYR]) ([Appendix, Table 6-6](#)). The rate of ‘thyroid neoplasms’ for total liraglutide was 0.43% (36 patients with 37 events, [0.55 events per 100 PYR]) versus the rate for total comparator 0.11% (4 patients with 4 events, [0.16 events per 100 PYR]) ([Appendix, Table 6-6](#)). Included in the above numbers for ‘thyroid neoplasm’ are 8 cases of benign C-cell hyperplasia (confirmed by pathological evaluation) with liraglutide (0.6 mg, 1.2 mg and 1.8 mg), and 2 pathology-confirmed cases of medullary thyroid C-cell neoplasia were identified (MTC and medullary carcinoma *in situ*,

respectively), both of which were on comparator treatment. Almost all of the cases of C-cell pathology were identified based on elevated baseline calcitonin levels (see section below) and subsequent evaluation and therapy while on drug treatment. One-third (12/37) of the 'thyroid neoplasms' reported with liraglutide and 3/4 events reported with comparator were reported in a single trial conducted in Japan (NN2211-1334). This trial included 4:1 randomization (4 dose levels) of liraglutide and 1 arm of placebo. In this trial, baseline thyroid ultrasounds were performed as part of the protocol and revealed a large number of thyroid lesions given the sensitive screening technique.

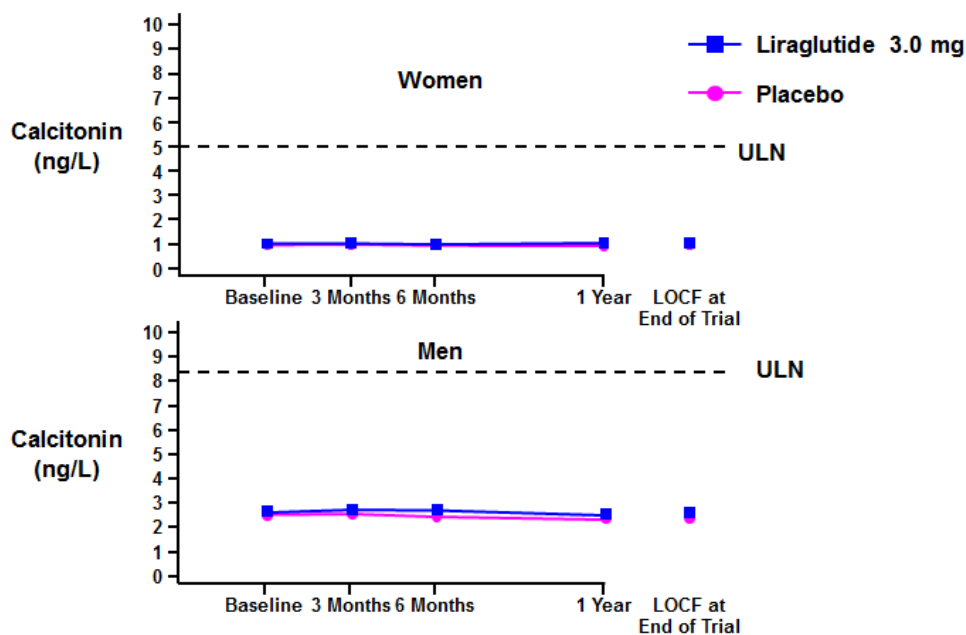
There have been no cases of MTC reported in patients exposed to liraglutide in completed clinical trials as of the date of submission of this briefing book (11 August 2014). One MTC event has occurred in the ongoing LEADER<sup>®</sup> trial, treatment allocation remains blinded. In the post-marketing setting, 12 spontaneous reports of MTC have been observed with Victoza<sup>®</sup> as of 30 June 2014 based on more than 3.3 million PYE. As of January 2014, 13 cases of MTC have been captured by the MTC registry; none of the patients have been exposed to GLP-1 receptor agonists.

### **Calcitonin**

Calcitonin is a specific biological marker of MTC<sup>192-194</sup> and a potential predictor of C-cell neoplasia at levels  $\geq 50$  ng/L.<sup>195</sup> Therefore, patients with calcitonin concentrations  $\geq 50$  ng/L were excluded from trial enrolment. Based on the mechanism established in rodents (Section [3.4.3](#)), calcitonin is also used as a marker of C-cell activation preceding C-cell neoplasia.<sup>84</sup>

In the phase 2 and 3 trials of the weight management pool, blood samples for calcitonin were drawn at screening (except trial 1807), at baseline, at end-of-treatment, at follow-up (not trial 3970), and at regular intervals (as a minimum every 3 months) during the treatment period; samples were analyzed by a central laboratory. Although the clinical significance of calcitonin fluctuations below 50 ng/L in patients without MTC is unknown, all confirmed cases of elevated calcitonin concentration ( $\geq 20$  ng/L) in the weight management pool were considered to be MESI and were subject to ongoing blinded review by an independent external group of thyroid experts.

Consistent with findings in all completed trials with liraglutide for T2DM of up to 2 years' duration<sup>86</sup> there was no indication of a liraglutide effect on blood calcitonin concentration in the weight management pool ([Figure 6-25](#)). Mean calcitonin levels remained stable over time and well below the upper limit of normal (ULN) for both genders.



Observed geometric mean of calcitonin, including LOCF at end of trial. ULN: Upper Limit of Normal

**Figure 6–25 Mean calcitonin levels – women (upper panel) and men (lower panel): weight management pool (NDA)**

On the individual level, the vast majority of patients (95%) started and remained below the ULN for calcitonin throughout the treatment period with either liraglutide 3.0 mg or placebo. Few patients in either group (mostly males) experienced calcitonin levels above 20 ng/L at any time during treatment (liraglutide 3.0 mg: 16, placebo: 7), and 3 patients (liraglutide 3.0 mg: 1, placebo: 2) had calcitonin levels above 50 ng/L at any time during treatment. Few patients (mostly males) experienced increase of calcitonin at all visits (liraglutide 3.0 mg: 14, placebo: 1). With exception of one patient shifting from <20 ng/L to  $\geq 20$  ng/L (but below 50 ng/L), all patients shifted to  $\leq 1.5 \times \text{ULN}$ . With placebo, 1 female patient had persistent increase of calcitonin levels to above 20 ng/L.<sup>196,197</sup>

None of the liraglutide-treated patients with elevated calcitonin levels with onset at any time during treatment had external EAC confirmed events of C-cell hyperplasia or MTC, confirming the lack of a clinically relevant effect of liraglutide on calcitonin levels. This is further supported by the lack of treatment effect observed in the non-human primates and the absence of any association between liraglutide exposure and MTC in clinical trials or practice.

As with Victoza<sup>®</sup>, the potential risk of MTC to humans will be monitored in the post-marketing setting. Please refer to Section 7 for continued risk assessment plan details.

### 6.3.5.7 Colorectal neoplasms, benign and malignant

#### Background

Colorectal cancer is the third most common cancer diagnosis among men and women in the US, affecting men more than women. More than 90% of colorectal cancers cases occur in people aged 50 or older.<sup>198</sup> The etiology of colorectal cancer includes both genetic and environmental factors although most cases are sporadic.<sup>199</sup> Increased body weight and obesity are recognized as environmental factors, which can contribute to the development of colorectal cancer. A recent meta-analysis of epidemiologic studies and and/or large cohort studies estimated that about 3% of US incident colorectal cancer could be attributed to obesity.<sup>200</sup>

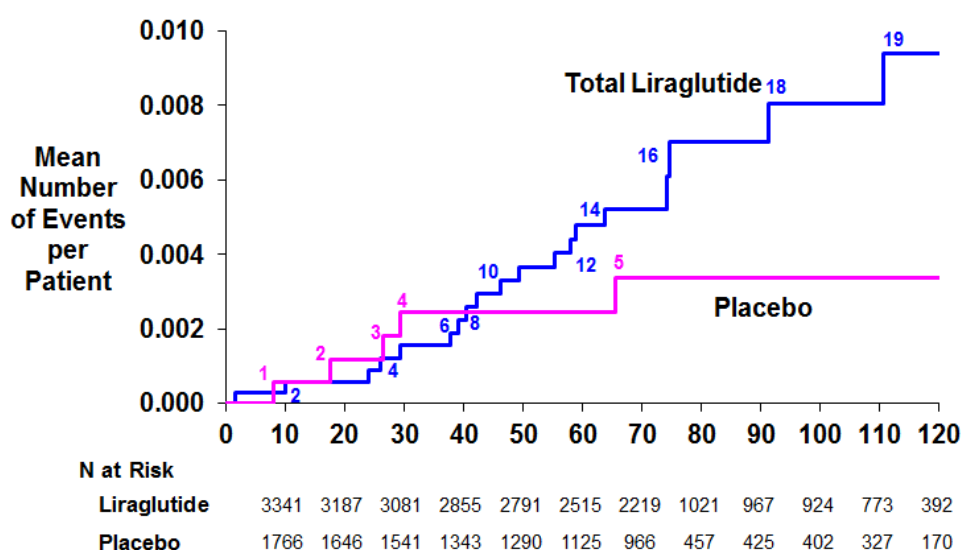
Neoplastic polyps of the colorectum, namely tubular and villous adenomas, are precursor lesions of colorectal cancer.<sup>201</sup> The lifetime risk of developing a colorectal adenoma is nearly 19% in the US population,<sup>202</sup> with nearly 95% of sporadic colorectal cancers developing from these adenomas.<sup>197</sup> Identified risk factors for colorectal adenomas include previous history of adenomas<sup>203</sup> and excess body weight.<sup>204</sup> A recent meta-analysis found that individuals with BMI of  $\geq 25$  kg/m<sup>2</sup> had significantly higher prevalence of colorectal adenomas as compared to individuals with a BMI  $< 25$  kg/m<sup>2</sup>, and that prevalence increased with increasing BMI category.<sup>204</sup> A similar relationship was reported for advanced neoplasia ( $> 10$  mm adenoma, villous, adenoma, high-grade dysplasia or cancer).<sup>205</sup> A long latency period, estimated at 5 to 10 years, is usually required for the development of malignancy from adenomas.<sup>203 206</sup> Detection and removal of an adenoma prior to malignant transformation may reduce the risk of colorectal cancer.<sup>207</sup> Screening and surveillance intervals are based on the likelihood of developing advanced neoplasia, with low risk adenomas defined as 1-2 tubular adenomas  $< 10$  mm, and high-risk adenomas defined as adenoma with villous histology, high-grade dysplasia,  $\geq 10$  mm, or 3 or more adenomas.<sup>208</sup>

#### Colorectal neoplasms in the weight management program

More patients treated with liraglutide than with placebo had EAC-confirmed benign colorectal neoplasms. All events with liraglutide occurred at the liraglutide 3.0 mg dose, consistent with its relative contribution to overall liraglutide exposure. Based on all events reported through the 120-Day Safety Update, 17 liraglutide 3.0 mg-treated patients had 17 benign colorectal neoplasms (0.52%, [0.38 events per 100 PYR]), compared to 4 events in 4 patients (0.22%, [0.17 events per 100 PYR]) treated with placebo (exact odds ratio [95% CI]: 2.39 [0.78; 9.76]). The events were colon (and rectal) adenomas. Approximately half of the events (9/21) occurred in males above the age of 50 years, consistent with the demographics for patients with colon adenomas.<sup>209 210</sup> The majority of these had a pertinent past medical history or family history for colonic lesions. Thirteen of 17 with liraglutide 3.0 mg and 3/4 with placebo were diagnosed by routine colonoscopy ([Table 6–20](#)). Information about patients' baseline status and colonoscopy procedures during the clinical trial program was not collected, and it is therefore not known whether the frequency differed between treatment groups.

The majority (14 with liraglutide and 3 with placebo) of lesions were small (<10 mm); of the 10 with available histopathology 1 lesion (>10 mm) was associated with high-grade dysplasia. This patient was previously diagnosed with large colon polyps during a routine colonoscopy. The polyps were marked with ink at that time but were not resected.

Events occurred at a constant rate throughout the treatment period in the liraglutide group, based on all available data through the 120-Day Safety Update ([Figure 6–26](#)), as well as in trial 1839, the only trial in which patients were exposed for more than a year. One event was identified in the placebo group after week 30 ([Figure 6–26](#)).



Output based on 1839 including re-randomized period and 120-Day safety update, 1922 and 1923 including 12 weeks follow-up period, and 3970. Patients are allocated according to treatment in the main treatment period. Risk time is defined as the time between first drug date and last contact as non-treatment emergent events are included. Numbers in plot represent cumulative colon neoplasms at that time point.

**Figure 6–26 Mean cumulative events of EAC-confirmed benign (n=21) and malignant (n=3) colorectal neoplasms over time: phase 3 trials (through 120-Day Safety Update)**

Two patients with liraglutide 3.0 mg (0.06%, [0.04 events per 100 PYR]) and 1 with placebo (0.05%, [0.04 events per 100 PYR]) had EAC-confirmed malignant colorectal neoplasms ([Table 6–20](#)). The latter was a neuroendocrine carcinoid tumor reported during the 120-Day Safety Update. Due to the low number of events no firm conclusions can be made on the difference between frequencies with liraglutide 3.0 mg and placebo.



**Table 6–20 Details of EAC-confirmed benign and malignant colorectal neoplasms: phase 3 trials (through 120-Day Safety Update)**

| Treatment          | Diagnosis Study Day     | Age/Sex/BMI | Country | Trial | Detected on Routine Colonoscopy | EAC diagnosis                | Histology   | Size ≥ 10 mm | High Grade Dysplasia | Indication for colonoscopy/ Relevant information  |
|--------------------|-------------------------|-------------|---------|-------|---------------------------------|------------------------------|---|--------------|----------------------|---|
| Liraglutide 3.0 mg | <i>Benign Neoplasms</i> |             |         |       |                                 |                              |   |              |                      |   |
|                    | 10                      | 54/F/40.0   | IL      | 1839  | Y                               | Colon polyp                  | 1) tubular adenoma<br>2) hyperplastic polyp                               | N            | Unknown              | Screening/colonoscopy   |
|                    | 70                      | 60/M/39.2   | ES      | 1839  | N                               | Colon adenoma                | villous adenoma   | Unknown      | Unknown              | Symptoms/ intermittent abdominal pain since 2006  |
|                    | 182                     | 56/M/29.9   | TR      | 1922  | N                               | Colon adenoma                | tubular adenoma   | N            | N (mild)             | Symptoms/change in bowel routine  |
|                    | 206                     | 64/F/33.4   | IL      | 1922  | Y                               | Tubulo-villous adenoma       | 1) tubular adenoma<br>2) tubulovillous adenoma                            | Y            | N (moderate)         | Medical history/diverticulosis, history of inflammatory colon polyp   |
|                    | 263                     | 65/M/33.4   | US      | 1839  | Y                               | Tubular adenoma of the colon | tubular adenoma   | N            | Unknown              | Medical history/benign polyp 1999, polypectomy, diverticulosis  |
|                    | 283                     | 47/M/42.2   | IL      | 1922  | N                               | Colon adenoma                | 1) tubular adenoma<br>2) polypoid fragment of colonic mucosa              | N            | Unknown              | Symptoms/GI complaints  |
|                    | 295                     | 62/F/41.9   | IT      | 1839  | Y                               | Adenoma                      | 1) tubulovillous adenoma<br>2) Tubular adenoma<br>3&4) Hyperplastic polyp | N            | N (low)              | Symptoms/positive hemocult. Family history – father; intestinal polyps  |
|                    | 324                     | 64/F/46.9   | US      | 1922  | Y                               | Colon adenoma                | 1&2) tubular adenoma  | N            | Unknown              | Medical history/polypectomy 2007  |
|                    | 344                     | 51/M/29.9   | HK      | 1839  | N                               | Colon adenoma                | tubular adenoma   | N            | N (low)              | Symptoms/one year of constipation   |
|                    | 387                     | 56/M/31.3   | US      | 1922  | Y                               | Tubular adenoma              | tubular adenoma   | N            | Unknown              | Medical history/bladder cancer, intermittent diverticulitis<br>Family history; first degree relative with colon cancer. |

| Diagnosis Study Day | Age/Sex/BMI | Country | Trial    | Detected on Routine Colonoscopy | EAC diagnosis | Histology  | Size ≥ 10 mm | High Grade Dysplasia | Indication for colonoscopy/ Relevant information  |
|---------------------|-------------|---------|----------|---------------------------------|---------------|--|--------------|----------------------|---|
| 406                 | 44/M/44.9   | US      | 1922     | Y                               | Adenoma       | 1) tubular adenomatous polyp ,<br>2,3) tubulovillous adenomatous polyp,<br>4,5) tubular adenomas               | Y            | Y                    | Medical history/polyps identified during prior colonoscopy 2010 but not removed                       |
| 412                 | 55/M/36.8   | CA      | 1839-ext | Y                               | Colon adenoma | tubular adenoma  | N            | N                    | Family history/father; colon cancer. Medical history - bladder cancer, previous colonoscopy 2004.     |
| 446                 | 60/M/31.4   | US      | 1839-ext | Y                               | Adenoma       | tubular adenoma  | N            | Unknown              | Screening/colonoscopy   |
| 519                 | 42/F/40.4   | AT      | 1839-ext | Y                               | Adenoma       | tubular adenoma  | N            | N                    | Family history-mother; colon carcinoma/Medical history - previous colonoscopy 2006.                   |
| 522                 | 60/F/45.8   | US      | 1839-ext | Y                               | Colon adenoma | 10 fragments) Colon fragments - tubular adenomas. Rectal fragments - polypoid fragments of hyperplastic polyps | N            | N                    | Medical history/benign polyp 2009, polypectomy.   |
| 638                 | 49/M/36.4   | US      | 1839-ext | Y                               | Colon adenoma | 1,2&3) tubular adenoma   | N            | N                    | Screening/colonoscopy.  |
| 774                 | 53/M/39.2   | US      | 1839-ext | Y                               | Colon adenoma | 1) tubular polyp<br>2) hyperplastic polyp  | N            | Unknown              | Family history-colon polyps/Medical history - colon polyps, diverticulosis, irritable bowel syndrome. |

|                            | Diagnosis<br>Study<br>Day | Age/Sex/<br>BMI | Country | Trial        | Detected on<br>Routine<br>Colonoscopy | EAC diagnosis                     | Histology   | Size<br>≥ 10 mm | High<br>Grade<br>Dysplasia | Indication for colonoscopy/<br>Relevant information  |
|----------------------------|---------------------------|-----------------|---------|--------------|---------------------------------------|-----------------------------------|---|-----------------|----------------------------|--|
| Placebo                    | 56                        | 49/F/39.1       | US      | 1839         | N                                     | Colon polyps                      | 1,2&3) tubular adenoma  | N               | Unknown                    | Symptoms/ intermittent rectal bleeding   |
|                            | 122                       | 62/F/43.1       | US      | 1839         | Y                                     | Colon adenoma                     | tubular adenoma   | N               | N                          | Screening/colonoscopy  |
|                            | 185                       | 63/F/31.5       | US      | 1839         | Y                                     | Tubular adenoma                   | tubular adenoma   | N               | Unknown                    | Screening/colonoscopy  |
|                            | 204                       | 71/M/39.1       | IT      | 1839         | Y                                     | Colon adenoma                     | 1) hyperplastic glandular polyp with chronic inflammation<br>2) tubular adenoma | Y               | Unknown                    | Medical history/polypectomy 2010   |
| <b>Malignant Neoplasms</b> |                           |                 |         |              |                                       |                                   |   |                 |                            |  |
| Liraglutide<br>3.0 mg      | 168                       | 37/F/33.9       | AT      | 1839         | N                                     | Colon carcinoma/<br>Stage III     | tubular adenocarcinoma  | Y               | Not applicable             | Symptoms/recurrent tendency to constipation, haematachezia, melaena  |
|                            | 274                       | 67/M/29.2       | DE      | 1922         | N                                     | Rectal adenocarcinoma/<br>Stage I | rectal carcinoma  | Y               | Not applicable             | Symptoms/ hematochezia, occasional incontinency with diarrhea, Family history: intestinal/cervical/stomach/bladder cancer. |
| Placebo                    | 458                       | 51/M/31.1       | DE      | 1839<br>-ext | Y                                     | Carcinoid tumor                   | neuroendocrine tumor  | Y               | Not applicable             | Medical history/colon polypectomy May 2011 (pre-trial) - unclear histology.  |

EAC: event adjudication committee (and EAC assessment of onset day); F: female; M: male; BMI: body mass index; AT: Austria; CA: Canada; DE: Denmark; ES: Spain; HK: Hong Kong; IL: Israel; IT: Italy; TR: Turkey; US: United States

One additional event of 'adenocarcinoma' (sigmoideum, with metastasis in liver) (treatment emergent, not-adjudicated) was reported with liraglutide 2.4/2.4 mg in year 2 (day 410) of the phase 2 trial 1807

### Colorectal neoplasms in T2DM programs with liraglutide

Neoplasms in the T2DM programs were not adjudicated, and it should be noted that the term ‘neoplasm’ does not imply malignancy. Neoplasms were assessed based on data from all completed phase 2 and 3 clinical trials (as of July 2013) in T2DM programs in which one or more liraglutide treatment arms, irrespective of the dose, was used. Most T2DM trials employed a 2:1 randomization, and 3 trials were either uncontrolled (all patients on liraglutide throughout the trial period) or included an uncontrolled trial extension where patients on comparator were shifted to liraglutide in the extension (liraglutide: 8344 patients, 6747.6 PYR, comparator: 3671 patients, 2525.3 PYR). PYR or ‘patient years at risk’ is calculated based on “time at risk” which means until the last record of the individual patient prior to database lock for each individual trial (including extension and observational follow-ups). Rates include treatment-emergent and non-treatment-emergent events.

The rate of ‘gastrointestinal neoplasms malignant and unspecified’ (under the system organ class ‘neoplasms benign, malignant, and unspecified (incl cysts and polyps)’ for total liraglutide was 0.22% (18 patients with 18 events, [0.27 events per 100 PYR]) versus the rate for total comparator 0.16% (6 patients with 6 events, [0.24 events per 100 PYR]). Of these 24 patients, 8 patients had 8 events of ‘malignant or unclassified’ neoplasm of the colon or rectum in the liraglutide group, compared to 3 patients with 3 events with comparator in controlled trials ([Appendix, Table 6-7](#)).

The rate of ‘gastrointestinal neoplasms benign’ (under the system organ class ‘neoplasms benign, malignant, and unspecified (incl cysts and polyps)’ for total liraglutide was 0.06% (5 patients with 5 events, [0.07 events per 100 PYR]) versus the rate for total comparator 0.08% (3 patients with 3 events, [0.12 events per 100 PYR]). Of these, 3 of the events in liraglutide-treated patients and 2 of the events in comparator-treated patients were colon neoplasms ([Appendix, Table 6-7](#)).

The rate of ‘benign neoplasms gastrointestinal’ (under the system organ class ‘gastrointestinal disorders’) for total liraglutide was 0.42% (35 patients with 38 events, [0.56 events per 100 PYR]) versus the rate for total comparator 0.49% (18 patients with 20 events, [0.79 events per 100 PYR]). Of these, 27 events in liraglutide-treated patients and 14 events in comparator-treated patients were either colon or rectal polyps ([Appendix, Table 6-7](#)).

### Non-clinical data

No treatment-related colon abnormalities were seen in any of the non-clinical studies with liraglutide. Human colorectal carcinomas do not express GLP-1 receptors.<sup>58</sup> In normal human colon, only the myenteric nerve plexus expresses the GLP-1 receptor.<sup>58</sup> The effect of GLP-1 receptor activation in the myenteric nerve plexus is to regulate gastric motility.<sup>52</sup>

Two short-term studies in rodents have shown that treatment with GLP-1 receptor agonists can lead to an increased weight of the small intestine<sup>211,212</sup> and colon (minimal) in one<sup>211</sup> but not another study.<sup>212</sup> The effect on small intestine weight was reversible.<sup>212</sup> Importantly, despite the increase in

colon weight, liraglutide did not promote colon dysplasia or adenomas,<sup>211</sup> consistent with findings that GLP-1 receptor activation inhibits growth and augments apoptosis in murine colon cancer cells.<sup>213</sup>

Sustained activation of the GLP-2 receptor is associated with growth of the intestinal epithelium and causes colon adenomas.<sup>211,214</sup> Liraglutide has no cross-reactivity to the GLP-2 receptor.<sup>211,212</sup>

### **Conclusion for colorectal neoplasms**

Given the absence of a signal from non-clinical studies as well as clinical trial and post-marketing experience with liraglutide and other GLP-1 receptor agonists in the treatment of T2DM, and the presence of relevant medical history in the majority of cases, it is likely that the numerical excess in benign colorectal neoplasms observed with liraglutide in the weight management were not causally related to liraglutide exposure. Nevertheless, neoplasms are addressed by several post-approval commitments for Victoza<sup>®</sup> and by routine pharmacovigilance.

#### **6.3.5.8 Conclusion for neoplasms in the weight management program**

Neither liraglutide nor any of the other approved GLP-1 receptor agonists are mutagenic or genotoxic. No treatment-related tumors have been found in the non-clinical safety studies with liraglutide, with exception of thyroid C-cell tumors and skin fibrosarcomas for which the human relevance is considered low (Section [6.3.5.1](#)).

Consistent with the non-clinical studies, the overall risk of EAC-confirmed neoplasms and cancer in the weight management trials was low and balanced between treatment groups but with a numerical excess of infrequent cases of breast cancer/carcinoma *in situ* in female patients and benign colon adenomas, mainly in male patients, treated with liraglutide 3.0 mg. The majority of these cases were diagnosed during routine screening procedures and many had relevant medical history. Neither clinical trial nor post-marketing experience with liraglutide in T2DM, or any of the other marketed GLP-1 receptor agonists, have indicated similar imbalances.

Based on the low number of events, the tumor volume doubling times and nodal involvement for breast neoplasms, and the absence of a signal for breast and colon neoplasms in the non-clinical studies and T2DM programs, the imbalances in breast cancer and benign colorectal adenomas appear to be chance findings but will require further follow-up in the post-marketing period.

### **6.3.6 Hypoglycemia**

#### **6.3.6.1 Background**

Little is known about the prevalence of hypoglycemia in obese patients without T2DM, and comparatively little about the effects of lifestyle changes on the potential risk for hypoglycemic events. Based on publically available data from randomized clinical trials, the risk of symptomatic

hypoglycemia associated with a 5% to 10% weight loss induced by a combination of a pharmacological agent and lifestyle changes is low in patients without T2DM.<sup>215,216</sup>

In patients with T2DM, weight loss is associated with improved glycemic control and consequently can contribute to increased risk of hypoglycemia in patients on medical treatment for T2DM, in particular in those treated with sulfonylureas (SUs), if their glucose-lowering regimen is not adjusted according to weight-loss mediated improvement in insulin sensitivity.<sup>163,215-218</sup>

Like endogenous GLP-1, liraglutide directly and indirectly (through weight loss) lowers fasting and postprandial glycemia in a glucose-dependent manner, i.e., it acts predominantly when glucose levels are elevated. Consequently, in patients with T2DM, the risk of hypoglycemia at liraglutide doses up to 1.8 mg (the maximum approved dose for the treatment of T2DM) is low compared to many other glucose-lowering agents,<sup>15</sup> except when used in conjunction with SUs which uncouple the glucose-dependency of GLP-1 induced insulin secretion.<sup>60</sup>

#### 6.3.6.2 Recording of hypoglycemic episodes

- In agreement with the FDA's recommendations for weight management products, all hypoglycemic episodes were to be reported as AEs in the weight management trials, and severity was rated according to Sponsor's standard AE definition (mild, moderate or severe). In trials 1839, 1922 and 3970, hypoglycemic episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (i.e., 'severe hypoglycemic episodes') qualified as MESI. In trials 1807 and 1923, severe hypoglycemic episodes were reported as SAEs.
- Similar instructions regarding potential symptoms of hypoglycemia were given to patients with or without T2DM (paleness, shaking, sweating, increased heart rate/heart beat (palpitations), hunger, vision disorder, unusual behavior, drowsiness).
- Patients with T2DM were provided with blood glucose meters and hypoglycemia diaries, and were advised to measure their fasting blood glucose levels regularly or, at a minimum, whenever they experienced hypoglycemia symptoms. According to the protocol, 7-point profiles were to be recorded every 6 months before a scheduled clinic visit. Hypoglycemic episodes were further categorized according to the ADA definitions<sup>219</sup> and Novo Nordisk definition of minor hypoglycemia (plasma glucose < 56 mg/dL, regardless of symptoms). In addition to diary entries, glucose values recorded during clinic visits meeting ADA criteria for low glucose were also recorded as hypoglycemia AEs ('asymptomatic').
- Patients without T2DM were not provided with blood glucose meters or diaries; hence blood glucose was not measured in case of symptoms of hypoglycemia unless it coincided with a clinic visit. There were three sources of AEs of hypoglycemia in patients without T2DM:
  - Spontaneously reported, i.e., symptoms of hypoglycemia (not biochemically confirmed) occurring outside visits to the clinic

- Registered by site personnel during visits to the clinic where FPG was assessed ('FPG visit hypoglycemia'). All glucose values  $\leq 70$  mg/dL were to be reported as AEs, irrespective of symptoms.
- Registered during a visit to the clinic when an OGTT was performed ('OGTT visit hypoglycemia'). OGTTs were performed in trials 1807 and 1839 to rule out presence of T2DM (screening visit) and to diagnose/confirm new onset of T2DM (approximately every 6 months during the first year). No specific guidance was provided on when to report a low glucose value as a hypoglycemia AE.

### 6.3.6.3 Hypoglycemic episodes in patients with T2DM: Trial 1922

Hypoglycemic episodes reported in patients with T2DM should be viewed in the light of the observed improvement in glycemic control: from a baseline HbA<sub>1c</sub> of 8.0% and baseline FPG of 158.2 mg/dL, patients in the liraglutide 3.0 mg group had HbA<sub>1c</sub> and FPG reductions of 1.3%-points and 34.1 mg/dL, respectively; patients in the liraglutide 1.8 mg group had reductions of 1.1%-points and 25.2 mg/dL, whereas patients in the placebo group had reductions of 0.4%-points and 2.2 mg/dL, respectively ([5.4.7](#)).

The incidence of severe hypoglycemia was low and similar with liraglutide 3.0 mg and 1.8 mg, 0.7% of patients treated with liraglutide 3.0 mg (3 patients with 5 events, [13 events per 1000 PYE]) and 1.0% of patients treated with liraglutide 1.8 mg (2 patients with 3 events, [16 events per 1000 PYE]), all of whom were concomitantly treated with SUs which are known to increase the risk of hypoglycemia in patients co-treated with a GLP-1 receptor agonist.<sup>60</sup> No patients treated with placebo experienced an episode of severe hypoglycemia. As expected based on its glucose-lowering properties, non-severe hypoglycemic episodes (all ADA sub-categories and Novo Nordisk minor category) were reported more frequently in patients with T2DM treated with liraglutide than with placebo, with no differences between liraglutide 3.0 mg and 1.8 mg doses ([Table 6-21](#)). Patients taking SUs were more likely (3–4 times) to experience a hypoglycemic episode in any category compared with patients not taking SUs ([Table 6-21](#)).

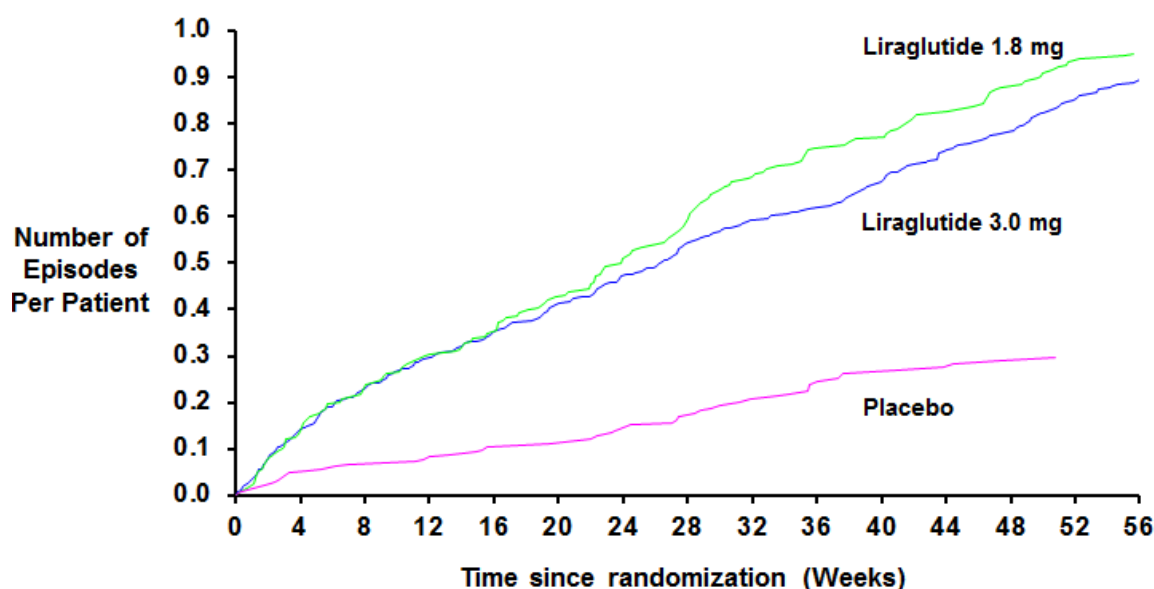
Hypoglycemic episodes occurred during the entire treatment period, as illustrated in [Figure 6-27](#) showing the cumulative number of documented symptomatic hypoglycemic episodes per patient by treatment week. By week 56, the cumulative number of documented symptomatic hypoglycemic episodes was 0.9–1.0 episodes per patient treated in liraglutide groups vs. 0.3 episodes per patient in patients treated with placebo. All episodes, including the 8 severe events, were mild in severity, reported as non-SAEs, and no patients were withdrawn due to unacceptable hypoglycemia during the trial.



**Table 6–21 AEs of hypoglycemia by SU use: Trial 1922 in patients with T2DM (NDA)**

|   | --- Liraglutide 3.0 mg --- |        |     |     | --- Liraglutide 1.8 mg --- |        |     |     | ----- Placebo ----- |        |    |     |
|---|----------------------------|--------|-----|-----|----------------------------|--------|-----|-----|---------------------|--------|----|-----|
|   | N                          | (%)    | E   | R   | N                          | (%)    | E   | R   | N                   | (%)    | E  | R   |
| <b>Patient taking SU as background medication</b>     |                            |        |     |     |                            |        |     |     |                     |        |    |     |
| Number of patients                                    | 110                        |        |     |     | 52                         |        |     |     | 55                  |        |    |     |
| ADA   | 67                         | (60.9) | 458 | 460 | 34                         | (65.4) | 296 | 619 | 28                  | (50.9) | 83 | 166 |
| Severe  | 3                          | (2.7)  | 5   | 5   | 2                          | (3.8)  | 3   | 6   | 0                   | (0.0)  | 0  | 0   |
| Documented symptomatic                                | 48                         | (43.6) | 214 | 215 | 23                         | (44.2) | 109 | 228 | 15                  | (27.3) | 41 | 82  |
| Asymptomatic  | 50                         | (45.5) | 222 | 223 | 25                         | (48.1) | 175 | 366 | 16                  | (29.1) | 35 | 70  |
| Probable symptomatic                                  | 4                          | (3.6)  | 7   | 7   | 1                          | (1.9)  | 1   | 2   | 0                   | (0.0)  | 0  | 0   |
| Relative  | 9                          | (8.2)  | 10  | 10  | 3                          | (5.8)  | 8   | 17  | 5                   | (9.1)  | 7  | 14  |
| Unclassifiable  | 9                          | (8.2)  | 35  | 35  | 5                          | (9.6)  | 5   | 10  | 1                   | (1.8)  | 2  | 4   |
| Novo Nordisk minor                                    | 33                         | (30.0) | 86  | 86  | 20                         | (38.5) | 65  | 136 | 7                   | (12.7) | 17 | 34  |
| <b>Patient not taking SU as background medication</b> |                            |        |     |     |                            |        |     |     |                     |        |    |     |
| Number of patients                                    | 312                        |        |     |     | 158                        |        |     |     | 157                 |        |    |     |
| ADA   | 121                        | (38.8) | 524 | 187 | 49                         | (31.0) | 191 | 135 | 30                  | (19.1) | 65 | 50  |
| Severe  | 0                          | (0.0)  | 0   | 0   | 0                          | (0.0)  | 0   | 0   | 0                   | (0.0)  | 0  | 0   |
| Documented symptomatic                                | 49                         | (15.7) | 115 | 41  | 24                         | (15.2) | 71  | 50  | 12                  | (7.6)  | 15 | 12  |
| Asymptomatic  | 86                         | (27.6) | 353 | 126 | 27                         | (17.1) | 94  | 66  | 19                  | (12.1) | 47 | 36  |
| Probable symptomatic                                  | 2                          | (0.6)  | 2   | 1   | 3                          | (1.9)  | 3   | 2   | 1                   | (0.6)  | 1  | 1   |
| Relative  | 18                         | (5.8)  | 54  | 19  | 11                         | (7.0)  | 23  | 16  | 2                   | (1.3)  | 2  | 2   |
| Unclassifiable  | 10                         | (3.2)  | 17  | 6   | 6                          | (3.8)  | 9   | 6   | 4                   | (2.5)  | 4  | 3   |
| Novo Nordisk minor                                    | 25                         | (8.0)  | 42  | 15  | 14                         | (8.9)  | 23  | 16  | 7                   | (4.5)  | 7  | 5   |

N: Number of patients. %: Percentage of patients with the event. E: Number of events. R: Event rate per 100 patient years of exposure. SU: sulphonylurea. Minor: FPG < 56 mg/dL. A treatment emergent hypoglycemic episode is defined as one that has onset date on or after the first day of randomized treatment and no later than 14 days after the last day of randomized treatment



**Figure 6–27 Documented treatment emergent hypoglycemic episodes: Trial 1922 in patients with T2DM**

The incidence of hypoglycemia in trial 1922 at the 3.0 mg dose was low and similar to that observed in the Victoza<sup>®</sup> trials when similar definitions of hypoglycemia (plasma glucose value  $\leq 56$  mg/dL) and background diabetes treatments were used.

Overall, these results indicate that neither the higher dose, nor the lifestyle intervention employed in the weight management program significantly alters the risk of hypoglycemia associated with liraglutide treatment in patients with T2DM. Not only was the overall risk of hypoglycemia low at  $\leq 1$  event per PYE, but the risk of hypoglycemia should be evaluated in the context of a greater glucose-lowering efficacy with liraglutide 3.0 mg as compared with 1.8 mg in trial 1922, a lower baseline HbA<sub>1c</sub> and FPG in this trial compared to the average T2DM clinical trial, and greater weight loss, all of which would be expected to increase the incidence of hypoglycemic episodes.

#### 6.3.6.4 Hypoglycemic episodes in patients without T2DM

No severe hypoglycemic events were reported in overweight or obese patients without T2DM. As shown in [Table 6–22](#), the proportion of patients reporting AEs of hypoglycemia outside the fasting FPG and OGTT visits ('spontaneously reported') was low, both with liraglutide 3.0 mg (1.6% of patients) and placebo (1.1% of patients). None of the spontaneously reported hypoglycemic AEs were SAEs. More patients treated with liraglutide 3.0 mg had hypoglycemia recorded at FPG or OGTT visits compared with placebo (FPG visits: 3.3% with liraglutide vs. 0.8% with placebo; OGTT visits: 8.0% with liraglutide 3.0 mg vs. 1.3% with placebo). The increased rate of hypoglycemia was consistent with a near-normalization of fasting and post-prandial glucose values in this group as compared to patients in the placebo group. The majority of these episodes were

reported as ‘asymptomatic’, further supporting that these were biochemical rather than clinically significant hypoglycemia.

**Table 6–22 Overview of AEs of hypoglycemia in patients without T2DM: weight management pool, excluding trial 1922 (NDA)**

|   | Liraglutide 3.0 mg |        |     | Placebo |       |    |
|---|--------------------|--------|-----|---------|-------|----|
|   | N                  | (%)    | E   | N       | (%)   | E  |
| All patients reporting an AE of hypoglycemia  |                    |        |     |         |       |    |
| Spontaneously reported                        | 46                 | (1.6)  | 59  | 19      | (1.1) | 23 |
| Reported at FPG visit                         | 97                 | (3.3)  | 119 | 13      | (0.8) | 14 |
| Reported at OGTT visit                        | 206                | (8.0)  | 283 | 18      | (1.3) | 21 |
| Normoglycemic patients (without pre-diabetes) |                    |        |     |         |       |    |
| Spontaneously reported                        | 16                 | (1.4)  | 22  | 6       | (0.9) | 6  |
| Reported at FPG visits                        | 54                 | (4.8)  | 65  | 9       | (1.3) | 10 |
| Reported at OGTT visits                       | 109                | (10.9) | 158 | 12      | (2.3) | 15 |
| Patients with pre-diabetes                    |                    |        |     |         |       |    |
| Spontaneously reported                        | 30                 | (1.6)  | 37  | 13      | (1.2) | 17 |
| Reported at FPG visits                        | 43                 | (2.3)  | 54  | 4       | (0.4) | 4  |
| Reported at OGTT visits                       | 97                 | (6.2)  | 125 | 6       | (0.7) | 6  |

N: Number of patients experiencing at least 1 episode, %: percentage of patients experiencing at least 1 episode, E: Number of events, FPG: fasting plasma glucose, OGTT: oral glucose tolerance test.

As expected based on the glucose-dependent mode of action, the majority of hypoglycemic AEs were associated with glucose values above 56 mg/dL ([Table 6–23](#) and [Table 6–24](#)), were single events with mild severity (i.e., no or transient symptoms, no interference with daily activities), resolved spontaneously, and rarely lead to treatment discontinuation. Fasting glucose values below 70 mg/dL are not uncommon in the general population; between 1% and 9% of adults without T2DM had glucose values <70 mg/dL (estimated percentages assuming normal distribution of FPG values).<sup>220–225</sup>

From [Table 6–24](#), it is clear that hypoglycemia during the OGTT occurred most frequently 90–120 minutes after glucose ingestion. Reactive hypoglycemia is a relatively common finding during OGTT,<sup>226</sup> depending on the definition, population, and duration and frequency of sampling during the test,<sup>227–229</sup> and is also relatively common in insulin-resistant states such as polycystic ovary syndrome (50% of patients with any post-load glucose value ≤70 mg/dL during a 4-hour OGTT).<sup>229</sup> The proposed mechanisms associated with reactive hypoglycemia include: 1) an exaggerated or delayed insulin response relative to the glucose peak; 2) accelerated gastric emptying leading to an exaggerated GLP-1 response to nutrients and subsequent hypersecretion of insulin; 3) increased insulin sensitivity and/or a blunted counter-regulatory response.<sup>230</sup> In the weight management trials (patients without T2DM), the occurrence of hypoglycemia AEs during OGTT was associated with younger age, female sex, a lower baseline body weight, and lower baseline HOMA-B and HOMA-IR. Patients experienced greater weight loss, had lower post-baseline HOMA-IR and HOMA-B, and had greater improvement of postprandial glycemic excursions and less pronounced insulin increment as compared to the overall population, all of

which indicate that hypoglycemia AEs reported during OGTT are a consequence of near-normalization of fasting and post-prandial glycemia due to direct and indirect effects of treatment, including an improvement in insulin sensitivity associated with weight loss (as indicated by lower post-baseline HOMA-IR). Importantly, late postprandial hypoglycemic events were not observed during mixed meal tests (trials 1807 and 3630) that represent a more physiologic caloric exposure than an OGTT.

**Table 6–23 FPG values in patients without T2DM with AEs of hypoglycemia reported at FPG visits: Weight management pool, excluding trial 1922 (NDA)**

|               |                | ----- Liraglutide 3.0 mg ----- |       |     | ----- Placebo ----- |       |    |
|---------------|----------------|--------------------------------|-------|-----|---------------------|-------|----|
|               | Criteria       | N                              | (%)   | E   | N                   | (%)   | E  |
| All patients  | FPG ≤70 mg/dL  | 92                             | (3.1) | 114 | 13                  | (0.8) | 14 |
|               | FPG < 56 mg/dL | 2                              | (0.1) | 2   | 1                   | (0.1) | 1  |
| Normoglycemic | FPG ≤70 mg/dL  | 52                             | (4.6) | 63  | 9                   | (1.3) | 10 |
|               | FPG < 56 mg/dL | 1                              | (0.1) | 1   | 1                   | (0.1) | 1  |
| Pre-diabetes  | FPG ≤70 mg/dL  | 40                             | (2.2) | 51  | 4                   | (0.4) | 4  |
|               | FPG < 56 mg/dL | 1                              | (0.1) | 1   | 0                   | (0.0) | 0  |

FPG: fasting plasma glucose. The number of events which fulfil the criteria are the number of adverse events for which there exists a plasma glucose measurement which fulfils the criteria on the same date as the patient has reported an episode. Note that events which fulfil the <56 mg/dL criteria also fulfil the ≤70 mg/dL criteria.

**Table 6–24 Glucose values in patients without T2DM with AEs of hypoglycemia reported at OGTT visits: Weight management pool, excluding trial 1922 (NDA)**

|                      |              | ----- Liraglutide 3.0 mg ----- |       |     | ----- Placebo ----- |       |    |
|----------------------|--------------|--------------------------------|-------|-----|---------------------|-------|----|
| Nominal time         | Criteria     | N                              | (%)   | E   | N                   | (%)   | E  |
| All patients         |              | 206                            | (8.0) | 283 | 18                  | (1.3) | 21 |
| Total during OGTT    | PG ≤70 mg/dL | 203                            | (7.9) | 279 | 16                  | (1.2) | 19 |
|                      | PG <56 mg/dL | 58                             | (2.3) | 76  | 2                   | (0.1) | 2  |
| Baseline (0 min)     | PG ≤70 mg/dL | 45                             | (1.7) | 61  | 2                   | (0.1) | 2  |
|                      | PG <56 mg/dL | 1                              | (0.0) | 1   | 0                   | (0.0) | 0  |
| Total after baseline | PG ≤70 mg/dL | 188                            | (7.3) | 264 | 15                  | (1.1) | 18 |
|                      | PG <56 mg/dL | 57                             | (2.2) | 75  | 2                   | (0.1) | 2  |
| 10 min               | PG ≤70 mg/dL | 10                             | (0.4) | 11  | 0                   | (0.0) | 0  |
|                      | PG <56 mg/dL | 1                              | (0.0) | 1   | 0                   | (0.0) | 0  |
| 30 min               | PG ≤70 mg/dL | 4                              | (0.2) | 7   | 1                   | (0.1) | 1  |
|                      | PG <56 mg/dL | 0                              | (0.0) | 0   | 0                   | (0.0) | 0  |
| 60 min               | PG ≤70 mg/dL | 34                             | (1.3) | 52  | 1                   | (0.1) | 2  |
|                      | PG <56 mg/dL | 7                              | (0.3) | 11  | 0                   | (0.0) | 0  |
| 90 min               | PG ≤70 mg/dL | 96                             | (3.7) | 141 | 5                   | (0.4) | 6  |
|                      | PG <56 mg/dL | 18                             | (0.7) | 23  | 1                   | (0.1) | 1  |
| 120 min              | PG ≤70 mg/dL | 149                            | (5.8) | 208 | 14                  | (1.0) | 16 |

| Nominal time | Criteria     | ---- Liraglutide 3.0 mg ---- |       |    | ----- Placebo ----- |       |   |
|--------------|--------------|------------------------------|-------|----|---------------------|-------|---|
|              |              | N                            | (%)   | E  | N                   | (%)   | E |
|              | PG <56 mg/dL | 43                           | (1.7) | 56 | 1                   | (0.1) | 1 |

OGTT: oral glucose tolerance test. PG: plasma glucose.

Number of events which fulfil the criteria are the number of AEs for which there exists a plasma blood glucose value which fulfils the criteria on the same date as the patient has reported an episode. Note that events which fulfil the <56 mg/dL criteria also fulfil the ≤70 mg/dL criteria. The 'total after baseline' category shows all AEs which were accompanied by at least one confirmatory measurement between 10 and 120 minutes, and the 'total during OGTT' shows all events which were accompanied by at least one confirmatory measurement between 0 and 120 minutes. Note that there can be several measurements which fulfil the ≤70 mg/dL and <56 mg/dL criteria for AEs reported on the same day as a OGTT profile which is the reason why the number of events per time point does not add up to the total number of events reported at the same day as OGTT profiles.

### 6.3.6.5 Conclusions for hypoglycemia in the weight management program

In the weight management trials, in patients without T2DM, the risk of hypoglycemia with liraglutide 3.0 mg was low, and the events were mostly 'biochemical' hypoglycemia recorded at OGTT visits. While the OGTT is a physiological stress test of both glucose excursions and insulin secretion, it does not represent routine carbohydrate ingestion in daily life. There was little overlap between patients reporting AEs of hypoglycemia spontaneously between visits and patients with hypoglycemia AEs recorded during either FPG or OGTT visits, further supporting that biochemical hypoglycemia recorded during an OGTT or at a fasting clinic visit does not represent the risk of hypoglycemia during routine daily life activities. In patients with T2DM, the risk of hypoglycemia with liraglutide 3.0 mg was higher than placebo, but comparable to that of liraglutide 1.8 mg in the 1922 trial and to the rates observed in Victoza<sup>®</sup> trials. Concurrent use of SUs and GLP-1 increased the risk of hypoglycemia (by 3-4 times), highlighting the importance of dose adjustment for anti-diabetic treatment in obese patients with T2DM undergoing weight management therapy.

The risk of hypoglycemia is addressed in the proposed labeling of liraglutide 3.0 mg.

### 6.3.7 Pregnancy

#### 6.3.7.1 Background

While it may improve the chance of pregnancy,<sup>231</sup> weight loss is not recommended during pregnancy because of increased potential for fetal harm. Accordingly, liraglutide (or any other weight loss medication) is not recommended for use in women who are pregnant or who plan to become pregnant.

Pregnancy and the intention of becoming pregnant were exclusion criteria in the liraglutide weight management trials, and women of child-bearing age were counselled on the necessity of using appropriate birth control methods when entering and during the trials. Women who became pregnant were to be immediately withdrawn from the trial and their pregnancy was followed through one month after the birth of the child. Nonetheless, a number of pregnancies occurred and their outcomes are reviewed below.

Liraglutide has not been systematically studied in pregnant or lactating women, and no information on the excretion of liraglutide in human milk or effects on the nursing infant is available. Victoza<sup>®</sup> is currently pregnancy Category C for the approved indication in T2DM.

### 6.3.7.2 Pregnancy in the weight management program

A total of 59 pregnancies (39 with liraglutide 3.0 mg and 20 with placebo) had been reported in exposed patients in the completed phase 2 and 3 trials through the 120-Day Safety Update ([Table 6–25](#)). The overall proportions of patients who became pregnant were similar in the 2 treatment groups (~1.5% of exposed women in the completed clinical trials).

All 18 babies born to mothers who had been exposed to liraglutide were healthy and had no congenital abnormalities; the proportion of pregnancies resulting in healthy births of children in the weight management population was similar between treatment groups (18 with liraglutide [46.2% of pregnancies] and 7 with placebo [35.0% of pregnancies]) ([Table 6–25](#)).

More pregnancies resulted in spontaneous abortions with liraglutide (10 events [25.6% of pregnancies]) than with placebo (2 events [10.0% of pregnancies]) ([Table 6–25](#)). For spontaneous abortions, a review of concomitant medications, weight change before and after the time of conception, other AEs reported, and medical history did not reveal potential relationships or explanations. However, of the 10 cases of spontaneous abortion with liraglutide, 6 women had relevant medical history, including prior miscarriages, thyroid disease (chronic autoimmune thyroiditis and hypothyroidism), polycystic ovary syndrome (PCOS), ectopic pregnancy and irregular menstrual cycles.

In general, spontaneous abortions occur in 12–15% of all pregnancies.<sup>232</sup> Of these, approximately 80% occur during the first trimester.<sup>233</sup> Evidence suggests that obese women have an increased risk of adverse maternal and perinatal outcomes, including spontaneous abortions.<sup>61–63</sup> In addition, pre-eclampsia, gestational diabetes mellitus and fetal death occur at increased frequency with maternal obesity compared to the normal weight population.<sup>61</sup> Thus, the proportion of female patients experiencing spontaneous abortions in the completed weight management trials (25.6% for liraglutide and 10.0% for placebo) were within the range found in epidemiological data from literature, showing that up to 25–37% of pregnancies in obese women result in a spontaneous abortion.<sup>63,232</sup>

**Table 6–25 Pregnancies: weight management population through 120-Day Safety Update**

|   | Total Liraglutide <sup>a</sup><br>N (%) | Placebo<br>N (%)       |
|---|---|------------------------|
| Females in safety analysis set          | 2379                                    | 1300                   |
| Pregnancies (% of females) <sup>b</sup> | 39 (1.6%)                               | 20 (1.5%)              |
| Outcome of pregnancies <sup>c</sup>     |   |                        |
| Healthy children                        | 18 (46.2%)                              | 7 (35.0%)              |
| Spontaneous abortion <sup>d</sup>       | 10 (25.6%)                              | 2 <sup>e</sup> (10.0%) |
| Abortion                                | 1 (2.6%)                                | 0                      |
| Elective abortion                       | 4 (10.3%)                               | 3 (15.0%)              |
| Ectopic pregnancy                       | 1 (2.6%)                                | 3 (15.0%)              |
| Lost to follow-up/unknown               | 1 (2.6%)                                | 3 (15.0%)              |
| Ongoing                                 | 4 (10.3%)                               | 2 (10.0%)              |

N: number of patients; %: percentage of patients. The table includes reported cases as of the cut-off date 14 March 2014

**a:** All pregnancies were reported in patients treated with liraglutide 3.0 mg **b:** In addition, 1 pregnancy was reported in a woman who was not treated with trial product (trial 1807), this case is not included in this overview; **c:** The percentages for the pregnancy outcomes as well as types of contraception have been estimated from the total number of pregnancies in each group; **d:** 1 event (in Patient 421019) could not be confirmed; **e:** includes 1 event of ‘fetal death’ at week 26 (trial 1839)

### 6.3.7.3 Developmental and reproductive toxicity results from non-clinical studies

Developmental and reproductive toxicity studies with liraglutide have been conducted in rats and rabbits and the results are summarized in Section 3.4.4. The relevance of the non-clinical findings to humans is unknown, since liraglutide has not been studied systematically in pregnant women.

### 6.3.7.4 Conclusions for pregnancy in the weight management program

As per the cut-off date 14 March 2014, the overall proportions of patients who became pregnant were similar in the 2 treatment groups (~1.5% of exposed women in the completed clinical trials), and the proportion of pregnancies resulting in healthy children was also similar between treatment groups. There were no congenital abnormalities in the babies born of women who had been exposed to liraglutide. While there were more reports of spontaneous abortions with liraglutide, a causal relationship could not be established. The proportion was within the expected range of pregnancies that result in spontaneous abortions in obese women.<sup>63,232</sup>

Experience from clinical trials and marketed use of Victoza<sup>®</sup> in T2DM has not indicated any safety concerns in relation to use in pregnancy. However, if liraglutide is used with the intention of increasing fertility by weight reduction, it is important that treatment with liraglutide be discontinued before conception is attempted. Similar to other weight loss medicines, the labeling will include a pregnancy category X, informing prescribers that liraglutide 3.0 mg should not be used to lose weight during pregnancy or by women who intend to become pregnant.



### 6.3.8 Neuropsychiatric safety

#### 6.3.8.1 Background

A significant proportion of overweight and obese patients have a history of psychiatric disorders. Obese patients were found to have a 55% increased risk of developing depression<sup>234</sup>, most pronounced in the American population. In addition, depression was found to be predictive of developing obesity, with 58% of individuals with clinically diagnosed depression developing obesity.<sup>234</sup> Female gender also appeared to confer some risk as the prevalence of depression was almost twice as high in women compared to men.<sup>235,236</sup>

Two validated mental health questionnaires, Patient Health Questionnaire 9 (PHQ-9)<sup>237</sup> and Columbia Suicide Severity Rating Scale (C-SSRS),<sup>238</sup> were used in all phase 3 weight management trials with liraglutide 3.0 mg as signal detection tools of new onset depression and/or suicidal ideation and behavior, in accordance with the FDA's guidance for centrally acting drugs<sup>239</sup> and advice from FDA on the phase 3 protocols.

Based on the mode of action of liraglutide in the brain, it was not anticipated to have adverse neuropsychiatric effects.

#### 6.3.8.2 Neuropsychiatric function in the weight management program

At baseline, 9.5% of patients in the weight management trials had a history of depression and 7.0% had a history of anxiety; 9.0% of patients in the liraglutide 3.0 mg group and 10.1% of patients in the placebo group were treated with antidepressants at baseline.

The overall proportions of patients reporting events were comparable between groups (liraglutide 3.0 mg: 10.8%, [15.4 events per 100 PYE]; placebo: 10.1%, [15.3 events per 100 PYE]) ([Table 6–26](#)), as were the proportions reporting SAEs (0.1% in both groups). Most events were mild or moderate in severity; severe events occurred as single cases in single patients and overall were reported by a lower proportion of patients treated with liraglutide 3.0 mg than placebo. Few events led to patient withdrawal; the rate of withdrawal appeared lower with liraglutide 3.0 mg (0.4% of patients, [0.6 events per 100 PYE]) than with placebo (0.7% of patients, [0.9 events per 100 PYE]).

**Table 6–26 Treatment-emergent psychiatric disorder events identified by the MedDRA search: weight management pool (NDA)**

|                           | Liraglutide 3.0 mg<br>(n=3384) | Placebo<br>(n=1941) |
|---------------------------|--------------------------------|---------------------|
| Number of patients, N (%) | 366 (10.8)                     | 197 (10.1)          |
| Number of events          | 459                            | 245                 |
| Rate (events per 100 PYE) | 15.4                           | 15.3                |

PYE: patient years of exposure

The most frequently reported psychiatric disorders with liraglutide 3.0 mg were ‘insomnia’ (2.4% vs. 1.7% with placebo), ‘anxiety’ (2.0% vs. 1.6% with placebo) and ‘depression’ (1.8% vs. 1.6% with placebo). Overall, there were no imbalances in reported disorders between the 2 groups except for the aforementioned slightly higher prevalence of insomnia and anxiety with liraglutide 3.0 mg; the majority of insomnia and anxiety events in the liraglutide 3.0 mg group were mild in severity, and rarely lead to withdrawal. While anxiety events appeared throughout the treatment period, the imbalance in insomnia events was mainly seen during the first 3 months of treatment, after which the incidence rate appeared similar between the two groups. A similar imbalance for insomnia (but not anxiety or depression) was observed with liraglutide in T2DM, albeit with lower incidence (1.3% vs. 0.8%, for total liraglutide vs. total comparator, respectively).

A total of 3 events of suicidal ideation were reported by 3 patients treated with liraglutide 3.0 mg and none with placebo. All events were non-serious and there was no co-reporting of the severe type of ideation (with intent to act) on the suicidality assessment questionnaire. Five events of overdose (including accidental overdose) were reported with liraglutide 3.0 mg and 4 with placebo. Medical review of the investigator-reported terms for the events of overdose did not indicate suicidal behavior or intent to self-harm.

In three trials with longer follow-up periods (1839, 1922 and 1923), the proportions of patients reporting psychiatric disorder events were lower after treatment discontinuation compared to those during treatment in both groups. The proportions of patients reporting psychiatric disorder events after treatment discontinuation were comparable between liraglutide 3.0 mg and placebo.

### ***Mental health questionnaires***

The questionnaire results were consistent with the reporting of psychiatric disorder adverse events. Overall, there were no imbalances between liraglutide 3.0 mg and placebo and no signal for depression or suicidality with liraglutide 3.0 mg.

PHQ-9 is a 9-item self-administered depression assessment module of the patient health questionnaire. The total score can range from 0 to 27, with a higher score indicative of greater depression severity. Mean PHQ-9 scores were low and comparable between arms at baseline (liraglutide 3.0 mg: 2.8, placebo: 2.9) and decreased/improved to a similar degree in both groups at the end of treatment (liraglutide 3.0 mg: 1.8, placebo: 1.9, [Table 6–27](#)).

**Table 6–27 Overview of PHQ-9 results during treatment – phase 3 trials (NDA)**

| PHQ-9   | Liraglutide 3.0 mg | Placebo |
|---|--------------------|---------|
| Mean scores   |                    |         |
| Mean PHQ-9 total score at end-of-treatment            | 1.8                | 1.9     |
| Mean of PHQ-9 highest scores over treatment period    | 3.7                | 3.7     |
| Percentage of patients with total score above cut-off |                    |         |
| ≥10 at end-of-treatment (week 56 LOCF)                | 1.9%               | 1.7%    |
| ≥10 at any time during trial                          | 6.1%               | 6.8%    |
| ≥15 at end-of-treatment (week 56 LOCF)                | 0.4%               | 0.4%    |
| ≥15 at any time during trial                          | 1.1%               | 1.5%    |
| ≥20 at end-of-treatment (week 56 LOCF)                | <0.1%              | 0.2%    |
| ≥20 at any time during trial                          | 0.2%               | 0.4%    |

LOCF: last observation carried forward; PHQ-9: patient health questionnaire 9.

At the individual patient level, approximately 70% of patients in each group had no change in their baseline depression severity category during treatment. Similar proportions of patients in both groups either shifted to less severe (~10%) or more severe (~20%) categories from baseline at the end of treatment ([Table 6–28](#)).

**Table 6–28 PHQ-9 total score – shift to maximum until end of trial – phase 3 trials (NDA)**

|   | Liraglutide 3.0 mg |        | Placebo |        |
|---|--------------------|--------|---------|--------|
|   | N                  | (%)    | N       | (%)    |
| Number of patients  | 3291               |        | 1843    |        |
| Total number of patients improving from baseline to highest score | 317                | (9.6)  | 182     | (9.9)  |
| Mild to none  | 231                | (7.0)  | 132     | (7.2)  |
| Moderate to none  | 27                 | (0.8)  | 12      | (0.7)  |
| Moderate to mild  | 59                 | (1.8)  | 35      | (1.9)  |
| Moderately severe to moderate                                     | 0                  | (0.0)  | 0       | (0.0)  |
| Moderately severe to mild   | 0                  | (0.0)  | 1       | (0.1)  |
| Moderately severe to none   | 0                  | (0.0)  | 2       | (0.1)  |
| Severe to moderately severe                                       | 0                  | (0.0)  | 0       | (0.0)  |
| Severe to moderate  | 0                  | (0.0)  | 0       | (0.0)  |
| Severe to mild  | 0                  | (0.0)  | 0       | (0.0)  |
| Severe to none  | 0                  | (0.0)  | 0       | (0.0)  |
| Total number of patients worsening from baseline to highest score | 653                | (19.8) | 347     | (18.8) |
| None to mild  | 483                | (14.7) | 251     | (13.6) |
| None to moderate  | 66                 | (2.0)  | 40      | (2.2)  |
| None to moderately severe   | 9                  | (0.3)  | 10      | (0.5)  |
| None to severe  | 1                  | (0.0)  | 4       | (0.2)  |
| Mild to moderate  | 69                 | (2.1)  | 29      | (1.6)  |
| Mild to moderately severe   | 13                 | (0.4)  | 6       | (0.3)  |
| Mild to severe  | 2                  | (0.1)  | 2       | (0.1)  |
| Moderate to moderately severe                                     | 7                  | (0.2)  | 4       | (0.2)  |
| Moderate to severe  | 3                  | (0.1)  | 1       | (0.1)  |
| Moderately severe to severe                                       | 0                  | (0.0)  | 0       | (0.0)  |
| No change   | 2291               | (69.6) | 1293    | (70.2) |
| Missing   | 30                 | (0.9)  | 21      | (1.1)  |

N: Number of patients, %: Proportion of randomized patients, PHQ-9: Patient health questionnaire 9

Table is based on trials 1839, 1922, 3970 and 1923

No depression: PHQ-9 total score of 0-4; Mild depression: PHQ-9 total score of 5-9; Moderate depression: PHQ-9 total score of 10-14; Moderate severe depression: PHQ-9 total score of 15-19; Severe depression: PHQ-9 total score of  $\geq 20$

The Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire, a tool for systematic assessment of suicidal ideation and behavior, was administered by trained and medically qualified personnel. At screening, a dedicated questionnaire version assessed patients' lifetime history of suicidal ideation/behavior; thereafter, changes since prior visits were assessed. The lifetime C-SSRS assessment identified similar proportions of patients with suicidal behavior/ideation in both groups (liraglutide 3.0 mg: 3.3%, placebo: 3.6%); very few of these patients had a history of suicidal behavior (liraglutide 3.0 mg: 0.18%, placebo: 0.11%). At baseline, very few patients reported current suicidal ideation (without plan or intent) or behavior (liraglutide 3.0 mg: 5 patients, placebo: 3 patients). During the treatment period, no patients attempted suicide and 1 patient (liraglutide 3.0 mg) reported unspecific suicidal behavior. The proportions of patients with events of suicidal ideation (mainly without a plan/intent to act) were low and similar between the two groups during the treatment period (liraglutide 3.0 mg: 21 patients, 0.6%; placebo: 14 patients, 0.8%) ([Table 6-29](#)). In trials with longer follow-up periods, treatment discontinuation did not appear to affect mean PHQ-9 scores or the number of patients reporting suicidal ideation/behavior.

**Table 6–29 Post-baseline C-SSRS (any time during the treatment period) - suicidal behavior and suicidal ideation – phase 3 trials**

|  | --- Liraglutide 3.0 mg --- |    |        | ----- Placebo ----- |    |        |
|--|----------------------------|----|--------|---------------------|----|--------|
|  | N                          | n  | (%)    | N                   | n  | (%)    |
| Number of patients   | 3291                       |    |        | 1843                |    |        |
| Number of patients answering the C-SSRS                                    | 3270                       |    |        | 1832                |    |        |
| Years of exposure  | 2898.6                     |    |        | 1527.7              |    |        |
| Patients with suicidal behavior and/or ideation                            |                            | 22 | (0.67) |                     | 14 | (0.76) |
| Patients with suicidal ideation on the C-SSRS                              |                            | 21 | (0.64) |                     | 14 | (0.76) |
| 1. Wish to be dead   |                            | 18 | (0.55) |                     | 13 | (0.71) |
| 2. Active suicidal ideation, non-specific thoughts                         |                            | 9  | (0.27) |                     | 6  | (0.33) |
| 3. Active suicidal ideation with any methods (no plan) without intent      |                            | 5  | (0.15) |                     | 3  | (0.16) |
| 4. Active suicidal ideation with some intent to act, without specific plan |                            | 1  | (0.03) |                     | 1  | (0.05) |
| 5. Active suicidal ideation with specific plan and intent                  |                            | 0  | (0)    |                     | 1  | (0.05) |
| Patients with suicidal behavior on the C-SSRS                              |                            | 0  | (0)    |                     | 0  | (0)    |
| 1. Completed Suicide   |                            | 0  | (0)    |                     | 0  | (0)    |
| 2. Actual suicide attempt  |                            | 0  | (0)    |                     | 0  | (0)    |
| 3. Interrupted attempt   |                            | 0  | (0)    |                     | 0  | (0)    |
| 4. Aborted suicide attempt   |                            | 0  | (0)    |                     | 0  | (0)    |
| 5. Preparatory acts towards imminent suicidal behaviors                    |                            | 0  | (0)    |                     | 0  | (0)    |
| Suicidal behavior (item)   |                            | 1  | (0.03) |                     | 0  | (0)    |
| Non-suicidal self-injurious behavior                                       |                            | 1  | (0.03) |                     | 0  | (0)    |

C-SSRS: Columbia-suicide severity rating scale, N: Number of patients, n: Number of patients answering yes, %: Percentages are based on total N.

Table is based on trials 1839, 1923 1922, and 3970

### 6.3.8.3 Conclusion for neuropsychiatric function in the weight management program

There was no imbalance in the overall prevalence of psychiatric disorder events between liraglutide 3.0 mg and placebo in the weight management pool, or between liraglutide doses up to 1.8 mg versus comparator in the type 2 diabetes development programs. In the weight management pool, most adverse events were mild or moderate in severity and few led to patient withdrawal in either group. There was no imbalance in events of depression, but reporting of insomnia and anxiety was slightly higher (by <1%) with liraglutide 3.0 mg compared to placebo. The results of the mental health questionnaires were consistent with the reporting of psychiatric disorder events; overall, there were no imbalances between liraglutide 3.0 mg and placebo and no signal for depression or suicidality with liraglutide 3.0 mg. There was no indication that discontinuation of liraglutide 3.0 mg treatment resulted in withdrawal or rebound psychiatric effects as assessed by the two mental health questionnaires.

## 7 Plan for Continued Assessment of Benefit/Risk Post-approval

The liraglutide 3.0 mg clinical development program was designed according to FDA guidance for weight management products and included almost 6,000 patients. These data are in addition to the more than 3.3 million patient years of exposure worldwide with Victoza<sup>®</sup> for T2DM. The safety profile with liraglutide 3.0 mg is generally as predicted based on the liraglutide diabetes program and from clinical experience with other approaches to weight loss, and supports a favorable benefit/risk profile. The post-marketing risk management program for liraglutide 3.0 mg will build upon the ongoing Victoza<sup>®</sup> post-marketing program, and will emphasize appropriate patient selection, patient and physician education on the potential risks and further investigations on the uncertainties identified.

### 7.1 Labeling

The packaging for liraglutide 3.0 mg will include a physician insert along with a Medication Guide that is targeted to patients. As with Victoza<sup>®</sup> and other GLP-1 receptor agonists, based on non-clinical rodent findings, liraglutide 3.0 mg will include a boxed warning regarding the potential risk of medullary thyroid cancer (MTC). The labeling will also include information on pancreatitis, gallbladder disorders, heart rate, and breast cancer. In addition and similar to other weight loss medicines, the labeling will include a pregnancy category X which will recommend that women do not become pregnant while using liraglutide 3.0 mg.

### 7.2 Risk Evaluation and Mitigation Strategy (REMS)

Liraglutide 3.0 mg will include a Risk Evaluation and Mitigation Strategy (REMS). The objective of the REMS will be to inform on:

- the potential risk of medullary thyroid cancer
- the risk of acute pancreatitis (including necrotizing pancreatitis)
- appropriate patient selection (including information that liraglutide 3.0 mg and Victoza<sup>®</sup> should not be used together)

The REMS includes a Communication Plan consisting of a REMS Letter that will be mailed within 60 days of product approval and again at 12 and 24 months after product approval. The REMS Letter will be sent to health care providers who are likely to prescribe liraglutide 3.0 mg. These will include, but will not be limited to, general practitioners, family practitioners, internists, gynecologists, endocrinologists, cardiologists, and nurse practitioners/physician assistants. In order to further facilitate prescriber training and education, within 60 days of product approval, and again at 12 and 24 months after product approval, Novo Nordisk will send the REMS Letter to 21 professional organizations, and will request that the REMS Letter be provided to the members of the professional organizations.

The REMS will also include a dedicated REMS website and a Factsheet for Prescribers. The REMS Factsheet for Prescribers will be distributed through Novo Nordisk sales or medical representatives

during the initial detailing visit with healthcare providers during the first 12 months after product approval.

The effectiveness of the REMS will be assessed at 1, 2, 3 and 7 years after approval and adjustments will be made as needed.

### **7.3 Medullary Thyroid Carcinoma (MTC) registry**

Liraglutide 3.0 mg will be incorporated into the national MTC registry that is already ongoing for the Victoza<sup>®</sup> program. The ongoing MTC registry systematically monitors the annual incidence of MTC in the U.S. through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 receptor agonists into the U.S. market.

### **7.4 Prospective medical claims database**

A prospective medical claims database will be established to evaluate the incidence of breast cancer in patients initiating liraglutide 3.0 mg compared with other weight management pharmacotherapies. The database will also evaluate pancreatic safety, gallbladder disorders, and neoplasms, as is already being done for the Victoza<sup>®</sup> program with liraglutide doses up to 1.8 mg.

### **7.5 Mechanistic study to evaluate gallbladder function**

It is planned to conduct a 2-arm randomized, parallel-group short mechanistic study to assess gallbladder emptying (induced by a meal) with or without liraglutide 3.0 mg in steady state and to assess serum pancreatic enzyme activity (lipase and amylase) in connection with a meal. The objective of the study is two-fold, to better understand the mechanism for the increased incidence of gallbladder-related AEs with liraglutide, and to clarify whether pancreatic enzymes increase in the blood following a meal, and if this response is enhanced with liraglutide.

### **7.6 Post-marketing Program for Victoza<sup>®</sup>**

As part of the post-marketing program for Victoza<sup>®</sup>, three non-clinical studies have been completed which further evaluated the potential risks of pancreatitis and MTC. The program also includes a REMS and the ongoing national MTC registry and 5 year prospective medical claims database study that are mentioned above. Novo Nordisk is also conducting a cardiovascular outcome trial (LEADER<sup>®</sup>) to evaluate the risk of major adverse cardiovascular events. The ongoing trial, for which enrolment at 410 sites in 32 countries has been completed, compares liraglutide 1.8 mg to placebo in more than 9,000 patients with T2DM.<sup>53</sup> The mean age of the patients at baseline was 64.3 years and mean BMI was 32.5 kg/m<sup>2</sup> (more than 7,500 had a BMI >27 kg/m<sup>2</sup> and more than 5,500 had a BMI >30 kg/m<sup>2</sup>). Approximately 81% of patients had prior cardiovascular disease; the remainder were high-risk individuals without prior cardiovascular disease. Patients will be followed for up to 5 years. The primary endpoint is the time from randomization to a composite outcome consisting of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or



nonfatal stroke. Other safety endpoints, including neoplasms, pancreatitis and gallbladder disease, will also be evaluated. It is expected that the LEADER<sup>®</sup> trial, which is due to be reported in 2016, will provide conclusive data regarding the cardiovascular safety of liraglutide, albeit at a lower dose of 1.8 mg.

## 8 Benefit/Risk Assessment

Obesity is a complex and multifactorial chronic disease that can affect physical and mental health, as well as quality of life, in numerous ways.<sup>17</sup> It is associated with increased risk of mortality<sup>21</sup> and multiple comorbid conditions, including T2DM, hypertension, dyslipidemia, coronary artery disease and stroke, liver and gallbladder disease, OSA, and certain types of cancer.<sup>17-21</sup> Individuals with obesity also suffer physical symptoms (e.g., joint pain, urinary incontinence), functional limitations (e.g., impaired mobility), and psycho-social problems (e.g., body image disorders, bullying, depression, and dementia).<sup>23-27</sup>

Weight loss of at least 5% of initial body weight can have significant health benefits, including prevention of T2DM in individuals with impaired glucose regulation, improvement in glycemic control in individuals with T2DM, as well as improvements in OSA severity, urinary incontinence, depression, physical functioning and mobility, and general quality of life.<sup>29-32</sup> Current treatment guidelines recommend weight loss as an integral part of the management of overweight and obese individuals with T2DM<sup>240</sup> or OSA.<sup>73,74</sup>

Lifestyle intervention in the form of dietary, behavioral and exercise counselling is traditionally the primary treatment for obesity, but weight loss by lifestyle intervention alone is difficult to achieve and maintain.<sup>17,33,34</sup> Neither behavioral modification nor bariatric surgery fully address the needs of all patients with obesity.<sup>17,35</sup> Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention in achieving and sustaining clinically relevant weight loss, and may also have the potential to moderate the metabolic responses that favor weight regain.<sup>17</sup> There are currently few safe and effective pharmacological treatment options available for obese individuals trying to lose weight, and additional efficacious therapies are needed to meet the clinical needs of the diverse patient population affected by overweight and obesity and their co-morbidities.<sup>36</sup>

GLP-1 is a physiological regulator of appetite and food intake<sup>7-12</sup> and, as a GLP-1 receptor agonist, liraglutide 3.0 mg represents a new drug class within weight management. Liraglutide at doses up to 1.8 mg once-daily is approved as Victoza<sup>®</sup> for the treatment of T2DM in more than 70 countries worldwide and has been available on the market since 2009 and in the U.S. since 2010.<sup>15</sup> Considerable experience has therefore accumulated from not only non-clinical and clinical trials but also post-marketing use of liraglutide over several years. The cumulative post-marketing exposure is estimated to be more than 3.3 million PYE. Due to the combined actions on appetite regulation, glucose metabolism and cardio-metabolic risk factors such as blood pressure, liraglutide holds unique potential for weight management.

### 8.1 Benefits of treatment

The weight management clinical development program in total randomized almost 6,000 overweight or obese patients with common weight-related co-morbidities, including pre-diabetes, T2DM and OSA. In each of the five phase 2 and 3 trials in the weight management program,

liraglutide 3.0 mg as an adjunct to a reduced-calorie diet and increased physical activity induced weight loss that was superior to placebo on all 3 co-primary mean and categorical weight loss endpoints. In each of the trials, the proportion of patients in the liraglutide 3.0 mg group achieving at least 5% weight loss at the end of the trial was greater than 35%, and more than double that in the placebo group, supporting that liraglutide is effective for weight management according to FDA guidance.<sup>37</sup> In trial 1839, the largest phase 3 trial, 64% of patients lost at least 5% of their initial body weight with liraglutide 3.0 mg and 33% lost more than 10% (using LOCF imputation), compared to 27% and 10%, respectively, in the placebo group. Across the 5 trials, approximately 90% of patients in the liraglutide 3.0 mg group lost some weight compared to approximately 65% with placebo, with one-year mean weight losses of up to 9.2% (8.8 kg) and 3.1% (3.0 kg) in the liraglutide 3.0 mg and placebo groups, respectively. As expected, the mean and categorical weight loss was greater in patients completing a full year of treatment as well as in the patients achieving a minimum of 5% weight loss at the end of the trial (the 5% responders), whose mean weight loss with liraglutide 3.0 mg was 11.5% (12.0 kg).

Importantly, a clinically meaningful weight loss was observed with liraglutide 3.0 mg in all sub-populations investigated. These included patients with T2DM, who often respond less favorably to weight management pharmacotherapy,<sup>107</sup> and patients with OSA, a serious health condition which can be ameliorated by weight loss but is dominated by males who typically do not seek treatment for obesity.<sup>241</sup> Weight loss was generally maintained as long as participants remained on treatment, and was sustained for up to 2 years in trial 1807. In trial 1923, liraglutide 3.0 mg provided an additional weight loss of 6.3% (6.0 kg) over the 56-week treatment period, over and above the 6.0% (6.3 kg) lost during the 4-12 week low-calorie dietary run-in. Moreover, there was better maintenance of the diet-induced weight loss with liraglutide 3.0 mg than with placebo in this trial. In all trials, the robustness of the weight-loss results was confirmed by several sensitivity analyses. Together, the effects demonstrate a potential benefit for liraglutide in enhancing long-term weight loss achieved by lifestyle intervention, as well as in sustaining the weight loss.<sup>242</sup> Maintenance of weight loss and prevention of weight gain are important secondary efficacy criteria for weight management products.<sup>37</sup>

Weight loss with liraglutide 3.0 mg was accompanied by consistent positive effects on multiple secondary efficacy parameters, including those stipulated in weight management guidelines as providing meaningful health benefits.<sup>37,243</sup> These included improvement in waist circumference and total body fat, insulin resistance, fasting and postprandial glycemic control, prevalence of pre-diabetes and incidence of progression to T2DM, blood pressure, lipids and cardiovascular biomarkers, as well as patient-reported quality of life.

The improvements in glycemia, lipid profiles and blood pressure occurred with liraglutide 3.0 mg despite lower net use of concomitant medication to control these co-morbidities. Effects were typically most pronounced in the patients with more significant disease at baseline (i.e., in those with greatest need for improvement) and correlated with the degree of weight loss (i.e., greater

benefit with more weight loss). This relationship also applied to OSA severity in trial 3970, where a particularly strong correlation was observed between degree of weight loss and improvement in AHI (apnea-hypopnea index, a key indicator of sleep apnea severity) in patients having severe OSA at enrolment, as well as in the overall trial population. The effects on body weight and glycemic control were dose-dependent, as indicated by statistically significantly greater effects with 3.0 mg as compared with 1.8 mg.

Weight loss achieved with liraglutide 3.0 mg, as adjunct to diet and exercise, also provided important benefits in terms of improvements in the physical and mental/emotional health aspects of obesity, based on questionnaires widely used in obesity clinical research. Notably, improvements in physical function scores were demonstrated using 2 independent instruments, the SF-36 (in 2 trials) and the IWQoL-lite (in 3 trials). An improved score may be directly translated into functional benefits for the individual in terms of improved mobility, greater ease in dressing and undressing, and improved physical symptoms such as joint pain.<sup>40,41</sup> Liraglutide 3.0 mg also improved the mental and psycho-social dimensions of the SF-36 questionnaire, an effect which has not consistently been seen with other weight management products.<sup>215,216</sup> The recent George Washington University consensus report on weight management stressed the importance of dealing with quality of life issues in relation to the treatment of obesity.<sup>17</sup> The data obtained with liraglutide 3.0 mg on the SF-36 and IWQoL-lite demonstrate clinically relevant improvements in feeling and function and complement the actual weight losses achieved.

In summary, patients with or without T2DM and other co-morbidities such as OSA achieved and maintained clinically meaningful and statistically significant weight loss with liraglutide 3.0 mg, as adjunct to diet and exercise. The weight loss was associated with improvements in cardiovascular risk markers and weight-related comorbid conditions, as well as meaningful improvements in quality of life, notably physical function.

## **8.2 Risks of treatment**

The benefits of liraglutide 3.0 mg must be evaluated in the context of the types and severity of the adverse events associated with this therapy. Overall, the safety profile of liraglutide 3.0 mg in overweight and obese individuals with or without T2DM was similar to that of Victoza<sup>®</sup> at doses up to 1.8 mg, with no evidence of a dose-response relationship except for gastrointestinal adverse events, which tended to be early in onset and were not associated with irreversible sequelae. Retention rates were high, with 73% in the liraglutide 3.0 mg group completing the trials on treatment (vs. 67% with placebo). Approximately one-third of withdrawals in the liraglutide 3.0 mg group were due to adverse events, mostly gastrointestinal in nature.

Consistent with the pharmacodynamic effects of a GLP-1 receptor agonist, the most frequently reported AEs with liraglutide 3.0 mg were gastrointestinal disorders, notably nausea, diarrhea, constipation and vomiting, and accompanying symptoms such as decreased appetite, fatigue, and dizziness. Most events were transient, of mild or moderate severity and frequently resolved while

patients continued to take liraglutide; most (> 96%) resolved upon treatment discontinuation. In the majority of individuals who remain on treatment, tolerance to these effects develops over time. Gastrointestinal side effects are mitigated by gradual escalation of the liraglutide dose in weekly increments.

Events of cholelithiasis and cholecystitis occurred more frequently with liraglutide 3.0 mg as compared with placebo in the weight management trials. The absolute risks were low (cholelithiasis: 1.8 vs. 0.7 events per 100 PYE; cholecystitis acute: 0.5 vs. 0.1 events per 100 PYE; cholecystitis: 0.2 vs. <0.1 events per 100 PYE, for liraglutide 3.0 mg and placebo, respectively), and the risk of gallbladder-related SAEs diminished over time based on reports in the pre-planned, ongoing extension of trial 1839, where presumably no further substantial weight loss is observed. The risks were not appreciably greater than those observed in the background obese population.<sup>45,244</sup> The majority of events in both treatment groups occurred in females (who generally also lost more weight), and in those with a weight loss of 5% or greater, consistent with the known effects of weight loss and female sex on increased risk of gallbladder disease.<sup>42,43,130,131</sup> Nevertheless, an increased incidence of gallbladder-related AEs was observed across weight-loss categories, indicating that other factors than weight loss may be involved. Approximately 70% of patients with gallbladder-related AEs in both groups had a cholecystectomy (mostly elective) as a consequence of the event. The majority of patients with events recovered and continued on trial medication, or had liraglutide re-introduced after cholecystectomy. Patients taking liraglutide 3.0 mg for weight management should be informed about the risks and symptoms of cholelithiasis and cholecystitis and the importance of consulting a physician if symptoms recur. These types of events will be included in the proposed labeling for liraglutide 3.0 mg.

All GLP-1 based medicines, including Victoza<sup>®</sup>, carry label warnings concerning risk of pancreatitis. The true contribution of these medicines to the observed cases of pancreatitis remains a topic of debate and ongoing research.<sup>156</sup> Events of acute pancreatitis occurred in greater number with liraglutide 3.0 mg as compared with placebo in the weight management program. The absolute risk was low (0.4%, [0.26 events per 100 PYR] vs. <0.1%, [<0.1 events per 100 PYR]), for liraglutide 3.0 mg and placebo, respectively, based on all events through the 120-Day Safety Update), similar to the incidence observed with lower doses of liraglutide in T2DM, and comparable to that of the background obese population.<sup>45</sup> Pancreatitis events were generally uncomplicated and all liraglutide-treated patients recovered upon treatment discontinuation. Circulating amylase and lipase had poor predictive value for the development of pancreatitis, and these enzymes appear to be less useful than monitoring patient symptoms in the clinical setting. While there was no clear relationship between the occurrence of cholelithiasis and pancreatitis, approximately half of the pancreatitis cases in liraglutide-treated patients had gallstone-induced pancreatitis, indicated by gallstones on imaging and/or the presence of ALT levels 3 or more times the upper limit of normal range at admission to hospital.<sup>49</sup> Patients taking liraglutide 3.0 mg for weight management should be informed about the risk and symptoms of pancreatitis, and liraglutide and other potentially suspect medicinal products should be discontinued if pancreatitis is suspected,

and should not be re-started if pancreatitis is confirmed. Pancreatitis will be included in the proposed labeling for liraglutide 3.0 mg and addressed in the REMS (as described in Section 7.2). Close monitoring of these types of events will also be carried out in the cardiovascular outcome trial (LEADER<sup>®</sup>), as well as in the post-marketing setting and by routine pharmacovigilance.

The overall incidence of cancer in the weight management trials was low and comparable between treatments (1.15%, 0.88 events per 100 PYR vs. 1.03%, 0.96 events per 100 PYR, for liraglutide 3.0 mg and placebo, respectively). In non-clinical studies, liraglutide was neither genotoxic nor mutagenic, and no neoplasms, except C-cell tumors of the thyroid, were associated with lifetime liraglutide administration in rodent carcinogenicity studies. The risk to humans for liraglutide-induced C-cell tumors is considered to be low based on species differences in the GLP-1 receptor expression and action in the thyroid.<sup>88,245</sup> Liraglutide has not been associated with increased incidence of C-cell neoplasms during more than 3.3 million patient years of post-marketing use, or based on registry data. A single observed case of MTC in the program occurred in a patient treated with placebo. As with liraglutide at lower doses, liraglutide 3.0 mg was not associated with increases in circulating calcitonin,

More women treated with liraglutide 3.0 mg than with placebo were diagnosed with breast cancer (0.46%, 0.36 events per 100 PYR vs. 0.15%, 0.12 events per 100 PYR, respectively) and breast cancer *in situ* (0.13%, 0.09 events per 100 PYR vs. 0.08%, 0.06 events per 100 PYR). GLP-1 is not a mutagen and its specific receptor does not appear to be expressed in human breast cancers.<sup>58</sup> Furthermore, GLP-1 (and liraglutide) do not cross-react with other peptide hormone receptors, and the GLP-1 receptor agonist exendin-4 has been shown to inhibit *in vivo* growth of human breast cancer cells in a mouse model.<sup>59</sup> While there are potential indirect mechanisms by which GLP-1 could act as a progression factor for pre-existing neoplasms, available data do not lend support to such an effect. Based on the low number of events, the short interval between study entry and diagnosis of breast cancer with involvement of axillary lymph nodes in most cases, and no indication of an increased risk based on the substantial clinical experience with GLP-1 receptor agonists in T2DM, it is likely that the event imbalance observed in the weight management program is not causally related to liraglutide, but a chance finding or resulting from enhanced ascertainment. Women with events experienced greater than the average weight loss, and such weight loss could have led to increased mammography/breast examination uptake and/or accuracy and therefore earlier diagnosis. Nevertheless, the noted imbalance will be addressed by including this information in the product labeling and by performing additional studies in the post-marketing period.

Patients treated with liraglutide 3.0 mg also reported more benign colorectal neoplasms compared to placebo-treated patients (0.52%, 0.38 events per 100 PYR vs 0.22%, 0.17 events per 100 PYR, respectively). The events were mainly colon adenomas in males aged above 50 years with a relevant medical history, and the majority (13/17 with liraglutide 3.0 mg, 3/4 with placebo) were diagnosed by routine colonoscopy. Given the absence of a signal from non-clinical studies, clinical trials and post-marketing experience with liraglutide and other GLP-1R agonists in the treatment of T2DM,

and the presence of relevant medical history in the majority of cases, it is likely that the numerical excess in benign colorectal neoplasms in the weight management program occurred by chance. Neoplasm risk is addressed by several post-approval commitments for Victoza<sup>®</sup> and will be addressed by routine pharmacovigilance.

Weight loss can contribute to an increased risk of hypoglycemia in patients with T2DM, in particular those treated with SUs or insulin, if their glucose-lowering regimen is not adjusted according to weight-loss mediated improvement in insulin sensitivity and improved glycemic control. Weight loss with liraglutide was associated with low risk of clinically significant hypoglycemia in obese patients with or without T2DM, in accordance with the glucose-dependent actions of liraglutide.<sup>2-4</sup> Events were typically reported as mild and rarely lead to treatment (or trial) discontinuation. Importantly, the episodes of hypoglycemia requiring third party assistance (i.e., severe hypoglycemia) and documented symptomatic hypoglycemia events in obese patients with T2DM were similar to those observed with lower doses of liraglutide in the Victoza<sup>®</sup> program, indicating that neither the higher dose, the overweight/obese target population, nor the use of liraglutide as an adjunct to lifestyle intervention significantly alters the risk of hypoglycemia. As expected, severe hypoglycemia was only seen with concomitant use of SU, which is known to uncouple the glucose-dependency of GLP-1 receptor agonists.<sup>60</sup> Lowering the SU dose when initiating liraglutide treatment may reduce this risk; this information is included in the Victoza<sup>®</sup> label and in the proposed label for liraglutide 3.0 mg.

Experience from clinical trials and marketed use of Victoza<sup>®</sup> in T2DM has not indicated any safety concerns in relation to use in pregnancy. In the weight management program, the overall numbers of pregnancies were similar between liraglutide and placebo (~1.5% of exposed women through the 120-Day Safety Update). The proportion of pregnancies resulting in healthy babies was also similar between groups, and there were no congenital abnormalities in the babies born of women who had been exposed to liraglutide. While there were more reports of spontaneous abortions with liraglutide, the proportion was within the reported range for obese women in the general population.<sup>63,232</sup> However, if liraglutide is used with the intention of increasing fertility by weight reduction, it is important that treatment with liraglutide is discontinued before conception is attempted. Pregnancy is addressed in the product information, informing prescribers that liraglutide 3.0 mg should not be used during pregnancy or by women who intend to become pregnant.

Use of GLP-1 receptor agonists is associated with an increase in resting heart rate.<sup>15</sup> The underlying mechanism is not currently understood but does not appear to involve increased activation of the sympathetic nervous system. The presence of the GLP-1 receptor on the sino-atrial node suggests a direct chronotropic effect of treatment.<sup>52</sup> A persistent heart rate increase, defined as an increase at  $\geq 2$  consecutive visits of resting heart rate  $>20$  beats/min or  $\geq 100$  beats/min, occurred in 4.9% vs. 1.7% of patients and 0.9% vs. 0.3% of patients, with liraglutide 3.0 mg and placebo, respectively. Available data do not provide evidence of a dose relationship within the therapeutic dose range investigated in the T2DM and weight management trial programs. Importantly, liraglutide was



associated with decreases in blood pressure and improvement in multiple cardiovascular biomarkers, and was not associated with any evidence of an increased risk of MACE (hazard ratios and 95% confidence intervals: 0.40 [0.16; 1.01] for total liraglutide vs. total comparator [weight management pool, primary analysis through 120-Day Safety Update]). The ongoing placebo-controlled clinical trial LEADER<sup>®</sup> is further assessing cardiovascular outcomes in high-risk patients with liraglutide 1.8 mg (Victoza<sup>®</sup>).

Finally, liraglutide has no abuse potential (i.e., does not produce psychoactive effects such as sedation, euphoria, or mood change) and was not associated with increased risk of depression, suicidality, or any adverse alterations in cognitive function in the weight management trials.

In summary, the safety and tolerability profile of liraglutide 3.0 mg in the weight management clinical development program is well-described and generally consistent with that observed in the development program for Victoza<sup>®</sup> in patients with T2DM with liraglutide doses up to 1.8 mg. Most of the safety issues identified were as expected based on previous experience, and can be managed effectively in routine clinical practice, or based on clinical experience and information provided specifically in the label to address potential safety concerns. The safety profile is therefore considered acceptable given the wide range of clinically important benefits provided.

### **8.3 Benefit/risk conclusions**

Liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, is an attractive new treatment option for weight management with a different mechanism of action as compared with the other weight management products currently available. It has a well-documented safety profile based not only on non-clinical data, clinical trials in obese patients and a large clinical program in patients with T2DM (the Victoza<sup>®</sup> development program), but also extensive post-marketing use of Victoza<sup>®</sup>. Liraglutide 3.0 mg significantly increases the likelihood that a patient will achieve and maintain a clinically meaningful weight loss, and produces important improvements in multiple obesity-related co-morbidities.

Some of the liraglutide-associated health benefits are immediate (such as the effects on appetite, glycemia and blood pressure) and may encourage patients to remain on treatment and undertake enduring lifestyle changes. Other benefits become manifest with longer-term treatment and weight loss. These include functional benefits such as improvement in OSA and mobility, and benefits associated with how one feels on an average day, as indicated by total scores and consistent improvements across individual domains on health-related quality of life questionnaires. These are important patient-centered benefits related to general daily health, feeling and functioning.

Treatment with liraglutide 3.0 mg, as adjunct to a reduced-calorie diet and increased physical activity, was generally well-tolerated, with a side-effect profile that was overall consistent with that of Victoza<sup>®</sup>. Importantly, treatment was not associated with any of the side effects typically associated with centrally-acting obesity medications (cardiovascular or neuropsychiatric).<sup>11,64,65</sup>

There was no indication of a dose or exposure response for safety/tolerability parameters, except for gastrointestinal side effects, which generally occurred early in treatment, were of mild or moderate severity and resolved without sequelae. Adverse effects were mostly predictable based on the known effects of GLP-1 receptor agonists, were infrequent in the case of serious adverse drug reactions, and were easily diagnosed and monitored, which minimizes the concern associated with potential large exposure and misuse.

The target population for liraglutide is at serious risk from obesity and its associated major co-morbidities. Additional treatment options are needed. Liraglutide 3.0 mg produced significant sustained weight loss in all our trials. Importantly the weight loss promoted improvements in multiple weight related co-morbidities. Liraglutide 3.0 mg meets the regulatory criteria for an efficacious weight management agent, and has the additional advantage of directly improving abnormal glucose homeostasis. Thus, it has both direct and indirect effects on glucose metabolism that confer clinical benefits. Patients who took liraglutide 3.0 mg also experienced improvements in blood pressure, lipids, inflammatory markers of cardiovascular risk, quality of life and sleep apnea, as well as reduction in pre-diabetes and T2DM. The higher 3.0 mg dose of liraglutide is more efficacious than lower doses approved for treatment of T2DM (Victoza®) but does not seem to confer greater risk for serious adverse events. The extensive experience with Victoza® in the treatment of T2DM and its proven benefit/risk profile support the approval for liraglutide 3.0 mg for use in the treatment of medically significant obesity.

Overall, the efficacy and safety results presented in this briefing book demonstrate that liraglutide 3.0 mg, as adjunct to a reduced-calorie diet and increased physical activity, is a unique treatment option for weight management with a favorable benefit/risk profile.

## 9 References

- 1 Knudsen LB, Nielsen PF, Huusfeldt PO, Johansen NL, Madsen K, Pedersen FZ et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* 2000; 43(9):1664-1669.
- 2 Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab* 2002; 87(3):1239-1246.
- 3 Holst JJ. The physiology of glucagon-like peptide 1. *Physiological Reviews* 2007; 87(4):1409-1439.
- 4 Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2012; 8(12):728-742.
- 5 Drucker DJ. The biology of incretin hormones. *Cell Metab* 2006; 3(3):153-165.
- 6 Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. *Diabetes* 2011; 60(5):1561-1565.
- 7 Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 1996; 379(6560):69-72.
- 8 Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest* 1998; 101(3):515-520.
- 9 Goke R, Larsen PJ, Mikkelsen JD, Sheikh SP. Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. *Eur J Neurosci* 1995; 7(11):2294-2300.
- 10 Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J COMP NEUROL* 1999; 403(2):261-280.
- 11 Barrera JG, Jones KR, Herman JP, D'Alessio DA, Woods SC, Seeley RJ. Hyperphagia and increased fat accumulation in two models of chronic CNS glucagon-like peptide-1 loss of function. *J Neurosci* 2011; 31(10):3904-3913.
- 12 Vrang N, Larsen PJ. Preproglucagon derived peptides GLP-1, GLP-2 and oxyntomodulin in the CNS: Role of peripherally secreted and centrally produced peptides. *Prog Neurobiol* 2010; 92(3):442-462.

- 13 van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WHM. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite, and energy metabolism in obese, non-diabetic adults. *Int J Obes* 2014; 38:784-793.
- 14 Secher A, Jelsing J, Gonzalez AB, Hecksher-Sorensen J, Cowley MA, Dalboge LS et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest* 2014; Accepted for publication July 31st.
- 15 Victoza (liraglutide), US Prescribing Information. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/022341lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf). Jun 2013.
- 16 Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014; 311(8):806-814.
- 17 Ferguson C, David S, Divine L, Kahan S, Gallagher C, Gooding M et al. Obesity Drug Outcome Measures. A Consensus Report of Considerations Regarding Pharmacologic Intervention. <http://sphhs.gwu.edu/releases/obesitydrugmeasures.pdf>. 14 Aug 2012. Department of Health Policy, School of Public Health and Health Services, The George Washington University.
- 18 Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009; 9:doi:10.1186/1471-2458-9-88.
- 19 Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? *J Clin Endocrinol Metab* 2011; 96(6):1654-1663.
- 20 Khaodhiar L, Cummings S, Apovian CM. Treating diabetes and prediabetes by focusing on obesity management. *Curr Diab Rep* 2009; 9(5):348-354.
- 21 Masters RK, Reither EN, Powers DA, Yang YC, Burger AE, Link BG. The Impact of Obesity on US Mortality Levels: The Importance of Age and Cohort Factors in Population Estimates. *Am J Public Health* 2013; 103(10):1895-1901.
- 22 Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; 373(9669):1083-1096.
- 23 Phelan S, Kanaya AM, Subak LL, Hogan PE, Espeland MA, Wing RR et al. Prevalence and risk factors for urinary incontinence in overweight and obese diabetic women: action for health in diabetes (look ahead) study. *Diabetes Care* 2009; 32(8):1391-1397.
- 24 Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2010; 18(1):24-33.

- 25 Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab* 2004; 89(6):2583-2589.
- 26 Wadden TA, Stunkard AJ. Social and psychological consequences of obesity. *Ann Intern Med* 1985; 103(6 ( Pt 2)):1062-1067.
- 27 Garner RE, Feeny DH, Thompson A, Bernier J, McFarland BH, Huguet N et al. Bodyweight, gender, and quality of life: a population-based longitudinal study. *Qual Life Res* 2012; 21(5):813-825.
- 28 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380(9859):2224-2260.
- 29 Maggio CA, Pi-Sunyer FX. The prevention and treatment of obesity. Application to type 2 diabetes. *Diabetes Care* 1997; 20(11):1744-1766.
- 30 Pi-Sunyer FX. Weight loss and mortality in type 2 diabetes. *Diabetes Care* 2000; 23(10):1451-1452.
- 31 Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest* 2010; 137(3):711-719.
- 32 Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. *Obes Res* 2000; 8(3):270-278.
- 33 Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest* 2012; 122(1):153-162.
- 34 Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011; 365(17):1597-1604.
- 35 Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann Surg* 2000; 232(4):515-529.
- 36 Rueda-Clausen CF, Padwal RS, Sharma AM. New pharmacological approaches for obesity management. *Nat Rev Endocrinol* 2013; 9(8):467-478.
- 37 Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Developing products for weight management. Draft Guidance. <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf> . Feb 2007.

- 38 Hassan MK, Joshi AV, Madhavan SS, Amonkar MM. Obesity and health-related quality of life: a cross-sectional analysis of the US population. *Int J Obes Relat Metab Disord* 2003; 27(10):1227-1232.
- 39 Crosby RD, Kolotkin RL, Williams GR. An integrated method to determine meaningful changes in health-related quality of life. *J Clin Epidemiol* 2004; 57(11):1153-1160.
- 40 Ware JE, Kosinski M, Dewey JE. How to Score Version Two of the SF-36 Health Survey. Edition 3 ed. Lincoln RI: QualityMetric, Incorporated, 2000.
- 41 Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res* 2001; 9(2):102-111.
- 42 Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? *Curr Gastroenterol Rep* 2005; 7(2):132-140.
- 43 Erlinger S. Gallstones in obesity and weight loss. *Eur J Gastroenterol Hepatol* 2000; 12(12):1347-1352.
- 44 Li VK, Pulido N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duarte P. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. *Surg Endosc* 2009; 23(7):1640-1644.
- 45 Torgerson JS, Lindroos AK, Naslund I, Peltonen M. Gallstones, gallbladder disease, and pancreatitis: cross-sectional and 2-year data from the Swedish Obese Subjects (SOS) and SOS reference studies. *Am J Gastroenterol* 2003; 98(5):1032-1041.
- 46 Everhart JE. Contributions of obesity and weight loss to gallstone disease. *Ann Intern Med* 1993; 119(10):1029-1035.
- 47 Syngal S, Coakley EH, Willett WC, Byers T, Williamson DF, Colditz GA. Long-term weight patterns and risk for cholecystectomy in women. *Ann Intern Med* 1999; 130(6):471-477.
- 48 Jorgensen T, Jorgensen LM. Gallstones and diet in a Danish population. *Scand J Gastroenterol* 1989; 24(7):821-826.
- 49 Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *Am J Gastroenterol* 1994; 89(10):1863-1866.
- 50 Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014; doi:10.1016/S0140-6736(14)60976-4:Early Online Publication, 11 July.

- 51 Diamant M, Van GL, Stranks S, Northrup J, Cao D, Taylor K et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010; 375(9733):2234-2243.
- 52 Pyke C, Heller RS, Kirk RK, Orskov C, Reedtz-Runge S, Kastrup P et al. GLP-1 receptor localization in monkey and human tissue; Novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* 2014; 155(4):1280-1290.
- 53 Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J* 2013; 166(5):823-830.
- 54 Ryu EB, Chang JM, Seo M, Kim SA, Lim JH, Moon WK. Tumour volume doubling time of molecular breast cancer subtypes assessed by serial breast ultrasound. *Eur Radiol* 2014; [Epub ahead of print].
- 55 Hernandez-Boussard T, Ahmed SM, Morton JM. Obesity disparities in preventive care: findings from the National Ambulatory Medical Care Survey, 2005-2007. *Obesity (Silver Spring)* 2012; 20(8):1639-1644.
- 56 Maruthur NM, Bolen S, Brancati FL, Clark JM. Obesity and mammography: a systematic review and meta-analysis. *J Gen Intern Med* 2009; 24(5):665-677.
- 57 Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Byng J et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. Canadian Diet and Breast Cancer Prevention Study Group. *J Natl Cancer Inst* 1997; 89(7):488-496.
- 58 Korner M, Stockli M, Waser B, Reubi JC. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. *J Nucl Med* 2007; 48(5):736-743.
- 59 Ligumsky H, Wolf I, Israeli S, Haimsohn M, Ferber S, Karasik A et al. The peptide-hormone glucagon-like peptide-1 activates cAMP and inhibits growth of breast cancer cells. *Breast Cancer Res Treat* 2012; 132(2):449-461.
- 60 de Heer J, Holst JJ. Sulfonylurea compounds uncouple the glucose dependence of the insulinotropic effect of glucagon-like peptide 1. *Diabetes* 2007; 56(2):438-443.
- 61 Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008; 90(3):714-726.
- 62 Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. *Semin Reprod Med* 2011; 29(6):507-513.



- 63 Hamilton-Fairly D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. *Fertility and sterility* 1992; 99:128-131.
- 64 Hiatt WR, Goldfine AB, Kaul S. Cardiovascular risk assessment in the development of new drugs for obesity. *JAMA* 2012; 308(11):1099-1100.
- 65 Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. *N Engl J Med* 2012; 367(17):1577-1579.
- 66 Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)* 2008; 32(9):1431-1437.
- 67 Directorate-General for Health and Consumers. Strategy for Europe on nutrition, overweight and obesity related health issues. Implementation progress report Dec 2010. [http://ec.europa.eu/health/nutrition\\_physical\\_activity/docs/implementation\\_report\\_en.pdf](http://ec.europa.eu/health/nutrition_physical_activity/docs/implementation_report_en.pdf) . 2010.
- 68 Obesity is a Disease: Leading Obesity Groups Agree. The American Society for Metabolic and Bariatric Surgery, The Obesity Society, The American Society of Bariatric Physicians and the American Association of Clinical Endocrinologists Joint Press Release . 2013.
- 69 Wheaton AG, Perry GS, Chapman DP, Croft JB. Sleep disordered breathing and depression among U.S. adults: National Health and Nutrition Examination Survey, 2005-2008. *Sleep* 2012; 35(4):461-467.
- 70 Winslow DH, Bowden CH, DiDonato KP, McCullough PA. A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep* 2012; 35(11):1529-1539.
- 71 Thomsen M, Nordestgaard BG. Myocardial Infarction and Ischemic Heart Disease in Overweight and Obesity With and Without Metabolic Syndrome. *JAMA Intern Med* 2013; doi:10.1001/jamainternmed.2013.10522.
- 72 World Health Organization. The global burden of disease: 2004 update. Geneva: World Health Organization, 2008.
- 73 Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009; 5(3):263-276.
- 74 Qaseem A, Holty JC, Owens DK, Dallas P, Starkey M, Shekelle P. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2013; 159:471-483.

- 75 Sisley S, Gutierrez-Aguilar R, Scott M, D'Alessio DA, Sandoval DA, Seeley RJ. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *J Clin Invest* 2014; 124(6):2456-2463.
- 76 Raun K, Von-Voss P, Knudsen LB. Liraglutide, a once-daily human glucagon-like peptide-1 analog, minimizes food intake in severely obese minipigs. *Obesity* 2007; 15(7):1710-1716.
- 77 Raun K, Von-Voss P, Gotfredsen CF, Golozoubova V, Rolin B, Knudsen LB. Liraglutide, a long-acting glucagon-like peptide-1 analog, reduces body weight and food intake in obese candy-fed rats, whereas a dipeptidyl peptidase-IV inhibitor, vildagliptin, does not. *Diabetes* 2007; 56(1):8-15.
- 78 Larsen PJ, Fledelius C, Knudsen LB, Tang-Christensen M. Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats. *Diabetes* 2001; 50(11):2530-2539.
- 79 ICH. Topic M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, June 2009. Available from [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Multidisciplinary/M3\\_R2/Step4/M3\\_R2\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2_Guideline.pdf).
- 80 Gotfredsen CF, Mølck AM, Thorup I, Nyborg NC, Salanti Z, Knudsen LB et al. The human GLP-1 analogs liraglutide and semaglutide: absence of histopathological effects on the pancreas in nonhuman primates. *Diabetes* 2014; 63(7):2486-2497.
- 81 Nyborg NC, Mølck AM, Madsen LW, Knudsen LB. The human GLP-1 analog liraglutide and the pancreas: evidence for the absence of structural pancreatic changes in three species. *Diabetes* 2012; 61(5):1243-1249.
- 82 Vrang N, Jelsing J, Simonsen L, Jensen AE, Thorup I, Soeborg H et al. The effects of 13 wk of liraglutide treatment on endocrine and exocrine pancreas in male and female ZDF rats: a quantitative and qualitative analysis revealing no evidence of drug-induced pancreatitis. *Am J Physiol Endocrinol Metab* 2012; 303(2):E253-E264.
- 83 Greaves P. Integumentary system in Histopathology of Preclinical Toxicity studies. Amsterdam: Academic Press, 2007: 38-42.
- 84 Knudsen LB, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 2010; First published ahead of print March 4, 2010 as doi:10.1210/en.2009-1272.
- 85 Madsen LW, Knauf JA, Gotfredsen C, Pilling A, Sjogren I, Andersen S et al. GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. *Endocrinology* 2012; 153(3):1538-1547.

- 86 Hegedus L, Moses AC, Zdravkovic M, Le TT, Daniels GH. GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. *J Clin Endocrinol Metab* 2011; 96(3):853-860.
- 87 Boess F, Bertinetti-Lapatki C, Zoffmann S, George C, Pfister T, Roth A et al. Effect of GLP1R agonists taspoglutide and liraglutide on primary thyroid C-cells from rodent and man. *J Mol Endocrinol* 2013; 50(3):325-336.
- 88 Waser B, Beetschen K, Pellegata NS, Reubi JC. Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: relevance for incretin-based diabetes therapy. *Neuroendocrinology* 2011; 94(4):291-301.
- 89 Branch S, Rogers JM, Brownie CF, Chernoff N. Supernumerary lumbar rib: manifestation of basic alteration in embryonic development of ribs. *J Appl Toxicol* 1996; 16(2):115-119.
- 90 Rogers JM, Setzer RW, Branch S, Chernoff N. Chemically induced supernumerary lumbar ribs in CD-1 mice: size distribution and dose response. *Birth Defects Res B Dev Reprod Toxicol* 2004; 71(1):17-25.
- 91 Willems M, Quartero AO, Numans ME. How useful is paracetamol absorption as a marker of gastric emptying? A systematic literature study. *Dig Dis Sci* 2001; 46(10):2256-2262.
- 92 Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)* 2012; 36:843-854.
- 93 Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; 374:1606-1616.
- 94 Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study. *INT J OBES* 2013; 37(11):1443-1451.
- 95 American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2010; 33(suppl.1):S62-S69.
- 96 NCEP report. Implications of recent clinical trials for the national cholesterol education program Adult Treatment Panel III guidelines Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association. *Circulation* 2004; 110:227-239.

- 97 NCEP report. Definition of Metabolic Syndrome, report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109:433-438.
- 98 The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. *JAMA* 2003; 289(19):2560-2572.
- 99 Lean ME, Carraro R, Finer N, Hartvig H, Lindegaard ML, Rossner S et al. Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. *Int J Obes (Lond)* 2013; advance online publication(24 September 2013; doi: 10.1038/ijo.2013.149).
- 100 Grundy SM, Brewer Jr HB, Cleeman Jr, Smith Jr SC, Lenfant C. Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation* 2004; 109(3):433-438.
- 101 Weaver TE, Grunstein RR. Adherence to Continuous Positive Airway Pressure Therapy, The Challenge to Effective Treatment. *Proc Am Thorac Soc* 2008; 5:173-178.
- 102 Araghi MH, Chen Y, Jagielski A, Choudhury S, Banerjee D, Hussain S et al. Effectiveness of Lifestyle Interventions on Obstructive Sleep Apnea (OSA): Systematic Review and Meta-Analysis. *Sleep* 2013; 36(10):1553-1562.
- 103 National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press, 2010.
- 104 Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377(9774):1341-1352.
- 105 Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; 363(3):245-256.
- 106 Fabricatore AN, Wadden TA, Moore RH, Butryn ML, Gravalles EA, Erondy NE et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. *Obes Rev* 2009; 10(3):333-341.
- 107 Pi-Sunyer FX. Weight loss in type 2 diabetic patients. *Diabetes Care* 2005; 28(6):1526-1527.

- 108 Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; 22(9):1462-1470.
- 109 DeFronzo RA, Banerji MA, Bray GA, Buchanan TA, Clement S, Henry RR et al. Determinants of glucose tolerance in impaired glucose tolerance at baseline in the Actos Now for Prevention of Diabetes (ACT NOW) study. *Diabetologia* 2010; 53(3):435-445.
- 110 Bergstrom RW, Wahl PW, Leonetti DL, Fujimoto WY. Association of fasting glucose levels with a delayed secretion of insulin after oral glucose in subjects with glucose intolerance. *J Clin Endocrinol Metab* 1990; 71(6):1447-1453.
- 111 De-Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: Meta-regression analysis of prospective studies. *Eur Heart J* 2007; 28(7):850-856.
- 112 Rissanen A, Astrup A, Al Hakim M, Kunesova M, Lindegaard M, Rasmussen MF et al. Weight loss with liraglutide in obese adults is primarily due to reduction in fat tissue: a subgroup analysis of a 20-week randomised placebo-controlled trial. *Obesity reviews : an official journal of the International Association for the Study of Obesity Suppl. 1*, 224. 2010.
- 113 Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. *American journal of physiology Endocrinology and metabolism* 2003; 285(4):E906-E916.
- 114 Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology (Baltimore, Md )* 2010; 51(2):679-689.
- 115 Wadden TA, Anderson DA, Foster GD. Two-year changes in lipids and lipoproteins associated with the maintenance of a 5% to 10% reduction in initial weight: some findings and some questions. *Obes Res* 1999; 7(2):170-178.
- 116 Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M. Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1993; 77(5):1287-1293.
- 117 Mathieu P, Lemieux I, Després JP. Obesity, inflammation, and cardiovascular risk. *Clin Pharmacol Ther* 2010; 87(4):407-416.
- 118 Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* 2004; 109(25 Suppl 1):IV6-IV9.
- 119 Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; 291(14):1730-1737.

- 120 Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013; 24(2):302-308.
- 121 Johansson K, Hemmingsson E, Harlid R, Trolle LY, Granath F, Rossner S et al. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *BMJ* 2011; 342:d3017.
- 122 Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med* 2009; 169(17):1619-1626.
- 123 Brod M, Hammer M, Kragh N, Lessard S, Bushnell DM. Development and validation of the Treatment Related Impact Measure of Weight (TRIM-Weight). *Health Qual Life Outcomes* 2010; 8:19.
- 124 Bradley C. Diabetes treatment satisfaction questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. *Diabetes Care* 1999; 22(3):530-532.
- 125 Gibney EJ. Asymptomatic gallstones. *Br J Surg* 1990; 77(4):368-372.
- 126 Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. *Dig Dis Sci* 2007; 52(5):1313-1325.
- 127 Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, Lacroix AZ, Limacher MC et al. Effect of estrogen therapy on gallbladder disease. *JAMA* 2005; 293(3):330-339.
- 128 Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health* 1993; 83(8):1113-1120.
- 129 Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998; 280(7):605-613.
- 130 Amaral JF, Thompson WR. Gallbladder disease in the morbidly obese. *Am J Surg* 1985; 149(4):551-557.
- 131 Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Prospective study of abdominal adiposity and gallstone disease in US men. *Am J Clin Nutr* 2004; 80(1):38-44.

- 132 Sari R, Balci MK. Relationship between weight loss and gallbladder motility in obese women. *J Natl Med Assoc* 2006; 98(10):1670-1676.
- 133 Weinsier RL, Ullmann DO. Gallstone formation and weight loss. *Obes Res* 1993; 1(1):51-56.
- 134 Keller J, Trautmann ME, Haber H, Tham LS, Hunt T, Mace K et al. Effect of exenatide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects. *Regul Pept* 2012; 179(1-3):77-83.
- 135 Gullo L, Bolondi L, Scarpignato C, Priori P, Casanova P, Labo G. Effect of somatostatin and thyrotropin-releasing hormone on cholecystokinin-induced gallbladder emptying. *Dig Dis Sci* 1986; 31(12):1345-1350.
- 136 European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting on 7-10 October 2013 .  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Minutes/2013/11/WC500154424.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/11/WC500154424.pdf) . 2013.
- 137 Sadr-Azodi O, Orsini N, Andren-Sandberg A, Wolk A. Abdominal and total adiposity and the risk of acute pancreatitis: a population-based prospective cohort study. *Am J Gastroenterol* 2013; 108(1):133-139.
- 138 Martinez J, Johnson CD, Sanchez-Paya J, de ME, Robles-Diaz G, Perez-Mateo M. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatology* 2006; 6(3):206-209.
- 139 Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med* 2009; 169(11):1035-1045.
- 140 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352(9131):854-865.
- 141 Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010; 33(11):2349-2354.
- 142 Dore DD, Chaudhry S, Hoffman C, Seeger JD. Stratum-specific positive predictive values of claims for acute pancreatitis among commercial health insurance plan enrollees with diabetes mellitus. *Pharmacoepidemiol Drug Saf* 2011; 20(2):209-213.
- 143 Girman CJ, Kou TD, Cai B, Alexander CM, O'Neill EA, Williams-Herman DE et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes Obes Metab* 2010; 12(9):766-771.

- 144 Gonzalez-Perez A, Schlienger RG, Rodriguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care* 2010; 33(12):2580-2585.
- 145 Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2009; 32(5):834-838.
- 146 Ryder REJ, Thong KY, Blann AD, Phillips SM, Barwell ND, Kelly CJG et al. Liraglutide pancreatitis: The ABCD nationwide liraglutide audit. *The British Journal of Diabetes & Vascular Disease* 2013; 13:253-259.
- 147 Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagon-like peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med* 2013; 173(7):534-539.
- 148 Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011; 27 Suppl 3:57-64. doi: 10.1185/03007995.2011.602964.
- 149 Funch D, Gydesen H, Tornoe K, Major-Pedersen A, Arnold CK. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. *Diabetes Obes Metab* 2013;doi: 10.1111/dom.12230.
- 150 Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; 369(14):1317-1326.
- 151 White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; 369(14):1327-1335.
- 152 Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62(1):102-111.
- 153 Steinberg WM, Rosenstock J, Devries JH, Thomsen AB, Svendsen CB, Wadden T. Elevated serum lipase activity in adults with type 2 diabetes and no gastrointestinal symptoms. *Gastroenterology* 142[5 Suppl 1], S93-S94. 2012.
- 154 Steinberg WM, Devries JH, Wadden T, Jensen CB, Svendsen CB, Rosenstock J. Longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: Evidence from two phase 3 randomized clinical trials with the once-daily GLP-1 analog liraglutide. *Gastroenterology* 142[5 Suppl 1], S850-S851. 2012.



- 155 Bastyr EJ, Vinik A, Owyang C, Cheng C, Shu J, Hall NC. Surveillance of lipase and amylase levels in type 2 diabetes patients assessed during a randomized clinical study: the EGO study experience. 45th EASD Annual Meeting of the European Association for the Study of Diabetes, 30 September - 2 October 2009, Vienna, Austria. *Diabetologia* 52 (Suppl. 1), 2009: S303-S304.
- 156 Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med* 2014; 370(9):794-797.
- 157 Kern E, VanWagner LB, Yang GY, Rinella ME. Liraglutide-induced autoimmune hepatitis. *JAMA Intern Med* 2014; 174(6):984-987.
- 158 CIPRO (ciprofloxacin), US Prescribing Information.  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2004/019537s49\\_19847s27\\_19857s31\\_20780s13TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/019537s49_19847s27_19857s31_20780s13TOC.cfm) . 2004.
- 159 Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002; 162(16):1867-1872.
- 160 Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG et al. Obesity and the risk of heart failure. *N Engl J Med* 2002; 347(5):305-313.
- 161 Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 2002; 162(10):1182-1189.
- 162 Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013; 309(1):71-82.
- 163 Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes (supplementary appendix). *N Engl J Med* 2013; 369(2):145-154.
- 164 Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012; 33(2):187-215.
- 165 Marso SP, Lindsey JB, Stolker JM, House JA, Martinez RG, Kennedy KF et al. Cardiovascular safety of liraglutide assessed in a patient-level pooled analysis of phase 2: 3 liraglutide clinical development studies. *Diab Vasc Dis Res* 2011; 8(3):237-240.
- 166 Mouridsen MR, Bendsen NT, Astrup A, Haugaard SB, Binici Z, Sajadieh A. Modest weight loss in moderately overweight postmenopausal women improves heart rate variability. *Eur J Prev Cardiol* 2013; 20(4):671-677.

- 167 Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. *Diab Obesity Metabol* 2013; doi: 10.1111/dom.12175.
- 168 Scott LJ. Lixisenatide: a review of its use in patients with type 2 diabetes mellitus. *BioDrugs* 2013; 27(5):509-523.
- 169 National Cancer Institute. Fact Sheet: Obesity and cancer risk. <http://www.cancer.gov/cancertopics/factsheet/Risk/obesity> . 1 Mar 2012.
- 170 Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med* 2010; 61:301-16.
- 171 Birks S, Peeters A, Backholer K, O'Brien P, Brown W. A systematic review of the impact of weight loss on cancer incidence and mortality. *Obes Rev* 2012; 13(10):868-891.
- 172 Bydureon (exenatide extended-release for injectable suspension), US prescribing information. [http://documents.bydureon.com/Bydureon\\_PI.pdf](http://documents.bydureon.com/Bydureon_PI.pdf) . 27 Jan 2012.
- 173 Lyxumia (lixisenatide), EU Summary of Product Characteristics. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002445/human\\_med\\_001615.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002445/human_med_001615.jsp&mid=WC0b01ac058001d124) . 14 Mar 2013.
- 174 Drucker DJ, Sherman SI, Bergenstal RM, Buse JB. The safety of incretin-based therapies--review of the scientific evidence. *J Clin Endocrinol Metab* 2011; 96(7):2027-2031.
- 175 Lukanova A, Björ O, Kaaks R, Lenner P, Lindahl B, Hallmans G et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *International Journal of Cancer* 2006; 118(2):458-466.
- 176 Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA* 1997; 278(17):1407-1411.
- 177 Kaaks R, Van Noord PA, Den T, I, Peeters PH, Riboli E, Grobbee DE. Breast-cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. *Int J Cancer* 1998; 76(5):647-651.
- 178 Michels KB, Terry KL, Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. *Arch Intern Med* 2006; 166(21):2395-2402.
- 179 Tehard B, Lahmann PH, Riboli E, Clavel-Chapelon F. Anthropometry, breast cancer and menopausal status: use of repeated measurements over 10 years of follow-up-results of the French E3N women's cohort study. *Int J Cancer* 2004; 111(2):264-269.
- 180 Chang SC, Ziegler RG, Dunn B, Stolzenberg-Solomon R, Lacey JV, Jr., Huang WY et al. Association of energy intake and energy balance with postmenopausal breast cancer in the

- prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2006; 15(2):334-341.
- 181 Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Wolk A. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. *Int J Cancer* 2006; 119(7):1683-1689.
  - 182 Sweeney C, Blair CK, Anderson KE, Lazovich D, Folsom AR. Risk factors for breast cancer in elderly women. *Am J Epidemiol* 2004; 160(9):868-875.
  - 183 Eichholzer M, Huang DJ, Modlasiak A, Schmid SM, Schotzau A, Rohrmann S et al. Impact of body mass index on prognostically relevant breast cancer tumor characteristics. *Breast Care (Basel)* 2013; 8(3):192-198.
  - 184 Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev* 2014; 36(1):114-136.
  - 185 Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002; 20(17):3628-3636.
  - 186 Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Humans with increased Exocrine Pancreas Dysplasia and the potential for Glucagon-producing Neuroendocrine Tumors. *Diabetes* 22-Mar 2013; 62:2595-2604.
  - 187 Matveyenko AV, Dry S, Cox HI, Moshtaghian A, Gurlo T, Galasso R et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. *Diabetes* 2009; 58(7):1604-1615.
  - 188 Gier B, Matveyenko AV, Kirakossian D, Dawson D, Dry SM, Butler PC. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. *Diabetes* 2012; 61(5):1250-1262.
  - 189 Bonner-Weir S, In't Veld PA, Weir GC. Reanalysis of study of pancreatic effects of incretin therapy: methodological deficiencies. *Diabetes Obes Metab* 2014.
  - 190 Hu MI, Ying AK, Jimenez C. Update on medullary thyroid cancer. *Endocrinol Metab Clin North Am* 2014; 43(2):423-442.
  - 191 Matias-Guiu X, De LR. Medullary thyroid carcinoma: a 25-year perspective. *Endocr Pathol* 2014; 25(1):21-29.

- 192 Kurosawa M, Sato A, Shiraki M, Takahashi Y. Secretion of calcitonin from the thyroid gland increases in aged rats. *Arch Gerontol Geriatr* 1988; 7(3):229-238.
- 193 Karges W, Dralle H, Raue F, Mann K, Reiners C, Grussendorf M et al. Calcitonin measurement to detect medullary thyroid carcinoma in nodular goiter: German evidence-based consensus recommendation. *Exp Clin Endocrinol Diabetes* 2004; 112(1):52-58.
- 194 Wolfe HJ, Melvin KE, Cervi-Skinner SJ, Saadi AA, Juliar JF, Jackson CE et al. C-cell hyperplasia preceding medullary thyroid carcinoma. *N Engl J Med* 1973; 289(9):437-441.
- 195 Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. *J Clin Endocrinol Metab* 2007; 92(2):450-455.
- 196 US Cancer Statistics Working Group. United States Cancer Statistics: 1999-2010 Incidence and Mortality Web-based Report. Atlanta, GA. Dept of Health and Human Services, Centrs for Disease Control and Prevention & National Cancer Institute; 2009. Available at: [www.cdc.gov/uscs](http://www.cdc.gov/uscs). Accessed 08-08-2014. 2009.
- 197 American Cancer Society. Colorectal Cancer Facts & Figures 2014-2016. [http://www.cancer.org/docroot/STT/stt\\_0.asp](http://www.cancer.org/docroot/STT/stt_0.asp). Accessed Aug 8, 2014. 2014.
- 198 Ries LAG, Melbert D Krapcho M et al. SEER cancer statistics review, 1975-2005. Bethesda, MD. [http://www.cancer.org/docroot/STT/stt\\_0.asp](http://www.cancer.org/docroot/STT/stt_0.asp). Accessed Aug 8, 2014. 2008.
- 199 Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. *Lancet* 2005; 365(9454):153-165.
- 200 Polednak AP. Estimating the number of U.S. incident cancers attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. *Cancer Detect Prev* 2008; 32(3):190-199.
- 201 Janout V, Kollarova H. Epidemiology of colorectal cancer. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2001; 145(1):5-10.
- 202 Labianca R, Beretta GD, Mosconi S, Milesi L, Pessi MA. Colorectal cancer: screening. *Ann Oncol* 2005; 16 Suppl 2:ii127-ii132.
- 203 de Jong AE, Morreau H, Nagengast FM, Mathus-Vliegen EM, Kleibeuker JH, Griffioen G et al. Prevalence of adenomas among young individuals at average risk for colorectal cancer. *Am J Gastroenterol* 2005; 100(1):139-143.

- 204 Okabayashi K, Ashrafian H, Hasegawa H, Yoo JH, Patel VM, Harling L et al. Body mass index category as a risk factor for colorectal adenomas: a systematic review and meta-analysis. *Am J Gastroenterol* 2012; 107(8):1175-1185.
- 205 Stein B, Anderson JC, Rajapakse R, Alpern ZA, Messina CR, Walker G. Body mass index as a predictor of colorectal neoplasia in ethnically diverse screening population. *Dig Dis Sci* 2010; 55(10):2945-2952.
- 206 Davies RJ, Miller R, Coleman N. Colorectal cancer screening: prospects for molecular stool analysis. *Nat Rev Cancer* 2005; 5(3):199-209.
- 207 Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van BM, Hankey BF et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; 366(8):687-696.
- 208 Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012; 143(3):844-857.
- 209 Lieberman DA, Holub JL, Moravec MD, Eisen GM, Peters D, Morris CD. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA* 2008; 300(12):1417-1422.
- 210 Kitahara CM, Berndt SI, de Gonzalez AB, Coleman HG, Schoen RE, Hayes RB et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Clin Oncol* 2013; 31(19):2450-2459.
- 211 Kissow H, Hartmann B, Holst JJ, Viby NE, Hansen LS, Rosenkilde MM et al. Glucagon-like peptide-1 (GLP-1) receptor agonism or DPP-4 inhibition does not accelerate neoplasia in carcinogen treated mice. *Regul Pept* 2012; 179(1-3):91-100.
- 212 Simonsen L, Holst JJ, Deacon CF. Exendin-4, but not glucagon-like peptide-1, is cleared exclusively by glomerular filtration in anaesthetised pigs. *Diabetologia* 2006; 49(4):706-712.
- 213 Koehler JA, Kain T, Drucker DJ. Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. *Endocrinology* 2011; 152(9):3362-3372.
- 214 Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu Rev Physiol* 2014; 76:561-583.
- 215 Golden J. Center for Drug Evaluation and Research. Clinical Review of Belviq (lorcaserin hydrochloride).

- [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/022529Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022529Orig1s000MedR.pdf) . 19 Jun 2012.
- 216 Robert MD Center for Drug Evaluation and Research. Clinical Review of Qsymia (Phentermine/Topiramate).  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/022580Orig1s000SumR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022580Orig1s000SumR.pdf) . 13 Jul 2012.
- 217 Kelley DE, Bray GA, Pi-Sunyer FX, Klein S, Hill J, Miles J et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial. *Diabetes Care* 2002; 25(6):1033-1041.
- 218 O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; 20(7):1426-1436.
- 219 \* Workgroup on Hypoglycemia ADA. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; 28(5):1245-1249.
- 220 Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycemia and implications for the classification of diabetes. *Arch Intern Med* 2007; 167(14):1545-1551.
- 221 Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T et al. Normal fasting plasma glucose levels and type 2 diabetes in young men. *N Engl J Med* 2005; 353(14):1454-1462.
- 222 Lacher DA, Hughes JP, Carroll MD. Estimate of biological variation of laboratory analytes based on the third national health and nutrition examination survey. *Clin Chem* 2005; 51(2):450-452.
- 223 Widjaja A, Morris RJ, Levy JC, Frayn KN, Manley SE, Turner RC. Within- and between-subject variation in commonly measured anthropometric and biochemical variables. *Clin Chem* 1999; 45(4):561-566.
- 224 Mooy JM, Grootenhuys PA, de VH, Kostense PJ, Popp-Snijders C, Bouter LM et al. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 1996; 39(3):298-305.
- 225 Tchobroutsky G. Blood glucose levels in diabetic and non-diabetic subjects. *Diabetologia* 1991; 34(2):67-73.
- 226 Lev-Ran A, Anderson RW. The diagnosis of postprandial hypoglycemia. *Diabetes* 1981; 30(12):996-999.

- 227 Hofeldt FD. Reactive hypoglycemia. *Metabolism* 1975; 24(10):1193-1208.
- 228 Sorensen M, Johansen OE. Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. *Scand J Clin Lab Invest* 2010; 70:385-391.
- 229 Altuntas Y, Bilir M, Ucak S, Gundogdu S. Reactive hypoglycemia in lean young women with PCOS and correlations with insulin sensitivity and with beta cell function. *Eur J Obstet Gynecol Reprod Biol* 2005; 119(2):198-205.
- 230 Brun JF, Fedou C, Mercier J. Postprandial reactive hypoglycemia. *Diabetes Metab* 2000; 26(5):337-351.
- 231 Metwally M, Ledger WL, Li TC. Reproductive endocrinology and clinical aspects of obesity in women. *Ann N Y Acad Sci* 2008; 1127:140-146.
- 232 Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. *Fertility and sterility* 1996; 65(3):503-509.
- 233 Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. *Lancet* 1980; 2(8187):173-176.
- 234 Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010; 67(3):220-229.
- 235 Scott KM, Bruffaerts R, Simon GE, Alonso J, Angermeyer M, de GG et al. Obesity and mental disorders in the general population: results from the world mental health surveys. *Int J Obes (Lond)* 2008; 32(1):192-200.
- 236 Scott KM, McGee MA, Wells JE, Oakley Browne MA. Obesity and mental disorders in the adult general population. *J Psychosom Res* 2008; 64(1):97-105.
- 237 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16(9):606-613.
- 238 Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007; 164(7):1035-1043.
- 239 Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (Draft Guidance). <http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf> . Aug 2012.
- 240 Standards of medical care in diabetes. *Diabetes Care* 2014; 37(Supplement 1):S14-S80.

- 241 Young MD, Collins CE, Callister R, Plotnikoff RC, Doran CM, Morgan PJ. The SHED-IT weight loss maintenance trial protocol: a randomised controlled trial of a weight loss maintenance program for overweight and obese men. *Contemp Clin Trials* 2014; 37:84-97.
- 242 Yanovski SZ, Yanovski JA. Long-term Drug Treatment for Obesity: A Systematic and Clinical Review. *JAMA* 2014; 311:74-86.
- 243 European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical evaluation of medicinal products used in weight control. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003264.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003264.pdf) . 15 Nov 2007.
- 244 Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. *Am J Clin Nutr* 1992; 55(3):652-658.
- 245 Gallo M. Thyroid safety in patients treated with liraglutide. *J Endocrinol Invest* 2013; 36(2):140-145.



## **Liraglutide 3.0 mg for Weight Management**

### **Appendix**

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## 1 Additional trial information

**Table 1–1 Patient disposition in trial 1807, the phase 2 dose-finding trial\***

|                                     | Liraglutide     |                 |                 |                 |                  |  | Orlistat<br>N (%) |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|------------------|--|-------------------|
|                                     | 1.2 mg<br>N (%) | 1.8 mg<br>N (%) | 2.4 mg<br>N (%) | 3.0 mg<br>N (%) | Placebo<br>N (%) |  |                   |
| Randomized                          | 95 (100.0)      | 90 (100.0)      | 93 (100.0)      | 93 (100.0)      | 98 (100.0)       |  | 95 (100.0)        |
| Exposed                             | 95 (100.0)      | 90 (100.0)      | 93 (100.0)      | 93 (100.0)      | 98 (100.0)       |  | 95 (100.0)        |
| Withdrawn until week 20             | 10 (10.5)       | 16 (17.8)       | 20 (21.5)       | 11 (11.8)       | 19 (19.4)        |  | 16 (16.8)         |
| Adverse event                       | 4 (4.2)         | 5 (5.6)         | 9 (9.7)         | 5 (5.4)         | 3 (3.1)          |  | 3 (3.2)           |
| Ineffective therapy                 | 1 (1.1)         | 1 (1.1)         | 0 (0.0)         | 0 (0.0)         | 2 (2.0)          |  | 1 (1.1)           |
| Non-compliance with protocol        | 2 (2.1)         | 2 (2.2)         | 3 (3.2)         | 2 (2.2)         | 3 (3.1)          |  | 2 (2.1)           |
| Other                               | 3 (3.2)         | 8 (8.9)         | 8 (8.6)         | 4 (4.3)         | 11 (11.2)        |  | 10 (10.5)         |
| Completed 20 weeks                  | 85 (89.5)       | 74 (82.2)       | 73 (78.5)       | 82 (88.2)       | 79 (80.6)        |  | 79 (83.2)         |
| Discontinued before extension       | 17 (17.9)       | 15 (16.7)       | 8 (8.6)         | 10 (10.8)       | 12 (12.2)        |  | 12 (12.6)         |
| Enrolled in extension               | 68 (71.6)       | 59 (65.6)       | 65 (69.9)       | 72 (77.4)       | 67 (68.4)        |  | 67 (70.5)         |
| Withdrawn until week 52             | 17 (17.9)       | 20 (22.2)       | 27 (29.0)       | 18 (19.4)       | 24 (24.5)        |  | 28 (29.5)         |
| Adverse event                       | 5 (5.3)         | 6 (6.7)         | 12 (12.9)       | 7 (7.5)         | 3 (3.1)          |  | 4 (4.2)           |
| Ineffective therapy                 | 1 (1.1)         | 2 (2.2)         | 1 (1.1)         | 0 (0.0)         | 4 (4.1)          |  | 1 (1.1)           |
| Non-compliance with protocol        | 2 (2.1)         | 3 (3.3)         | 3 (3.2)         | 2 (2.2)         | 3 (3.1)          |  | 3 (3.2)           |
| Other                               | 9 (9.5)         | 9 (10.0)        | 11 (11.8)       | 9 (9.7)         | 14 (14.3)        |  | 21 (22.1)         |
| Completed 52 weeks                  | 61 (64.2)       | 55 (61.1)       | 58 (62.4)       | 65 (69.9)       | 62 (63.3)        |  | 55 (57.9)         |
| Withdrawn until week 104            | 32 (33.7)       | 37 (41.1)       | 40 (43.0)       | 36 (38.7)       | 39 (39.8)        |  | 38 (40.0)         |
| Adverse event                       | 8 (8.4)         | 12 (13.3)       | 13 (14.0)       | 9 (9.7)         | 6 (6.1)          |  | 3 (3.2)           |
| Ineffective therapy                 | 3 (3.2)         | 6 (6.7)         | 2 (2.2)         | 0 (0.0)         | 5 (5.1)          |  | 2 (2.1)           |
| Non-compliance with protocol        | 4 (4.2)         | 5 (5.6)         | 4 (4.3)         | 7 (7.5)         | 4 (4.1)          |  | 5 (5.3)           |
| Other                               | 17 (17.9)       | 14 (15.6)       | 21 (22.6)       | 20 (21.5)       | 24 (24.5)        |  | 28 (29.5)         |
| Completed 104 weeks                 | 46 (48.4)       | 38 (42.2)       | 45 (48.4)       | 47 (50.5)       | 47 (48.0)        |  | 45 (47.4)         |
| Safety analysis set                 | 95 (100.0)      | 90 (100.0)      | 93 (100.0)      | 93 (100.0)      | 98 (100.0)       |  | 95 (100.0)        |
| Full analysis set                   | 94 (98.9)       | 90 (100.0)      | 92 (98.9)       | 92 (98.9)       | 98 (100.0)       |  | 95 (100.0)        |
| Completers of extension (104 weeks) | 46 (48.4)       | 38 (42.2)       | 45 (48.4)       | 47 (50.5)       | 47 (48.0)        |  | 45 (47.4)         |

\*Total screened = 733, screening failures = 169, entered run-in = 616, failed run-in = 52. N: Number of patients. %: proportion of randomized patients.

**Table 1–2 Inclusion criteria of the phase 2 and 3 clinical trials**

| Inclusion criteria  | Trial 1807 | Trial 1839 | Trial 1923 | Trial 1922 | Trial 3970 |
|---|------------|------------|------------|------------|------------|
| Informed consent was obtained before any trial-related activities took place  | X          | X          | X          | X          | X          |
| Age $\geq 18$ years <sup>a</sup>  | X          | X          | X          | X          | X          |
| BMI $\geq 30.0$ kg/m <sup>2</sup> or $\geq 27$ kg/m <sup>2</sup> with co-morbidities of treated or untreated dyslipidemia and/or hypertension <sup>b,c</sup>  | X          | X          | X          | X          | X          |
| Stable body weight (less than 5 kg self-reported change during the previous 3 months) <sup>d</sup>  | X          | X          | X          | X          | X          |
| Preceding failed dietary effort   |            | X          | X          | X          |            |
| Fasting plasma glucose $< 126$ mg/dL (7.0 mmol/L)   | X          |            |            |            |            |
| Patients diagnosed with type 2 diabetes and treated with either diet and exercise alone or metformin, SU or glitazone as single-agent therapy or in combination. Treatment should have been stable for at least 3 months prior to screening |            |            |            | X          |            |
| HbA <sub>1c</sub> 7.0–10.0%   |            |            |            | X          |            |
| Diagnosis of moderate or severe OSA   |            |            |            |            | X          |
| No CPAP (or other positive airway pressure) treatment for at least 4 weeks prior to screening   |            |            |            |            | X          |
| Ability and willingness to comply with protocol procedures  |            |            |            |            | X          |

<sup>a</sup>Age 18–65 years for trial 1807;  $\geq 18$  years (or as allowed according to local labelling for metformin and SU treatment) for trial 1922; 18–64 years for trial 3970.

<sup>b</sup>BMI  $\geq 30.0$  and  $\leq 40.0$  kg/m<sup>2</sup> in trial 1807; 27.0 kg/m<sup>2</sup> in trial 1922;  $\geq 30$  kg/m<sup>2</sup> in trial 3970.

<sup>c</sup>Untreated dyslipidemia definition: low density lipoprotein  $\geq 160$  mg/dL, or triglycerides  $\geq 150$  mg/dL, or high density lipoprotein  $< 40$  mg/dL (males) and  $< 50$  mg/dL (females). Untreated hypertension definition: systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg.

<sup>d</sup>Less than 5% self-reported change during the previous 3 months in trials 1807 and 3970.

BMI: body mass index. CPAP: continuous positive airway pressure. OSA: obstructive sleep apnea. SU: sulfonylurea

**Table 1–3 Key exclusion criteria of the phase 2 and 3 clinical trials**

| Exclusion criteria   | Trial 1807 | Trial 1839 | Trial 1923 | Trial 1922 | Trial 3970 |
|--|------------|------------|------------|------------|------------|
| Previous treatment with GLP-1 receptor agonists within the last 3 months (1922/3970: also DPP-4 inhibitors or insulin)   | X          | X          | X          | X          | X          |
| Known/suspected hypersensitivity to trial product(s)   | X          | X          | X          | X          | X          |
| Untreated or uncontrolled hypothyroidism/ hyperthyroidism  | X          | X          | X          | X          | X          |
| Obesity induced by other endocrinologic disorders (e.g., Cushing Syndrome)   | X          | X          | X          | X          | X          |
| Current/history of treatment with drugs that may cause significant weight gain   | X          | X          | X          | X          | X          |
| Current participation in an organized weight reduction program (or within the last 3 months)   | X          | X          | X          | X          | X          |
| Participation in a clinical trial in the last 3 months   | X          | X          | X          | X          | X          |
| Previous participation in the randomized phase (1923: or run-in)   | X          | X          | X          | X          | X          |
| Receipt of any trial drug in the last 4 weeks (3970: last 3 months)  | X          | X          | X          |            | X          |
| Previous surgical treatment for obesity or scheduled surgery   | X          | X          | X          | X          | X          |
| Uncontrolled treated/untreated hypertension (SBP $\geq$ 160 mmHg and/or DBP $\geq$ 100 mmHg)   | X          | X          | X          | X          | X          |
| Cancer (past/present, except basal cell skin cancer/squamous cell skin cancer)   | X          | X          | X          | X          | X          |
| Known or suspected abuse of alcohol or narcotics   | X          | X          | X          | X          | X          |
| Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation  | X          | X          | X          | X          | X          |
| Females of child bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraception                               | X          | X          | X          | X          | X          |
| Diagnosis of type 1 or type 2 diabetes (investigator judgment)   | X          | X          | X          |            | X          |
| FPG $\geq$ 126 mg/dL (7.0 mmol/L) (trial 1839/1923) or 2-h post-challenge PG $\geq$ 200 mg/dL (11.1 mmol/L) (trial 1839) or HbA <sub>1c</sub> $\geq$ 6.5% (trial 3970) |            | X          | X          |            | X          |
| History of major depressive disorder within the last 2 years   |            | X          | X          | X          | X          |



| Exclusion criteria   | Trial 1807 | Trial 1839 | Trial 1923 | Trial 1922 | Trial 3970 |
|--|------------|------------|------------|------------|------------|
| History of other severe psychiatric disorders, e.g., schizophrenia, bipolar disorder   |            | X          | X          | X          | X          |
| A PHQ-9 score $\geq 15$ (1923: $>15$ )   |            | X          | X          | X          | X          |
| Lifetime history of a suicide attempt, or history of suicidal behavior   |            | X          | X          | X          | X          |
| Any suicidal ideation of type 4 or 5 on the C-SSRS in the last month   |            | X          |            | X          | X          |
| Screening calcitonin $\geq 50$ ng/L  |            | X          |            | X          | X          |
| Family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma                                      |            | X          |            | X          | X          |
| Personal history of non-familial medullary thyroid carcinoma   |            | X          |            | X          | X          |
| History of chronic pancreatitis or idiopathic acute pancreatitis   |            | X          |            | X          | X          |
| Clinically significant active cardiovascular disease, including history of myocardial infarction within the past 6 months and/or heart failure | X          |            | X          |            |            |
| Diagnosis of eating disorder, e.g., restrained eating, binge eating, bulimia   |            |            | X          |            |            |
| Treatment with any hypoglycemic agent(s) other than metformin, sulfonylurea or glitazone in the last 3 months                                  |            |            |            | X          |            |
| Recurrent major hypoglycemia or hypoglycemic unawareness   |            |            |            | X          |            |
| Use of any drug which could interfere with glucose levels  |            |            |            | X          |            |
| Receipt of any anti-diabetic investigational drug in last 3 months, or receipt of any non-diabetic investigational drug in last month          |            |            |            | X          |            |
| Known proliferative retinopathy/maculopathy requiring acute treatment  |            |            |            | X          |            |
| Exclusion criteria related to OSA <sup>a</sup>   |            |            |            |            | X          |

<sup>a</sup>Significant craniofacial abnormalities; respiratory and neuromuscular diseases; known diagnosis of periodic limb movement disorder; use of central stimulants, hypnotics, mirtazepine, opioids, trazodone in last 3 months; history of stroke or Acute Coronary Syndrome in the previous year; history of unstable angina or heart failure corresponding to New York Heart Association (NYHA) functional class III or IV in the previous year; history of arrhythmia.

C-SSRS: Columbia Suicidality Severity Rating Scale. DBP: diastolic blood pressure. DPP-4: dipeptidyl peptidase-4. FPG: fasting plasma glucose. GLP-1: glucagon-like peptide-1. OSA: obstructive sleep apnea. PHQ-9: Patient Health Questionnaire-9. SBP: systolic blood pressure. TSH: thyroid-stimulating hormone

**Table 1–4 Key withdrawal criteria of the phase 2 and 3 clinical trials**

| Withdrawal criteria  | Trial 1807 | Trial 1839 | Trial 1923 | Trial 1922 | Trial 3970 |
|--|------------|------------|------------|------------|------------|
| Patients could withdraw from the trial at will at any time   | X          | X          | X          | X          | X          |
| Patients could be withdrawn at the discretion of the investigator or sponsor due to safety concerns or if judged non-compliant with trial procedures   | X          | X          | X          | X          | X          |
| Patients were withdrawn if the allocated drug dose could not be tolerated  | X          | X          | X          | X          | X          |
| Patients were withdrawn due to pregnancy or intention to become pregnant   | X          | X          | X          | X          | X          |
| If the investigator suspected acute pancreatitis, suspected drugs were to be discontinued until confirmatory tests had been conducted and appropriate treatment initiated. Patients diagnosed with acute pancreatitis were withdrawn.  |            | X          | X          | X          | X          |
| Patients were referred to a MHP if they had a PHQ-9 score $\geq 10$ , or any suicidal behavior, or any suicidal ideation of type 4 or 5 on any C-SSRS assessment, or if deemed necessary for the safety of the patient. If the patient was considered to be adequately treated with psycho- and/or pharmacotherapy, then he/she could continue in the trial. Otherwise, the patient was withdrawn. |            | X          | X          | X          | X          |
| Patients developing diabetes were not withdrawn but were to receive the best standard of care (investigator's discretion). If insulin, a GLP-1 receptor agonist or DPP-4 inhibitor was considered the best option, patient was withdrawn   |            | X          |            |            | X          |
| Diagnosis of type 1 or type 2 diabetes   |            |            | X          |            |            |
| If adaptation of background OADs did not result in fasting plasma glucose or HbA <sub>1c</sub> levels below those specified as rescue criteria within 8 weeks  |            |            |            | X          |            |
| If a patient, despite lowering of background OADs, experiences severe episodes of major hypoglycemia or repeated minor hypoglycemic episodes   |            |            |            | X          |            |

C-SSRS: Columbia Suicidality Severity Rating Scale. CT: computed tomography. DPP-4: dipeptidyl peptidase-4. GLP-1: glucagon-like peptide-1. MHP: mental health professional. MRI: magnetic resonance imaging. OAD: oral antidiabetic drug. PHQ-9: Patient Health Questionnaire-9. UNR: upper limit of normal range

**Table 1–5 Liraglutide exposure by sub-populations: weight management pool – safety analysis set**

|                               | Liraglutide 3.0 mg |      |          | Total Liraglutide |      |          | Placebo |      |          |
|-------------------------------|--------------------|------|----------|-------------------|------|----------|---------|------|----------|
|                               | N                  | %    | (PYE)    | N                 | %    | (PYE)    | N       | %    | (PYE)    |
| Sex                           |                    |      |          |                   |      |          |         |      |          |
| Female                        | 2449               | 73.0 | (2172.2) | 2763              | 71.7 | (2418.4) | 1374    | 72.2 | (1155.7) |
| Male                          | 935                | 27.0 | (802.1)  | 1109              | 28.3 | (954.3)  | 567     | 27.8 | (445.2)  |
| Age Group (yrs)               |                    |      |          |                   |      |          |         |      |          |
| <65                           | 3152               | 93.3 | (2776.2) | 3604              | 93.2 | (3144.3) | 1825    | 93.2 | (1491.5) |
| ≥65 ; <75                     | 215                | 6.4  | (189.8)  | 249               | 6.5  | (218.1)  | 113     | 6.7  | (106.5)  |
| ≥75                           | 17                 | 0.3  | (8.2)    | 19                | 0.3  | (10.3)   | 3       | 0.2  | (2.9)    |
| Race                          |                    |      |          |                   |      |          |         |      |          |
| White                         | 2845               | 84.6 | (2516.3) | 3294              | 85.5 | (2883.4) | 1651    | 86.3 | (1381.7) |
| Black or African Am.          | 348                | 9.9  | (294.1)  | 378               | 9.4  | (318.1)  | 202     | 9.5  | (152.8)  |
| Asian                         | 115                | 3.3  | (98.9)   | 119               | 3    | (101.5)  | 53      | 2.8  | (45.3)   |
| Other                         | 76                 | 2.1  | (65.1)   | 81                | 2.1  | (69.7)   | 35      | 1.4  | (21.1)   |
| Ethnicity                     |                    |      |          |                   |      |          |         |      |          |
| Hispanic or Latino            | 341                | 9.5  | (282.5)  | 358               | 8.8  | (295.8)  | 193     | 9.3  | (148.2)  |
| Not Hisp. or Latino           | 2948               | 87.9 | (2613.9) | 3141              | 82.7 | (2790.3) | 1649    | 86.2 | (1379.2) |
| Not Applicable                | 95                 | 2.6  | (77.9)   | 373               | 8.5  | (286.6)  | 99      | 4.6  | (73.5)   |
| BMI [kg/m <sup>2</sup> ]      |                    |      |          |                   |      |          |         |      |          |
| <30                           | 149                | 4.4  | (130.5)  | 194               | 5.0  | (168.5)  | 117     | 6.3  | (100.6)  |
| ≥30 ; <35                     | 1142               | 34.0 | (1011.5) | 1366              | 35.2 | (1188.4) | 633     | 32.7 | (522.8)  |
| ≥35 ; <40                     | 1038               | 30.4 | (903.2)  | 1192              | 30.5 | (1027.6) | 606     | 31.0 | (496.8)  |
| ≥40                           | 1055               | 31.2 | (929.1)  | 1120              | 29.3 | (988.2)  | 585     | 30.0 | (480.7)  |
| Glycemic status               |                    |      |          |                   |      |          |         |      |          |
| Normoglycemic                 | 1129               | 33.1 | (984.0)  | 1264              | 31.9 | (1074.9) | 676     | 34.1 | (546.3)  |
| Pre-diabetes                  | 1833               | 54.1 | (1610.4) | 1976              | 51.2 | (1728.3) | 1053    | 54.7 | (875.0)  |
| Diabetes                      | 422                | 12.8 | (379.9)  | 632               | 16.9 | (569.6)  | 212     | 11.2 | (179.7)  |
| Hepatic function by ALT level |                    |      |          |                   |      |          |         |      |          |
| <75 Percentile                | 2608               | 77.2 | (2295.1) | 2953              | 76.2 | (2569.7) | 1469    | 76.9 | (1231.0) |
| ≥75 Percentile                | 776                | 22.8 | (679.2)  | 919               | 23.8 | (803.0)  | 472     | 23.1 | (369.9)  |
| Hepatic function by AST level |                    |      |          |                   |      |          |         |      |          |
| <75 Percentile                | 2646               | 78.2 | (2327.3) | 2987              | 77.1 | (2602.0) | 1459    | 75.9 | (1215.4) |
| ≥75 Percentile                | 738                | 21.8 | (647.0)  | 885               | 22.9 | (770.7)  | 480     | 23.9 | (383.3)  |
| Renal function                |                    |      |          |                   |      |          |         |      |          |
| Normal                        | 1758               | 51.9 | (1543.9) | 2015              | 51.9 | (1751.7) | 1044    | 53.3 | (853.7)  |
| Mild                          | 1461               | 43.2 | (1284.8) | 1670              | 43.2 | (1455.9) | 830     | 43.2 | (692.2)  |
| Moderate                      | 161                | 4.8  | (142.4)  | 181               | 4.8  | (160.6)  | 63      | 3.2  | (50.7)   |
| Severe                        | 3                  | 0.1  | (2.2)    | 4                 | 3.3  | (3.3)    | 2       | 0.1  | (2.1)    |
| History of CV disease         |                    |      |          |                   |      |          |         |      |          |
| Yes                           | 311                | 9.2  | (274.9)  | 351               | 9.2  | (311.0)  | 172     | 9.4  | (150.8)  |

Table is based on trials 1839, 1923, 1922, 3970, 1807 and 1807 (52-week period).

N: Number of patients, PYE: Patient years of exposure (1 PYE = 365.25 days), BMI: Body mass index. Patients with race recorded as 'Other', 'Unknown' or 'Not Applicable' have been grouped as 'Other'. Patients from France did not report race, Ethnicity was not collected in trial 1807.

CV disease (by MedDRA search) includes the SMQs Ischemic heart disease, Cardiac failure, and Central nervous system hemorrhages and cerebrovascular conditions and Embolic and thrombotic events. Renal impairment was based on estimated creatinine clearance according to the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation. Baseline renal function was mild (60–89 mL/min per 1.73 m<sup>2</sup>), moderate (30–59 mL/min per 1.73 m<sup>2</sup>), or severe (15–29 mL/min per 1.73 m<sup>2</sup>). Unless otherwise specified, sub-populations are defined based on baseline values

## 2 Efficacy results for phase 3 trials

### 2.1 Trial 1839 (phase 3 trial in patients without type 2 diabetes): Main 56-week trial

**Table 2–1 Baseline characteristics of randomized patients by treatment: Trial 1839**

|  | Liraglutide 3.0 mg<br>(N=2487) | Placebo<br>(N=1244) |
|--|--------------------------------|---------------------|
| Sex – n (%)  |                                |                     |
| Female   | 1957 (78.7)                    | 971 (78.1)          |
| Age – years  | 45.2±12.1                      | 45.0±12.0           |
| Race – n (%) <sup>a</sup>                          |                                |                     |
| White  | 2107 (84.7)                    | 1061 (85.3)         |
| Black or African American                          | 242 (9.7)                      | 114 (9.2)           |
| Asian  | 90 (3.6)                       | 46 (3.7)            |
| American Indian or Alaska Native                   | 5 (0.2)                        | 4 (0.3)             |
| Native Hawaiian or other Pacific Islander          | 2 (<0.1)                       | 2 (0.2)             |
| Other  | 41 (1.6)                       | 17 (1.4)            |
| Ethnic group – n (%) <sup>a</sup>                  |                                |                     |
| Hispanic or Latino                                 | 259 (10.4)                     | 134 (10.8)          |
| Weight ( kg)                                       | 106.2 (21.2)                   | 106.2 (21.7)        |
| BMI (kg/m <sup>2</sup> )                           | 38.3 (6.4)                     | 38.3 (6.3)          |
| BMI categories – n (%)                             |                                |                     |
| 27-29.9 – overweight                               | 66 (2.7)                       | 44 (3.5)            |
| 30-34.9 – obese class I                            | 806 (32.4)                     | 388 (31.2)          |
| 35-39.9 – obese class II                           | 787 (31.6)                     | 398 (32.0)          |
| >40 – obese class III                              | 828 (33.3)                     | 414 (33.3)          |
| Waist circumference (cm)                           | 115.0 (14.4)                   | 114.5 (14.3)        |
| HbA <sub>1c</sub> – %                              | 5.6 (0.4)                      | 5.6 (0.4)           |
| Fasting plasma glucose – mg/dL                     | 95.9 (10.6)                    | 95.5 (9.8)          |
| Fasting insulin – µIU/mL                           | 16.3 (80.1)                    | 16.1 (89.8)         |
| Blood pressure – mm Hg                             |                                |                     |
| Systolic   | 123.0 (13.0)                   | 123.3 (12.8)        |
| Diastolic  | 78.7 (8.6)                     | 78.9 (8.5)          |
| Cholesterol – mg/dL                                |                                |                     |
| Total  | 193.8 (19.1)                   | 194.4 (18.8)        |
| LDL  | 111.8 (27.9)                   | 112.3 (27.6)        |
| HDL  | 51.4 (26.3)                    | 51.0 (26.6)         |
| VLDL   | 25.2 (49.6)                    | 25.8 (49.5)         |
| Triglycerides – mg/dL                              | 126.3 (57.1)                   | 129.3 (61.1)        |
| Pre-diabetes – n (%) <sup>b</sup>                  | 1528 (61.4)                    | 757 (60.9)          |
| Dyslipidemia – n (%) <sup>b</sup>                  | 737 (29.6)                     | 359 (28.9)          |
| Hypertension – n (%) <sup>b</sup>                  | 850 (34.2)                     | 446 (35.9)          |
| Dyslipidemia and hypertension – n (%) <sup>b</sup> | 417 (16.8)                     | 213 (17.1)          |
| Treated with anti-hypertensive drugs – n (%)       | 754 (30.9)                     | 404 (33.0)          |
| Treated with lipid-lowering drugs – n (%)          | 386 (15.8)                     | 183 (14.9)          |
| Cardiovascular disease – n (%) <sup>c</sup>        | 216 (8.7)                      | 105 (8.5)           |

Data are mean (SD) or number (%). Data for fasting insulin, blood pressure and lipids are reported for the full analysis set (randomized individuals who were exposed to at least one dose of liraglutide or placebo and had at least one post-baseline assessment). For fasting insulin and lipids, data are geometric mean (CV).

BMI: body mass index. HDL: high-density lipoprotein. LDL: low-density lipoprotein. VLDL: very low density lipoprotein.

<sup>a</sup>Race and ethnic group were self-reported. Individuals from France did not report race or ethnicity.

<sup>b</sup>Pre-diabetes was defined according to ADA 2010 criteria. Dyslipidemia was defined as LDL cholesterol  $\geq 160$  mg/dl, triglycerides  $\geq 150$  mg/dl, or HDL cholesterol  $< 40$  mg/dl for males and  $< 50$  mg/dl for females. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg.

<sup>c</sup>Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events in exposed patients.

**Table 2–2 Mean changes in body weight-related endpoints at week 56: Trial 1839**

|  | Liraglutide 3.0 mg<br>FAS, N=2432 |   | Placebo<br>FAS, N=1220 |   | Treatment<br>difference/<br>odds ratio<br>Liraglutide vs.<br>placebo |
|--|-----------------------------------|---|------------------------|---|--|
|  | Baseline                          | Change<br>from<br>baseline<br>(LSMeans) | Baseline               | Change<br>from<br>baseline<br>(LSMeans) |  |
| Body weight (%) <sup>1)</sup>                                |                                   | -7.99                                   |                        | -2.60                                   | -5.39*   |
| Body weight (kg)   | 106.2                             | -8.37                                   | 106.2                  | -2.81                                   | -5.56*   |
| % of patients losing $\geq 5\%$ of body weight <sup>2)</sup> |                                   | 63.5                                    |                        | 26.6                                    | 4.80*  |
| % of patients losing $> 10\%$ of body weight <sup>3)</sup>   |                                   | 32.8                                    |                        | 10.1                                    | 4.34*  |
| BMI (kg/m <sup>2</sup> )                                     | 38.3                              | -3.04                                   | 38.4                   | -1.00                                   | -2.04*   |
| Waist circumference (cm)                                     | 115.0                             | -8.17                                   | 114.5                  | -3.97                                   | -4.20*   |

\* $p < 0.05$ ; <sup>1-3)</sup> Confirmatory co-primary endpoint shown in order of testing. Mean changes are analyzed by ANCOVA (presented with treatment differences) and categorical changes by logistic regression (presented with odds ratios).

BMI: body mass index. FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.) LS: least square. N: number of patients.

**Table 2–3 Mean changes in secondary parameters at week 56: Trial 1839**

|                                       | Liraglutide 3.0 mg<br>FAS, N=2437 |   | Placebo<br>FAS, N=1225 |   | Treatment<br>difference<br>Liraglutide<br>vs. placebo |
|---------------------------------------|-----------------------------------|---|------------------------|---|---|
|                                       | Baseline                          | Change<br>from<br>baseline<br>(LSMeans) | Baseline               | Change<br>from<br>baseline<br>(LSMeans) |   |
| <b>Glycemic control parameters</b>    |                                   |   |                        |   |   |
| HbA <sub>1c</sub> (%-points)          | 5.6                               | -0.29                                   | 5.6                    | -0.07                                   | -0.23*  |
| Fasting plasma glucose (mg/dL)        | 95.9                              | -7.00                                   | 95.5                   | -0.10                                   | -6.90*  |
| <b>Blood pressure</b>                 |                                   |   |                        |   |   |
| Systolic blood pressure (mmHg)        | 123.0                             | -4.28                                   | 123.3                  | -1.46                                   | -2.82*  |
| Diastolic blood pressure (mmHg)       | 78.7                              | -2.68                                   | 78.9                   | -1.79                                   | -0.89*  |
| <b>Patient reported outcome</b>       |                                   |   |                        |   |   |
| SF-36 (overall physical health score) | 48.3                              | 3.66                                    | 47.7                   | 1.93                                    | 1.73*   |
| SF-36 (overall mental health score)   | 53.8                              | 0.14                                    | 53.9                   | -0.76                                   | 0.90*   |
| IWQoL-Lite (total score)              | 73.1                              | 10.66                                   | 72.5                   | 7.54                                    | 3.13*   |
| TRIM-Weight (total score)             | –                                 | 83.11                                   | –                      | 80.97                                   | 2.14*   |
|                                       | Baseline                          | Relative<br>change from<br>baseline (%) | Baseline               | Relative<br>change from<br>baseline (%) | Relative<br>difference<br>Liraglutide<br>vs. placebo  |
| <b>Lipids</b>                         |                                   |   |                        |   |   |
| HDL cholesterol (mg/dL)               | 51.4                              | 2.33                                    | 50.9                   | 0.46                                    | 1.9*  |
| LDL cholesterol (mg/dL)               | 111.8                             | -3.15                                   | 112.3                  | -0.71                                   | -2.4*   |
| VLDL cholesterol (mg/dL)              | 25.2                              | -13.46                                  | 25.8                   | -4.78                                   | -9.1*   |
| Triglycerides (mg/dL)                 | 126.3                             | -13.61                                  | 129.3                  | -4.76                                   | -9.3*   |
| Total cholesterol (mg/dL)             | 193.8                             | -3.19                                   | 194.4                  | -0.89                                   | -2.3*   |
| Free fatty acids (mg/dL)              | 12.7                              | 0.79                                    | 13.0                   | 5.17                                    | -4.2*   |
| <b>Cardiovascular biomarkers</b>      |                                   |   |                        |   |   |
| hsCRP (mg/L)                          | 3.9                               | -37.60                                  | 3.8                    | -10.24                                  | -30.5*  |
| Fibrinogen (g/L)                      | 4.3                               | 0.91                                    | 4.3                    | 0.46                                    | 0.5   |
| PAI-1 (ng/mL)                         | 14.7                              | –                                       | 14.7                   | –                                       | -21.3*  |
| Adiponectin (µg/mL)                   | 7.4                               | 11.94                                   | 7.4                    | 3.20                                    | 8.5*  |
| Albumin/creatinine ratio (mg/g)       | 3.6                               | 11.49                                   | 3.6                    | 15.63                                   | -3.6  |

\*p&lt;0.05

For the TRIM-Weight questionnaire, actual changes are shown as the questionnaire was not completed at baseline.

PAI-1 was analyzed using different methods at baseline and week 56, therefore relative changes cannot be calculated.

FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.)

HDL: high-density lipoprotein. hsCRP: high-sensitivity C-reactive protein. IWQoL-Lite: Impact of Weight on Quality of Life-Lite questionnaire. LDL: low-density lipoprotein. LS: least square. N: number of patients. PAI-1: plasminogen activator inhibitor-1. SF-36: 36-item Short-Form health status survey. TRIM-Weight: Treatment Related Impact Measure-Weight questionnaire. VLDL: very low density lipoprotein.



## 2.2 Trial 1922 (phase 3 trial in patients with type 2 diabetes)

**Table 2–4 Patient disposition including all liraglutide doses: Trial 1922**

|  | Liraglutide 3.0 mg<br>N (%) | Liraglutide 1.8 mg<br>N (%) | Placebo<br>N (%) | Total<br>N (%) |
|--|-----------------------------|-----------------------------|------------------|----------------|
| Screened   |                             |                             |                  | 1361 (160.9)   |
| Screening failures   |                             |                             |                  | 515 ( 60.9)    |
| Withdrawn before randomization                                     |                             |                             |                  | 0 ( 0.0)       |
| Randomized   | 423 (100.0)                 | 211 (100.0)                 | 212 (100.0)      | 846 (100.0)    |
| Exposed  | 422 ( 99.8)                 | 210 ( 99.5)                 | 212 (100.0)      | 844 ( 99.8)    |
| Completer, week 56   | 324 ( 76.6)                 | 164 ( 77.7)                 | 140 ( 66.0)      | 628 ( 74.2)    |
| Withdrawn, week 56   | 99 ( 23.4)                  | 47 ( 22.3)                  | 72 ( 34.0)       | 218 ( 25.8)    |
| Adverse event  | 39 ( 9.2)                   | 18 ( 8.5)                   | 7 ( 3.3)         | 64 ( 7.6)      |
| Ineffective therapy  | 0 ( 0.0)                    | 0 ( 0.0)                    | 3 ( 1.4)         | 3 ( 0.4)       |
| Non-compliance with protocol                                       | 12 ( 2.8)                   | 8 ( 3.8)                    | 13 ( 6.1)        | 33 ( 3.9)      |
| Withdrawal criteria  | 32 ( 7.6)                   | 14 ( 6.6)                   | 37 ( 17.5)       | 83 ( 9.8)      |
| Withdrawn during first 56 weeks but<br>attended end of trial visit | 36 ( 36.4)                  | 12 ( 25.5)                  | 23 ( 31.9)       | 71 ( 32.6)     |
| Full analysis set  | 412 ( 97.4)                 | 204 ( 96.7)                 | 211 ( 99.5)      | 827 ( 97.8)    |
| Safety analysis set  | 422 ( 99.8)                 | 210 ( 99.5)                 | 212 (100.0)      | 844 ( 99.8)    |

N: Number of Patients. %: Proportion of randomized patients.

**Table 2–5 Baseline characteristics of randomized patients by treatment: Trial 1922**

|   | Liraglutide 3.0 mg<br>(N=423) <sup>d</sup> | Liraglutide 1.8 mg<br>(N=211) <sup>d</sup> | Placebo<br>(N=212) |
|---|--|--|--------------------|
| Sex – n (%)                               |  |  |                    |
| Female                                    | 203 (48.0)                                 | 103 (48.8)                                 | 115 (54.2)         |
| Age – years                               | 55.0 (10.8)                                | 54.9 (10.7)                                | 54.7 (9.8)         |
| Race – n (%) <sup>a</sup>                 |  |  |                    |
| White                                     | 353 (83.5)                                 | 177 (83.9)                                 | 175 (82.5)         |
| Black or African American                 | 44 (10.4)                                  | 27 (12.8)                                  | 27 (12.7)          |
| Asian                                     | 11 (2.6)                                   | 4 (1.9)                                    | 4 (1.9)            |
| American Indian or Alaska Native          | 4 (0.9)                                    | 0 (0.0)                                    | 0 (0.0)            |
| Native Hawaiian or other Pacific Islander | 0 (0.0)                                    | 0 (0.0)                                    | 0 (0.0)            |
| Other                                     | 9 (2.1)                                    | 3 (1.4)                                    | 5 (2.4)            |
| Ethnic group – n (%) <sup>a</sup>         |  |  |                    |
| Hispanic or Latino                        | 46 (10.9)                                  | 17 (8.1)                                   | 24 (11.3)          |
| Non-Hispanic                              | 375 (88.7)                                 | 194 (91.9)                                 | 187 (88.2)         |
| Not applicable                            | 2 (0.5)                                    | 0 (0.0)                                    | 1 (0.5)            |

|  | Liraglutide 3.0 mg<br>(N=423) <sup>d</sup> | Liraglutide 1.8 mg<br>(N=211) <sup>d</sup> | Placebo<br>(N=212) |
|--|--|--|--------------------|
| Fasting body weight (kg)                               | 105.7 (21.9)                               | 105.8 (21.0)                               | 106.5 (21.3)       |
| BMI (kg/m <sup>2</sup> )                               | 37.1 (6.5)                                 | 37.0 (6.9)                                 | 37.4 (7.1)         |
| BMI categories – n (%)                                 |  |  |                    |
| 25.0–29.9 kg/m <sup>2</sup> – pre-obese                | 52 (12.3)                                  | 34 (16.1)                                  | 30 (14.2)          |
| 30.0–34.9 kg/m <sup>2</sup> – obese class I            | 139 (32.9)                                 | 62 (29.4)                                  | 59 (27.8)          |
| 35.0–39.9 kg/m <sup>2</sup> – obese class II           | 108 (25.5)                                 | 50 (23.7)                                  | 60 (28.3)          |
| >40.0 kg/m <sup>2</sup> – obese class III              | 124 (29.3)                                 | 65 (30.8)                                  | 63 (29.7)          |
| Waist circumference (cm)                               | 118.1 (14.4)                               | 117.7 (14.8)                               | 117.3 (14.0)       |
| HbA <sub>1c</sub> (%)                                  | 7.9 (0.8)                                  | 8.0 (0.8)                                  | 7.9 (0.8)          |
| Fasting plasma glucose – mg/dL                         | 158.4 (32.8)                               | 160.4 (35.1)                               | 155.5 (33.0)       |
| Fasting insulin – pmol/L                               | 122.5 (79.2)                               | 120.2 (77.5)                               | 128.9 (303.0)      |
| Duration of diabetes (years)                           | 7.5 (5.65)                                 | 7.4 (5.16)                                 | 6.7 (5.07)         |
| Blood pressure – mm Hg                                 |  |  |                    |
| Systolic   | 128.9 (13.6)                               | 130.5 (14.5)                               | 129.2 (13.6)       |
| Diastolic  | 79.0 (8.6)                                 | 80.1 (9.3)                                 | 79.3 (9.5)         |
| Cholesterol – mg/dL                                    |  |  |                    |
| Total  | 171.0 (21.8)                               | 178.3 (26.4)                               | 169.4 (22.9)       |
| LDL  | 86.4 (35.5)                                | 91.5 (38.5)                                | 85.2 (39.3)        |
| HDL  | 45.2 (25.0)                                | 44.5 (27.2)                                | 45.4 (24.8)        |
| VLDL   | 31.8 (58.5)                                | 33.0 (76.6)                                | 31.1 (54.5)        |
| Triglycerides – mg/dL                                  | 162 (73)                                   | 170 (98)                                   | 158 (66)           |
| Diabetes – n (%)                                       | 422 (100.0)                                | 210 (100.0)                                | 212 (100.0)        |
| Dyslipidemia at baseline <sup>b</sup>                  | 295 (69.7)                                 | 143 (67.8)                                 | 126 (59.4)         |
| Hypertension at baseline <sup>b</sup>                  | 293 (69.3)                                 | 148 (70.1)                                 | 145 (68.4)         |
| Dyslipidemia and hypertension – n (%) <sup>b</sup>     | 220 (52.0)                                 | 110 (52.1)                                 | 92 (43.4)          |
| Treated with anti-hypertensive drugs – n (%)           | 278 ( 67.5)                                | 132 ( 64.7)                                | 143 ( 67.8)        |
| Treated with lipid-lowering drugs – n (%)              | 250 ( 60.7)                                | 114 ( 55.9)                                | 110 ( 52.1)        |
| History of cardiovascular disease – n (%) <sup>c</sup> | 69 ( 16.4)                                 | 31 ( 14.8)                                 | 26 ( 12.3)         |
| Subjects taking OADs at baseline                       | 366 (88.8%)                                | 175 (85.8%)                                | 191 (90.5%)        |
| Subjects not taking SU                                 | 259 (84.9%)                                | 124 (81.0%)                                | 136 (87.2%)        |

Data are mean (SD) or n (%). Data for fasting insulin, blood pressure and lipids are reported for the full analysis set (randomized individuals who were exposed to at least one dose of liraglutide or placebo and had at least one post-baseline assessment). For fasting insulin and lipids, data are geometric mean (CV).

<sup>a</sup>Race and ethnic group were self-reported. Individuals from France did not report race or ethnicity.

<sup>b</sup>Dyslipidemia was defined as LDL  $\geq$  160 mg/dL or triglycerides  $\geq$  150 mg/dL or HDL  $<$  40 mg/dL for males and  $<$  50 mg/dL for females. Hypertension was defined as systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg.

<sup>c</sup>Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events in exposed patients.

<sup>d</sup>In the Liraglutide 3.0 mg group, 423 patients were randomized and 422 were exposed. In the Liraglutide 1.8 mg group, 211 patients were randomized and 210 were exposed.



**Table 2–6 Mean changes in body weight-related endpoints at 56 week: Trial 1922**

|   | Lira 3.0 mg<br>FAS, N=412 |   | Lira 1.8 mg<br>FAS, N=204 |   | Placebo<br>FAS, N=211 |   | Treatment difference/<br>odds ratio: |                          |                        |
|---|---------------------------|---|---------------------------|---|-----------------------|---|--------------------------------------|--------------------------|------------------------|
|   | Baseline                  | Change<br>from<br>baseline<br>(LSMeans) | Baseline                  | Change<br>from<br>baseline<br>(LSMeans) | Baseline              | Change<br>from<br>baseline<br>(LSMeans) | Lira 3.0 mg vs. placebo,             | Lira 1.8 mg vs. placebo, | Lira 3.0 mg vs. 1.8 mg |
| Body weight (%) <sup>1)</sup>                             |                           | -5.93                                   |                           | -4.58                                   |                       | -1.98                                   | -3.97*                               | -2.62*                   | -1.35*                 |
| Body weight (kg)  | 105.6                     | -6.24                                   | 106.1                     | -4.79                                   | 106.7                 | -2.16                                   | -4.08*                               | -2.65*                   | -1.45*                 |
| % of patients losing ≥5% of<br>body weight <sup>2)</sup>  |                           | 49.8                                    |                           | 35.0                                    |                       | 13.5                                    | 6.39*                                | 3.69*                    | 1.84*                  |
| % of patients losing >10% of<br>body weight <sup>3)</sup> |                           | 22.9                                    |                           | 13.3                                    |                       | 4.2                                     | 6.81*                                | 3.84*                    | 1.85*                  |
| BMI (kg/m <sup>2</sup> )                                  | 37.1                      | -2.24                                   | 37.0                      | -1.68                                   | 37.4                  | -0.74                                   | -1.50*                               | -0.95*                   | -0.56*                 |
| Waist circumference (cm)                                  | 118.1                     | -6.02                                   | 117.7                     | -4.85                                   | 117.3                 | -2.81                                   | -3.21*                               | -2.06*                   | -1.16*                 |

\*p<0.05; <sup>1-3)</sup> confirmatory co-primary endpoint shown in order of testing. Mean changes are analyzed by ANCOVA (presented with treatment differences) and categorical changes by logistic regression (presented with odds ratios).

BMI: body mass index. FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.) LS: least square. N: number of patients.

**Table 2–7 Mean changes in secondary parameters at week 56: Trial 1922**

|   | Lira 3. 0mg<br>FAS, N=412 |   | Lira 1.8mg<br>FAS, N=204 |   | Placebo<br>FAS, N=211 |   | Treatment difference<br>or odds ratio (HbA <sub>1c</sub><br>≤6.5%)<br>Lira 3.0 mg vs. placebo,<br>Lira 1.8 mg vs. placebo,<br>Lira 3.0 mg vs. 1.8 mg |        |        |
|---|---------------------------|---|--------------------------|---|-----------------------|---|--|--------|--------|
|   | Baseline                  | Change<br>from<br>baseline<br>(LSMeans)       | Baseline                 | Change<br>from<br>baseline<br>(LSMeans)       | Baseline              | Change<br>from<br>baseline<br>(LSMeans)       |  |        |        |
| <b>Glycemic control parameters</b>      |                           |   |                          |   |                       |   |  |        |        |
| HbA <sub>1c</sub> (%-points)            | 7.9                       | -1.32   | 8.0                      | -1.13   | 7.9                   | -0.38   | -0.93*   | -0.74* | -0.19* |
| % patients with HbA <sub>1c</sub> ≤6.5% |                           | 56.7  |                          | 44.9  |                       | 12.0  | 9.6*   | 6.0*   | 1.6*   |
| FPG (mg/dL)                             | 158.4                     | -34.1   | 160.3                    | -25.2   | 155.5                 | -2.2  | -31.9*   | -23.0  | -8.8   |
| <b>Vital signs</b>                      |                           |   |                          |   |                       |   |  |        |        |
| Systolic BP (mmHg)                      | 128.9                     | -2.98   | 130.5                    | -3.07   | 129.2                 | -0.40   | -2.58*   | -2.68* | 0.09   |
| Diastolic BP (mmHg)                     | 79.0                      | -1.00   | 80.1                     | -0.82   | 79.3                  | -0.63   | -0.37  | -0.19  | -0.17  |
| <b>Patient reported outcome</b>         |                           |   |                          |   |                       |   |  |        |        |
| IWQoL-Lite (total score)                | 72.6                      | 11.15   | 74.6                     | 9.19  | 75.7                  | 8.41  | 2.75*  | 0.78   | 1.96   |
| DTSQ (total score)                      | 27.6                      | 4.08  | 28.0                     | 3.77  | 27.9                  | 2.63  | 1.44*  | 1.14   | 0.30   |
|   | Baseline                  | Relative<br>change<br>from<br>baseline<br>(%) | Baseline                 | Relative<br>change<br>from<br>baseline<br>(%) | Baseline              | Relative<br>change<br>from<br>baseline<br>(%) | <b>Relative difference</b><br>Lira 3.0 mg vs. placebo,<br>Lira 1.8 mg vs. placebo,<br>Lira 3.0 mg vs. 1.8 mg   |        |        |
| <b>Lipids</b>                           |                           |   |                          |   |                       |   |  |        |        |
| HDL (mg/dL)                             | 45.2                      | 4.70  | 44.5                     | 4.45  | 45.4                  | 1.93  | 3*   | 2      | 1      |
| LDL (mg/dL)                             | 86.4                      | 0.58  | 91.5                     | -3.07   | 85.2                  | 5.02  | -2   | -5     | 3      |
| VLDL (mg/dL)                            | 31.8                      | -14.10  | 33.0                     | -8.14   | 31.1                  | 0.53  | -13*   | -6     | -7*    |
| Triglycerides (mg/dL)                   | 162                       | -14.68  | 170                      | -9.45   | 158                   | 0.41  | -14*   | -7     | -7*    |
| Total cholesterol (mg/dL)               | 171.0                     | -1.46   | 178.3                    | -2.20   | 169.4                 | 3.80  | -4*  | -3     | -1     |
| Free fatty acids (mmol/L)               | 0.56                      | -13.57  | 0.56                     | -12.66  | 0.57                  | -9.02   | -6   | -5     | -1     |
| <b>Cardiovascular biomarkers</b>        |                           |   |                          |   |                       |   |  |        |        |
| hsCRP (mg/L)                            | 3.44                      | -33.51  | 3.92                     | -33.34  | 3.64                  | -10.45  | -27*   | -25*   | -3     |
| PAI-1 (IU/mL)                           | 21.4                      | –   | 20.2                     | –   | 20.3                  | –   | -24*   | -16    | -10    |
| Fibrinogen (g/L)                        | 4.13                      | 4.54  | 4.28                     | 1.68  | 4.27                  | -3.11   | 5*   | 4      | 1      |
| Adiponectin (µg/mL)                     | 5.6                       | 6.6   | 5.9                      | 3.5   | 5.6                   | 1.3   | 6  | 7      | -1     |
| Albumin/creatinine ratio (mg/mmol/L)    | 1.0                       | -18.36  | 1.1                      | -10.79  | 1.0                   | -2.34   | -20*   | -8     | -14    |

\*p&lt;0.05

PAI-1 was analyzed using different methods at baseline and week 56, therefore relative changes cannot be calculated.  
DTSQ: Diabetes Treatment Satisfaction Questionnaire. FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.)

HDL: high-density lipoprotein. hsCRP: high-sensitivity C-reactive protein. IWQoL-Lite: Impact of Weight on Quality of Life-Lite questionnaire. LDL: low-density lipoprotein. LS: least square. N: number of patients. PAI-1: plasminogen activator inhibitor-1. VLDL: very low density lipoprotein.

### 2.3 Trial 1923 (phase 3 weight maintenance trial in patients without type 2 diabetes)

**Table 2–8 Baseline characteristics of randomized patients by treatment: Trial 1923**

| Characteristic                            | Liraglutide 3.0 mg<br>(N=212) | Placebo<br>(N=210) |
|---|-------------------------------|--------------------|
| Sex – n (%)                               |                               |                    |
| Female                                    | 178 (84.0)                    | 165 (78.6)         |
| Age – years                               | 45.9 (11.9)                   | 46.5 (11.0)        |
| Race – n (%) <sup>a</sup>                 |                               |                    |
| White                                     | 170 (80.2)                    | 185 (88.1)         |
| Black or African American                 | 32 (15.1)                     | 24 (11.4)          |
| Asian                                     | 1 (0.5)                       | 0 (0.0)            |
| American Indian or Alaska Native          | 0 (0.0)                       | 0 (0.0)            |
| Native Hawaiian or other Pacific Islander | 2 (0.9)                       | 0 (0.0)            |
| Other                                     | 7 (3.3)                       | 1 (0.5)            |
| Ethnic group – n (%) <sup>a</sup>         |                               |                    |
| Hispanic or Latino                        | 17 (8.0)                      | 11 (5.2)           |
| Weight – kg                               |                               |                    |
| At screening                              | 106.7 (21.8)                  | 105.0 (22.4)       |
| At randomization                          | 100.4 (20.8)                  | 98.7 (21.2)        |
| BMI (kg/m <sup>2</sup> )                  |                               |                    |
| At screening                              | 38.2 (6.2)                    | 37.5 (6.2)         |
| At randomization                          | 36.0 (5.9)                    | 35.2 (5.9)         |
| BMI categories – n (%) at screening       |                               |                    |
| 27-29.9 – overweight                      | 3 ( 1.4)                      | 6 ( 2.9)           |
| 30-34.9 – obese class I                   | 69 (32.5)                     | 80 (38.1)          |
| 35-39.9 – obese class II                  | 69 (32.5)                     | 58 (27.6)          |
| >40 – obese class III                     | 71 (33.5)                     | 66 (31.4)          |
| Waist circumference (cm)                  | 109.6 (15.3)                  | 107.9 (15.3)       |
| HbA <sub>1c</sub> – %                     | 5.6 (0.4)                     | 5.5 (0.4)          |
| HbA <sub>1c</sub> categories – n (%)      |                               |                    |
| <5.5                                      | 83 (39.2)                     | 88 (41.9)          |
| ≥5.5                                      | 129 (60.8)                    | 122 (58.1)         |
| Fasting glucose – mg/dL                   | 97.5                          | 98.5               |
| Fasting insulin – μIU/mL                  | 9.32                          | 9.18               |
| Blood pressure – mm Hg                    |                               |                    |
| Systolic                                  | 116.7 (12.6)                  | 117.7 (10.8)       |
| Diastolic                                 | 74.3 ( 9.0)                   | 75.8 ( 7.2)        |
| Cholesterol – mg/dL                       |                               |                    |
| Total                                     | 170.1                         | 176.3              |
| LDL                                       | 95.1                          | 99.2               |
| HDL                                       | 44.8                          | 44.9               |
| VLDL                                      | 26.4                          | 27.9               |
| Triglycerides – mg/dL                     | 98.9                          | 105.0              |

| Characteristic                               | Liraglutide 3.0 mg<br>(N=212) | Placebo<br>(N=210) |
|--|-------------------------------|--------------------|
| Pre-diabetes – n (%) <sup>b</sup>            | 141 ( 66.5)                   | 131 ( 62.4)        |
| Dyslipidemia – n (%)                         | 59 ( 27.8)                    | 65 ( 31.0)         |
| Hypertension – n (%)                         | 70 ( 33.0)                    | 60 ( 28.6)         |
| Dyslipidemia and hypertension – n (%)        | 36 ( 17.0)                    | 29 ( 13.8)         |
| Treated with anti-hypertensive drugs – n (%) | 62 (30.0)                     | 53 (25.7)          |
| Treated with lipid-lowering drugs – n (%)    | 32 (15.5)                     | 33 (16.0)          |
| Cardiovascular disease – n (%) <sup>c</sup>  | 17 ( 8.0)                     | 24 ( 11.4)         |

Data are mean (SD) or number (%). Data for fasting glucose, fasting insulin, blood pressure and lipids are reported for the full analysis set (randomized individuals who were exposed to at least one dose of liraglutide or placebo and had at least one post-baseline assessment). For fasting insulin and lipids, data are geometric mean.

BMI: body mass index. HDL: high-density lipoprotein. LDL: low-density lipoprotein. VLDL: very low density lipoprotein.

<sup>a</sup>Race and ethnic group were self-reported.

<sup>b</sup>Pre-diabetes was defined according to ADA 2010 criteria. Dyslipidemia was defined as LDL cholesterol  $\geq 160$  mg/dl, triglycerides  $\geq 150$  mg/dl, or HDL cholesterol  $< 40$  mg/dl for males and  $< 50$  mg/dl for females. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg.

<sup>c</sup>Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events in exposed patients.

**Table 2–9 Changes during low-calorie dietary run-in: Trial 1923 All Randomized Patients**

|                                 | Run-in         | Baseline       | Change from Run-in | Relative Change from Run-in (%) |
|---------------------------------|----------------|----------------|--------------------|---------------------------------|
| Body weight (kg)                | 105.85 (22.19) | 99.55 (20.96)  | -6.29 (1.57)       | -5.95 (7.08)                    |
| FPG (mg/dL)                     | 101.79 (10.23) | 98.03 (9.48)   | -3.76 (8.85)       | -3.28 (8.43)                    |
| HbA <sub>1c</sub> (%)           | 5.55 (0.41)    | 5.55 (0.39)    | 0.00 (0.25)        | 0.09 (60.64)                    |
| Insulin (uIU/mL)                | 15.79 (9.98)   | 11.23 (7.30)   | -4.57 (7.63)       | -19.22 (47.60)                  |
| Beta-cell function, HOMA-B (%)  | 144.90 (91.30) | 114.40 (78.33) | -31.25 (72.34)     | -21.56 (79.24)                  |
| Insulin resistance, HOMA-IR (%) | 3.89 (2.64)    | 2.65 (1.82)    | -1.23 (2.05)       | -31.64 (77.74)                  |
| Waist circumference (cm)        | 113.51 (15.45) | 108.58 (15.24) | -4.93 (4.99)       | -4.34 (32.30)                   |
| BMI (kg/m <sup>2</sup> )        | 37.85 (6.20)   | 35.60 (5.88)   | -2.25 (0.47)       | -5.94 (7.57)                    |
| Diastolic BP (mmHg)             | 78.61 (8.01)   | 75.06 (8.18)   | -3.55 (7.79)       | -4.51 (97.26)                   |
| Systolic BP (mmHg)              | 122.95 (12.69) | 117.23 (11.73) | -5.73 (11.05)      | -4.66 (87.14)                   |
| Pulse (beats/minute)            | 72.22 (9.49)   | 68.77 (9.12)   | -3.44 (8.81)       | -4.77 (92.78)                   |
| HDL-Cholesterol (mg/dL)         | 50.68 (12.89)  | 46.32 (11.84)  | -4.36 (6.28)       | -7.79 (12.09)                   |
| LDL-Cholesterol (mg/dL)         | 113.77 (29.05) | 101.17 (28.79) | -12.65 (19.83)     | -10.22 (16.69)                  |
| VLDL-Cholesterol (mg/dL)        | 29.89 (12.61)  | 28.94 (10.75)  | -0.93 (9.69)       | 6.07 (46.91)                    |
| Total Cholesterol (mg/dL)       | 194.34 (35.78) | 176.43 (34.76) | -17.94 (23.08)     | -8.72 (11.18)                   |
| Triglycerides (mg/dL)           | 134.89 (74.70) | 111.75 (53.45) | -22.96 (50.96)     | -8.93 (37.60)                   |
| Free fatty acids (mg/dL)        | 13.48 (6.06)   | 15.02 (6.15)   | 1.55 (6.97)        | 30.70 (81.01)                   |
| Adiponectin (μg/mL)             | 6.34 (4.37)    | 5.94 (3.98)    | -0.40 (2.10 )      | -6.34 (48.19)                   |
| hs-CRP (mg/L)                   | 1.63 (2.03)    | 1.41 (1.50)    | -0.21 (1.60)       | 5.48 (135.97)                   |
| Fibrinogen (g/L)                | 3.97 (1.02)    | 3.82 (0.90)    | -0.15 (0.93)       | -3.81 (91.25)                   |

Data are mean (SD) and for the 422 patients that were subsequently randomized to treatment.

HDL: high-density lipoprotein. hsCRP: high-sensitivity C-reactive protein. LDL: low-density lipoprotein. VLDL: very low density lipoprotein.

**Table 2–10 Mean changes in body weight-related endpoints at 56 week: Trial 1923**

|   | Lira 3.0 mg<br>FAS, N=207 |   | Placebo<br>FAS, N=206 |   | Treatment<br>difference/<br>odds ratio:<br>Lira 3.0 mg<br>vs. placebo |
|---|---------------------------|---|-----------------------|---|---|
|   | Baseline                  | Change<br>from<br>baseline<br>(LSMeans) | Baseline              | Change<br>from<br>baseline<br>(LSMeans) |   |
| Body weight (%) <sup>1)</sup>   |                           | -6.26                                   |                       | -0.20                                   | -6.06*  |
| Body weight (kg)  | 100.4                     | -6.01                                   | 98.7                  | -0.15                                   | -5.86*  |
| Maintained the $\geq 5\%$ weight loss achieved<br>during LCD run-in (% of patients) <sup>2)</sup> |                           | 81.4                                    |                       | 48.9                                    | 4.82*   |
| % of patients losing $\geq 5\%$ of body weight <sup>3)</sup>                                      |                           | 50.7                                    |                       | 21.3                                    | 3.81*   |
| % of patients losing $>10\%$ of body weight   |                           | 27.4                                    |                       | 6.8                                     | 5.14*   |
| BMI (kg/m <sup>2</sup> )  | 36.0                      | -2.07                                   | 35.2                  | -0.02                                   | -2.05*  |
| Waist circumference (cm)  | 109.6                     | -4.68                                   | 107.9                 | -1.19                                   | -3.49*  |

\* $p < 0.05$ ; <sup>1-3)</sup> Confirmatory co-primary endpoint shown in order of testing. Mean changes are analyzed by ANCOVA (presented with treatment differences) and categorical changes by logistic regression (presented with odds ratios). BMI: body mass index. FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.) LS: least square. N: number of patients.

**Table 2–11 Mean changes in secondary parameters at week 56: Trial 1923**

|                                    | Lira 3.0 mg<br>FAS, N=207 |   | Placebo<br>FAS, N=206 |   | Treatment<br>difference                              |
|------------------------------------|---------------------------|---|-----------------------|---|--|
|                                    | Baseline                  | Change<br>from<br>baseline<br>(LSMeans) | Baseline              | Change<br>from<br>baseline<br>(LSMeans) | Lira 3.0 mg<br>vs. placebo                           |
| <b>Glycemic control parameters</b> |                           |   |                       |   |  |
| HbA <sub>1c</sub> (%-points)       | 5.6                       | -0.14                                   | 5.6                   | 0.13                                    | -0.27*   |
| FPG (mg/dL)                        | 97.5                      | -9.57                                   | 98.5                  | -2.73                                   | -6.84  |
| <b>Vital signs</b>                 |                           |   |                       |   |  |
| Systolic BP (mmHg)                 | 116.7                     | 0.13                                    | 117.7                 | 2.86                                    | -2.72*   |
| Diastolic BP (mmHg)                | 74.3                      | 1.13                                    | 75.8                  | 1.47                                    | -0.33  |
|                                    | Baseline                  | Relative<br>change from<br>baseline (%) | Baseline              | Relative<br>change from<br>baseline (%) | Relative<br>difference<br>Lira 3.0 mg<br>vs. placebo |
| <b>Lipids</b>                      |                           |   |                       |   |  |
| HDL (mg/dL)                        | 44.8                      | 12.66                                   | 44.9                  | 11.94                                   | 0.6  |
| LDL (mg/dL)                        | 95.1                      | 7.80                                    | 99.2                  | 11.51                                   | -3.3   |
| VLDL (mg/dL)                       | 26.4                      | -24.01                                  | 27.9                  | -20.20                                  | -4.8   |
| Triglycerides (mg/dL)              | 98.9                      | -4.69                                   | 105.0                 | 4.25                                    | -8.6*  |
| Total cholesterol (mg/dL)          | 170.1                     | 4.36                                    | 176.3                 | 6.58                                    | -2.1   |
| <b>Cardiovascular biomarkers</b>   |                           |   |                       |   |  |
| hsCRP (mg/L)                       | 0.96                      | -33.21                                  | 0.76                  | -8.49                                   | -27.0*   |
| Fibrinogen (g/L)                   | 3.7                       | 1.52                                    | 3.7                   | -2.25                                   | 3.9  |
| Adiponectin (µg/mL)                | 4.7                       | 33.89                                   | 5.1                   | 28.24                                   | 4.4  |

\*p&lt;0.05

FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.)

HDL: high-density lipoprotein. hsCRP: high-sensitivity C-reactive protein. LDL: low-density lipoprotein. VLDL: very low density lipoprotein. LS: least square. N: number of patients.



## 2.4 Trial 3970 (phase 3 trial in patients with obstructive sleep apnea)

**Table 2–12 Baseline characteristics of randomized patients by treatment: Trial 3970**

| Characteristic                              | Liraglutide 3.0 mg<br>(N=180) | Placebo<br>(N=179) |
|---|-------------------------------|--------------------|
| Sex – n (%)                                 |                               |                    |
| Female                                      | 51 (28.3)                     | 50 (27.9)          |
| Age – years                                 | 48.6 ( 9.9)                   | 48.4 ( 9.5)        |
| Race – n (%) <sup>a</sup>                   |                               |                    |
| White                                       | 130 (72.2)                    | 135 (75.4)         |
| Black or African American                   | 33 (18.3)                     | 36 (20.1)          |
| Asian                                       | 13 ( 7.2)                     | 3 ( 1.7)           |
| American Indian or Alaska Native            | -                             | -                  |
| Native Hawaiian or other Pacific Islander   | 1 ( 0.6)                      | 2 ( 1.1)           |
| Other                                       | 3 ( 1.7)                      | 3 ( 1.7)           |
| Ethnic group – n (%) <sup>a</sup>           |                               |                    |
| Hispanic or Latino                          | 19 ( 10.6)                    | 24 ( 13.4)         |
| Weight – kg                                 | 116.5 (23.0)                  | 118.7 (25.4)       |
| BMI (kg/m <sup>2</sup> )                    | 38.9 ( 6.4)                   | 39.4 (7.4)         |
| BMI categories – n (%)                      |                               |                    |
| 27-29.9 – overweight                        | 0 ( 0.0)                      | 1 ( 0.6)           |
| 30-34.9 – obese class I                     | 58 ( 32.2)                    | 51 ( 28.5)         |
| 35-39.9 – obese class II                    | 59 ( 32.8)                    | 62 ( 34.6)         |
| >40 – obese class III                       | 63 ( 35.0)                    | 65 ( 36.3)         |
| Waist circumference (cm)                    | 122.3 (14.5)                  | 122.7 (15.0)       |
| HbA <sub>1c</sub> – %                       | 5.7 ( 0.4)                    | 5.6 ( 0.4)         |
| Fasting glucose – mg/dL                     | 97.1 ( 11.1)                  | 97.0 ( 15.7)       |
| Blood pressure – mm Hg                      |                               |                    |
| Systolic                                    | 125.8 ( 11.5)                 | 127.1 ( 12.3)      |
| Diastolic                                   | 81.2 ( 7.6)                   | 82.2 ( 8.8)        |
| Cholesterol – mg/dL                         |                               |                    |
| Total                                       | 190.4                         | 191.5              |
| LDL   | 111.6                         | 111.4              |
| HDL   | 45.7                          | 44.5               |
| VLDL  | 28.0                          | 28.9               |
| Triglycerides – mg/dL                       | 140.3                         | 144.7              |
| Pre-diabetes – n (%) <sup>b</sup>           | 115 ( 63.9)                   | 112 ( 62.6)        |
| Dyslipidemia – n (%)                        | 65 ( 36.1)                    | 55 ( 30.7)         |
| Hypertension – n (%)                        | 75 ( 41.7)                    | 77 ( 43.0)         |
| Dyslipidemia and hypertension – n (%)       | 41 ( 22.8)                    | 35 ( 19.6)         |
| Cardiovascular disease – n (%) <sup>c</sup> | 5 ( 2.8)                      | 16 ( 8.9)          |

Data are mean (SD) or number (%). Data for blood pressure and lipids are reported for the full analysis set (randomized individuals who were exposed to at least one dose of liraglutide or placebo and had at least one post-baseline assessment). Data for lipids are geometric means.



BMI: body mass index. HDL: high-density lipoprotein. LDL: low-density lipoprotein. VLDL: very low density lipoprotein.

<sup>a</sup>Race and ethnic group were self-reported. Individuals from France did not report race or ethnicity.

<sup>b</sup>Pre-diabetes was defined according to ADA 2010 criteria. Dyslipidemia was defined as LDL cholesterol  $\geq 160$  mg/dl, triglycerides  $\geq 150$  mg/dl, or HDL cholesterol  $< 40$  mg/dl for males and  $< 50$  mg/dl for females. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg.

<sup>c</sup>Based on standardized MedDRA queries ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events in exposed patients.

**Table 2–13 Mean changes in body weight-related endpoints at 32 week: Trial 3970**

|  | Lira 3.0 mg<br>FAS, N=180 |   | Placebo<br>FAS, N=179 |   | Treatment<br>difference/<br>odds ratio<br>Lira 3.0 mg<br>vs. placebo |
|--|---------------------------|---|-----------------------|---|--|
|  | Baseline                  | Change<br>from<br>baseline<br>(LSMeans) | Baseline              | Change<br>from<br>baseline<br>(LSMeans) |  |
| Body weight (%)                                | -                         | -5.73                                   | -                     | -1.58                                   | -4.15*   |
| Body weight (kg)                               | 116.5                     | -6.76                                   | 118.7                 | -1.84                                   | -4.92*   |
| % of patients losing $\geq 5\%$ of body weight | -                         | 46.4                                    | -                     | 18.1                                    | 3.92*  |
| % of patients losing $> 10\%$ of body weight   | -                         | 22.4                                    | -                     | 1.5                                     | 18.96*   |
| BMI ( $\text{kg}/\text{m}^2$ )                 | 38.9                      | -2.21                                   | 39.4                  | -0.62                                   | -1.59*   |
| Waist circumference (cm)                       | 122.3                     | -6.35                                   | 122.7                 | -3.14                                   | -3.22*   |

\* $p < 0.05$ . Mean changes are analyzed by ANCOVA (presented with treatment differences) and categorical changes by logistic regression (presented with odds ratios).

BMI: body mass index. FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.) LS: least square. N: number of patients.

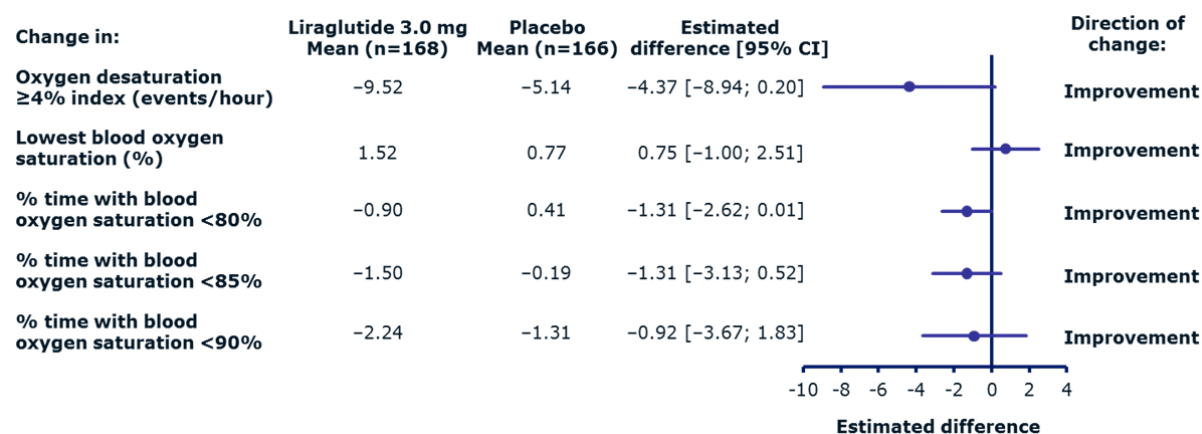
**Table 2–14 Mean changes in secondary parameters at week 32: Trial 3970**

|                                    | Lira 3.0 mg<br>FAS, N=180 |   | Placebo<br>FAS, N=179 |   | Treatment<br>difference<br>Lira 3.0 mg<br>vs. placebo |
|------------------------------------|---------------------------|---|-----------------------|---|---|
|                                    | Baseline                  | Change from<br>baseline<br>(LSMeans)    | Baseline              | Change from<br>baseline<br>(LSMeans)    |   |
| <b>Glycemic control parameters</b> |                           |   |                       |   |   |
| HbA <sub>1c</sub> (%-points)       | 5.7                       | -0.36                                   | 5.6                   | -0.17                                   | -0.19*  |
| FPG (mg/dL)                        | 97.1                      | -2.52                                   | 97.0                  | 2.90                                    | -5.42*  |
| <b>Vital signs</b>                 |                           |   |                       |   |   |
| Systolic BP (mmHg)                 | 125.8                     | -3.74                                   | 127.1                 | 0.38                                    | -4.12*  |
| Diastolic BP (mmHg)                | 81.2                      | -1.03                                   | 82.2                  | -0.06                                   | -0.97   |
| <b>Patient reported outcome</b>    |                           |   |                       |   |   |
| SF-36 (overall physical score)     | 46.5                      | 2.84                                    | 47.0                  | 1.99                                    | 0.86  |
| SF-36 (overall mental score)       | 53.0                      | 1.47                                    | 52.8                  | 0.88                                    | 0.59  |
| FOSQ (total score)                 | 17.1                      | 1.29                                    | 17.2                  | 1.07                                    | 0.21  |
| ESS (total score)                  | 9.2                       | -2.70                                   | 10.3                  | -2.16                                   | -0.54   |
|                                    | Baseline                  | Relative<br>change from<br>baseline (%) | Baseline              | Relative<br>change from<br>baseline (%) | Relative<br>difference<br>Lira 3.0 mg vs.<br>placebo  |
| <b>Lipids</b>                      |                           |   |                       |   |   |
| HDL (mg/dL)                        | 45.7                      | 1.45                                    | 44.5                  | 1.56                                    | -0.1  |
| LDL (mg/dL)                        | 111.6                     | -5.00                                   | 111.4                 | -0.86                                   | -4.2  |
| VLDL (mg/dL)                       | 28.0                      | -9.44                                   | 28.9                  | -4.57                                   | -5.1  |
| Triglycerides (mg/dL)              | 140.3                     | -9.41                                   | 144.7                 | -4.09                                   | -5.5  |
| Total cholesterol (mg/dL)          | 190.4                     | -3.86                                   | 191.5                 | -1.43                                   | -2.5  |
| <b>Cardiovascular biomarkers</b>   |                           |   |                       |   |   |
| hsCRP (mg/L)                       | 3.7                       | -20.62                                  | 3.6                   | -8.51                                   | -13.2   |
| Albumin/creatinine ratio (mg/g)    | 3.4                       | 8.39                                    | 3.7                   | 6.81                                    | 1.5   |

\*p&lt;0.05

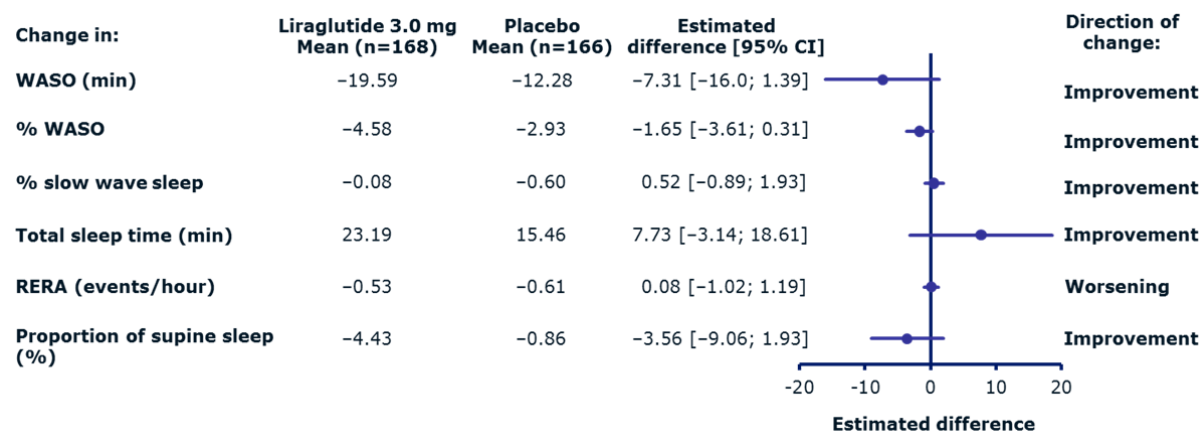
FAS: full analysis set (defined as all randomized patients who were exposed to at least one dose of trial product and had at least one post-baseline assessment of any efficacy endpoint.)

LS: least square. N: number of patients. SF-36: Short Form (36) Health Survey. FOSQ: Functional Outcomes of Sleep Questionnaire. ESS: Epworth Sleepiness Scale. HDL: high-density lipoprotein. hsCRP: high-sensitivity C-reactive protein. LDL: low-density lipoprotein. VLDL: very low density lipoprotein.



Data are estimated means and treatment differences for the full analysis set with last observation carried forward imputation. The panel at the right illustrates the estimated treatment difference and the 95% confidence interval.

**Figure 2–1 Change from baseline in parameters related to oxygen saturation after 32 weeks: Trial 3970**



Data are estimated means and treatment differences for the full analysis set with last observation carried forward imputation. The panel at the right illustrates the estimated treatment effect and the 95% confidence interval. RERA: respiratory event related arousals. WASO: wake time after sleep onset.

**Figure 2–2 Change from baseline in parameters related to sleep architecture after 32 weeks: Trial 3970**

## 2.5 Confirmatory testing of prespecified secondary endpoints

**Table 2–15 Confirmatory secondary endpoints tested in hierarchical manner in the pool of all 5 trials, compared with results of the same endpoints in each individual trial**

| Parameter                       | Trial 1839<br>Phase 3 patients<br>without T2DM | Trial 1923<br>Phase 3 weight<br>maintenance | Trial 1922<br>Phase 3 patients<br>with T2DM | Trial 3970<br>Phase 3 patients<br>with OSA | Trial 1807<br>Phase 2 | All trials pooled<br>Estimated mean<br>(95% CI) | All trials<br>pooled<br>P value |
|---------------------------------|--|---|---|--|-----------------------|---|---------------------------------|
| Waist circumference (cm)        | -4.20*   | -3.49*                                      | -3.21*                                      | -3.22*                                     | -4.72*                | -3.98 (-4.4; -3.6)                              | p<0.0001                        |
| HbA <sub>1c</sub> (%-points)    | -0.23*   | -0.27*                                      | -0.93*                                      | -0.19*                                     | -0.26*                | -0.23 a) (-0.25; -0.21)                         | p<0.0001                        |
| Fasting plasma glucose (mg/dL)  | -6.90*   | -6.84*                                      | -31.92*                                     | -5.42*                                     | -8.57*                | -6.88 a) (-7.43; -6.32)                         | p<0.0001                        |
| Systolic blood pressure (mmHg)  | -2.82*   | -2.72*                                      | -2.58*                                      | -4.12*                                     | -3.43*                | -2.93 (-3.54; -2.31)                            | p<0.0001                        |
| Triglycerides (%)#              | 0.907*   | 0.914*                                      | 0.863*                                      | 0.945                                      | 0.891*                | 0.904 (0.885; 0.923)                            | p<0.0001                        |
| LDL cholesterol (%)#            | 0.976*   | 0.967                                       | 0.978                                       | 0.958                                      | 0.961                 | 0.973 (0.96; 0.99)                              | p<0.0001                        |
| Total cholesterol (%)#          | 0.977*   | 0.979                                       | 0.964*                                      | 0.975                                      | 0.971                 | 0.975 (0.967; 0.983)                            | p<0.0001                        |
| SF-36 (physical function score) | 1.57 *   | NA  | NA  | 0.45                                       | NA                    | 1.40 (0.91; 1.89)                               | p<0.0001                        |
| IWQoL-Lite (physical function)  | 4.80*  | NA  | 4.92*                                       | NA   | 4.45*                 | 4.81 (3.83; 5.79)                               | p<0.0001                        |
| SF-36 (general health score)    | 1.87*  | NA  | NA  | 1.41*                                      | NA                    | 1.77 (1.27; 2.27)                               | p<0.0001                        |
| HDL cholesterol (%)#            | 1.019*   | 1.006                                       | 1.028*                                      | 0.999                                      | 1.014                 | 1.017 (1.008; 1.026)                            | p=0.0003                        |
| Use of anti-hypertensive drug§  | 1.59*  | 1.97*                                       | 1.31  | NA   | NA                    | 1.61 (1.31; 1.97)                               | p<0.0001                        |
| Use of lipid lowering drug§     | 1.50*  | 2.14  | 2.16*                                       | NA   | NA                    | 1.59 (1.19; 2.11)                               | p=0.0014                        |
| Use of oral anti-diabetic drug§ | NA   | NA  | 5.08*                                       | NA   | NA                    | 5.08 (3.25; 7.94)                               | p<0.0001                        |
| Diastolic blood pressure (mmHg) | -0.89*   | -0.33                                       | -0.37                                       | -0.97                                      | -2.55*                | -0.84 (-1.27; -0.41)                            | p=0.0001                        |

Data are estimated treatment differences/ratios (ANCOVA) or odds ratios§ (logistic regression), \*p<0.05. #Treatment ratios from ANCOVA on a log scale. a) Excluding trial 1922 in T2DM. The confirmatory testing was done in the pooled group of all 5 trials, since the individual trials did not control for multiplicity for secondary endpoints, but are shown for comparison.

ANCOVA: analysis of covariance. CI: confidence interval. HDL: high-density lipoprotein. IWQoL-Lite: Impact of Weight on Quality of Life-Lite version. LDL: low-density lipoprotein. OSA: obstructive sleep apnea. SF-36: 36-item Short-Form health status survey. T2DM: type 2 diabetes mellitus.

## 3 Sensitivity analyses performed in the phase 2 and 3 clinical trials

### 3.1 Description of the sensitivity analyses performed

The sensitivity analyses performed in each of the clinical trials are shown in [Table 3–1](#) and described in more detail below.

#### **Completer analysis**

Analysis performed only on patients completing the trial with a valid end of trial efficacy measurement

#### **Per Protocol population**

Analysis on the per protocol population (defined prior to un-blinding). Only performed on 1807 and 1923.

#### **LOCF variants**

##### ***All available measurements:***

Includes all measurements taken whether they are fasting or non-fasting, after cessation of drug, after start of rescue medication for diabetes treatment (if required), or at the nominal week 56 follow-up visit for those patients who withdrew early from the trial.

##### ***All available measurements but excluding values after rescue medication:***

Similar to all available measurements, as described above, but excluding measurements after start of rescue medication for diabetes treatment (if required).

##### ***Baseline observation carried forward (BOCF) for patients without a valid post baseline measurement:***

The primary LOCF analysis only includes patients with a valid post baseline efficacy measurement and as such is a modified intention-to-treat (ITT) analysis. This brings it closer to a genuine ITT analysis by including all randomized patients.

#### **Multiple imputations**

Multiple imputations can be implemented in many ways. Here missing data after patient withdrawal were imputed based on how similar patients in the placebo arm have continued. Note that this applied for both groups, thus withdrawals in the liraglutide arm were regarded as placebo-treated patients, with similar profiles after withdrawal.

#### **Repeated measures**

All non-imputed measurements at planned post baseline visits were analyzed assuming an unstructured covariance matrix across visits (i.e., not imposing any structure on how observations

for the same patient over time were correlated), with testing performed at week 56. In this way, the repeated measures analyses were expected to accurately estimate what would have been the result at end of trial had all patients remained in the trial and on drug.

**Baseline observation carried forward (LOCF if last observation is weight gain)**

This very conservative sensitivity analysis assumes that any weight loss is regained by the end of the trial, regardless of the degree of weight loss achieved or when the patient dropped out. For example, even if a patient were to drop out at week 50 with a 12% weight loss, the weight loss at week 56 would be counted as 0. For any patient having a weight gain at time of withdrawal, that value was used in the analysis, as it was considered unlikely that withdrawing from treatment would lead to weight loss.

**3.2 Results of the sensitivity analyses**

Results of the sensitivity analysis on the primary endpoints are presented in [Table 3–2](#), [Table 3–3](#) and [Table 3–4](#).

**Table 3–1 Pre-specified (unless stated) sensitivity analyses of primary endpoints\* for the phase 2 and 3 trials**

| Endpoints                                   | Type of sensitivity analysis   | Trial   |
|---|--|---|
| 1, 2 and 3                                  | All measurements except values after rescue medication*                                | 1839, 1923 <sup>a</sup> , 1922, 1807 (52-week) <sup>b,c</sup>   |
| Mean and categorical weight loss endpoints* | All measurements including values after rescue medication*                             | 1839, 1922  |
|   | Multiple imputations   | 1839, 1923 <sup>a,b</sup> , 1922, 3970 <sup>b,d</sup> , 1807 (52-week) <sup>b,c</sup>                         |
|   | Completer population   | 1839, 1923 <sup>b</sup> , 1922, 3970 <sup>b,d</sup> , 1807 (52-week) <sup>b,c</sup>                           |
|   | Per protocol population  | 1923 <sup>a</sup>   |
|   | Baseline weight carried forward for patients without a valid post-baseline measurement | 1839, 1923 <sup>b</sup> , 1922, 3970 <sup>b,d</sup> , 1807 (52-week) <sup>b,c</sup>                           |
| 1 only                                      | Repeated measures analysis   | 1839, 1923 <sup>b</sup> , 1922, 3970 <sup>d</sup> , 1807 (52-week) <sup>b</sup>                               |
| Mean weight loss endpoint*                  | Baseline weight carried forward for all patient withdrawals                            | 1839 <sup>b</sup> , 1923 <sup>b</sup> , 1922 <sup>b</sup> , 3970 <sup>b</sup> , 1807 (52-week) <sup>b,c</sup> |
| 2 and 3 only                                | All patient withdrawals counted as non-responders                                      | 1839 <sup>b</sup> , 1923 <sup>b</sup> , 1922 <sup>b</sup> , 3970 <sup>b</sup>                                 |
| Categorical weight loss endpoints*          |  |   |
| 1 and 2 endpoints only*                     | Per protocol population  | 1807 <sup>b, e</sup>  |

\*1: Change in body weight. 2: Proportion of patients achieving  $\geq 5\%$  reduction of baseline body weight (5% responders). 3: Proportion of patients achieving  $>10\%$  reduction of baseline body weight (10% responders).

<sup>a</sup> For trial 1923, endpoint 2 was: Proportion of patients maintaining fasting weight loss achieved during low-calorie diet run-in. Endpoint 3 was: Proportion of patients achieving  $\geq 5\%$  reduction of baseline body weight; <sup>b</sup> Post-hoc sensitivity analyses performed in connection with analyses for the NDA; <sup>c</sup> Sensitivity analysis performed for primary endpoint change in body weight only in trial 1807 (52-week period). <sup>d</sup> For trial 3970, the primary endpoint was change in apnea/hypopnea index; <sup>e</sup> For trial 1807, endpoint 2 was: Proportion of patients achieving  $>5\%$  reduction of baseline body weight.



**Table 3–2 Sensitivity analysis results of primary endpoint: change in body weight (%)**

| <b>Trial</b>   | <b>1807</b>         |                       | <b>1839</b>         |                       | <b>1923</b>         |                       | <b>1922</b>         |                       | <b>3970</b>         |                       | <b>All trials</b>   |                       |
|--|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|
| Type of analysis   | N<br>Lira3.0<br>pbo | Treat.<br>diff. esti. | N<br>Lira3.0<br>pbo | Treat.<br>diff. esti. | N<br>Lira3.0<br>pbo | Treat.<br>diff. esti. | N<br>Lira3.0<br>pbo | Treat.<br>diff. esti. | N<br>Lira3.0<br>pbo | Treat.<br>diff. esti. | N<br>Lira3.0<br>pbo | Treat.<br>diff. esti. |
| <b>Primary analysis</b>                                    | 89<br>94            | -6.08*                | 2432<br>1220        | -5.39*                | 194<br>188          | -6.06*                | 411<br>210          | -3.97*                | 175<br>178          | -4.15*                | 3301<br>1890        | -5.18*                |
| <b>Sensitivity analysis</b>                                |                     |                       |                     |                       |                     |                       |                     |                       |                     |                       |                     |                       |
| Completer  | 65<br>62            | -6.55*                | 1781<br>798         | -5.69*                | 156<br>144          | -6.88*                | 317<br>116          | -3.95*                | 133<br>142          | -4.94*                | 2319<br>1120        | -5.64*                |
| BOCF for patients without a valid post baseline            | 93<br>98            | -5.74*                | 2481<br>1239        | -5.26*                | 212<br>210          | -5.52*                | 422<br>212          | -3.81*                | 179<br>179          | -4.03*                | 3387<br>1938        | -5.02*                |
| Only excluding values after rescue medication <sup>a</sup> | 92<br>98            | -6.07*                | 2437<br>1225        | -5.36*                | 207<br>206          | -5.56*                | 412<br>210          | -3.93*                | —<br>—              | —<br>—                | 3326<br>1918        | -5.12*                |
| All available measurements <sup>b</sup>                    | —                   | —                     | 2437<br>1225        | -5.35*                | —                   | —                     | 412<br>211          | -3.96*                | —                   | —                     | —                   | —                     |
| Multiple imputation  | 92<br>98            | -5.69*                | 2437<br>1225        | -5.52*                | 207<br>206          | -5.76*                | 412<br>211          | -4.00*                | 180<br>179          | -4.25*                | 3328<br>1919        | -5.23*                |
| Repeated measures analysis                                 | 89<br>94            | -6.85*                | 2432<br>1220        | -5.83*                | 193<br>185          | -6.18*                | 411<br>210          | -4.39*                | 173<br>174          | 4.55*                 | 2945<br>1646        | -5.57*                |
| Per protocol population                                    | 62<br>61            | -6.53*                | —<br>—              | —<br>—                | 148<br>141          | -6.76*                | —<br>—              | —<br>—                | —<br>—              | —<br>—                | —<br>—              | —<br>—                |
| BOCF (or last if higher than baseline) for all withdrawals | 93<br>98            | -4.72*                | 2481<br>1239        | -4.64*                | 212<br>210          | -5.24*                | 422<br>212          | -3.60*                | 179<br>179          | -3.65*                | 3387<br>1938        | -4.48*                |

\*P&lt;0.05. BOCF: Baseline observation carried forward.

<sup>a</sup>Similar to all available measurements, as described below, but excluding measurements after start of rescue medication for diabetes treatment (if required).<sup>b</sup>Includes all measurements taken whether they are fasting or non-fasting, after cessation of drug, after start of rescue medication for diabetes treatment (if required), or at the nominal week 56 follow-up visit for those patients who withdrew early from the trial.



**Table 3–3 Sensitivity analysis results of primary endpoint: proportion of patients achieving  $\geq 5\%$  loss of baseline weight (%)**

| <b>Trial</b>   | <b>1807</b>         |                      | <b>1839</b>         |                      | <b>1923</b>         |                      | <b>1922</b>         |                      | <b>3970</b>         |                      | <b>All trials</b>   |                      |
|--|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|
| Type of analysis   | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio |
| <b>Primary analysis</b>                                    | 89<br>94            | 8.47*                | 2432<br>1220        | 4.80*                | 194<br>188          | 3.81*                | 411<br>210          | 6.39*                | 175<br>178          | 3.92*                | 3301<br>1890        | 4.80*                |
| <b>Sensitivity analysis</b>                                |                     |                      |                     |                      |                     |                      |                     |                      |                     |                      |                     |                      |
| Completer  | 65<br>62            | 7.98*                | 1781<br>798         | 4.96*                | 156<br>144          | 4.30*                | 317<br>116          | 5.96*                | 133<br>142          | 4.59*                | 2319<br>1120        | 5.00*                |
| BOCF for patients without a valid post baseline            | 93<br>98            | 7.04*                | 2481<br>1239        | 4.64*                | 212<br>210          | 3.69*                | 422<br>212          | 6.34*                | 179<br>179          | 3.77*                | 3387<br>1938        | 4.61*                |
| Only excluding values after rescue medication <sup>a</sup> | 92<br>98            | 7.92*                | 2437<br>1225        | 4.71*                | 207<br>206          | 3.02*                | 412<br>210          | 7.15*                | —<br>—              | —<br>—               | 3326<br>1918        | 4.65*                |
| All available measurements <sup>b</sup>                    | —<br>—              | —<br>—               | 2437<br>1225        | 4.71*                | —<br>—              | —<br>—               | 412<br>211          | 6.66*                | —<br>—              | —<br>—               | —<br>—              | —<br>—               |
| Multiple imputation  | 92<br>98            | 5.02*                | 2437<br>1225        | 4.38*                | 207<br>206          | 3.42*                | 412<br>211          | 4.69*                | 180<br>179          | 4.18*                | 3328<br>1919        | 4.22*                |
| Withdrawals counted as non-responders                      | 93<br>98            | 4.20*                | 2481<br>1239        | 3.80*                | 212<br>210          | 3.79*                | 422<br>212          | 6.71*                | 179<br>179          | 3.47*                | 3322<br>1914        | 4.00*                |
| Per protocol population                                    | 62<br>61            | 7.48*                | —<br>—              | —<br>—               | 148<br>141          | 4.15*                | —<br>—              | —<br>—               | —<br>—              | —<br>—               | —<br>—              | —<br>—               |

\*P&lt;0.05. BOCF: Baseline observation carried forward.

<sup>a</sup>Similar to all available measurements, as described below, but excluding measurements after start of rescue medication for diabetes treatment (if required).<sup>b</sup>Includes all measurements taken whether they are fasting or non-fasting, after cessation of drug, after start of rescue medication for diabetes treatment (if required), or at the nominal week 56 follow-up visit for those patients who withdrew early from the trial.

**Table 3–4 Sensitivity analysis results of primary endpoint: proportion of patients achieving >10% loss of baseline weight (%)**

| <b>Trial</b>   | <b>1807</b>         |                      | <b>1839</b>         |                      | <b>1923</b>         |                      | <b>1922</b>         |                      | <b>3970</b>         |                      | <b>All trials</b>   |                      |
|--|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|
| Type of analysis   | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio | N<br>Lira3.0<br>pbo | Treat.<br>odds ratio |
| <b>Primary analysis</b>                                    | 89<br>94            | 5.21                 | 2432<br>1220        | 4.34*                | 194<br>188          | 5.14*                | 411<br>210          | 6.81*                | 175<br>178          | 18.96*               | 3301<br>1890        | 4.78*                |
| <b>Sensitivity analysis</b>                                |                     |                      |                     |                      |                     |                      |                     |                      |                     |                      |                     |                      |
| Completer  | 65<br>62            | 5.16*                | 1781<br>798         | 4.05*                | 156<br>144          | 5.65*                | 317<br>116          | 4.73*                | —<br>—              | —<br>—               | 2319<br>1120        | 4.24*                |
| BOCF for patients without a valid post baseline            | —                   | —                    | 2481<br>1239        | 4.27*                | —                   | —                    | 422<br>212          | 6.84*                | —                   | —                    | 3387<br>1938        | 4.70*                |
| Only excluding values after rescue medication <sup>a</sup> | —                   | —                    | 2437<br>1225        | 4.31*                | —                   | —                    | 412<br>210          | 6.18*                | —                   | —                    | 3326<br>1918        | 4.68*                |
| All available measurements <sup>b</sup>                    | —                   | —                    | 2437<br>1225        | 4.31*                | —                   | —                    | 412<br>211          | 5.68*                | —                   | —                    | —<br>—              | —<br>—               |
| Multiple imputation  | —                   | —                    | 2437<br>1225        | 4.01*                | —                   | —                    | 412<br>211          | 4.91*                | —                   | —                    | 3328<br>1919        | 4.25*                |
| All withdrawals counted as non-responders                  | —                   | —                    | 2432<br>1220        | 4.05*                | —                   | —                    | 412<br>211          | 5.94*                | —                   | —                    | 3322<br>1914        | 4.29*                |

\*P&lt;0.05. BOCF: Baseline observation carried forward.

<sup>a</sup>Similar to all available measurements, as described below, but excluding measurements after start of rescue medication for diabetes treatment (if required).<sup>b</sup>Includes all measurements taken whether they are fasting or non-fasting, after cessation of drug, after start of rescue medication for diabetes treatment (if required), or at the nominal week 56 follow-up visit for those patients who withdrew early from the trial.

## 4 Dose considerations

**Table 4–1 Mean and categorical weight loss by liraglutide dose at weeks 20 and 52: Trial 1807**

| <b>Trial 1807 (obese patients without T2DM)</b>   | <b>Placebo</b> | <b>1.2 mg</b> | <b>1.8 mg</b> | <b>2.4 mg</b> | <b>3.0 mg</b> | <b>p-value for</b>   |
|---|----------------|---------------|---------------|---------------|---------------|----------------------|
| <b>20 weeks</b>                                   | <b>N=98</b>    | <b>N=89</b>   | <b>N=89</b>   | <b>N=85</b>   | <b>N=88</b>   | <b>dose response</b> |
| Body weight change in %                           | -3.26          | -5.71*#       | -6.37*#       | -6.93*        | -7.95*        | 0.0003               |
| Body weight change in kg                          | -3.15          | -5.44*#       | -6.14*#       | -6.76*        | -7.66*        | 0.0003               |
| % of patients losing ≥5% of baseline body weight  | 31.0           | 56.2*#        | 56.3*#        | 63.9*#†       | 78.6*†        | 0.0015               |
| % of patients losing >10% of baseline body weight | 2.0            | 7.4#          | 19.3*         | 22.9*         | 27.9*         | 0.0007               |
| <b>52 weeks</b>                                   | <b>N=98</b>    | <b>N=89</b>   | <b>N=89</b>   | <b>N=85</b>   | <b>N=88</b>   |                      |
| Body weight change in %                           | -3.09          | -5.29*#       | -6.81*#       | -7.45*        | -9.18*†       | <0.0001              |
| Body weight change in kg                          | -3.00          | -4.97*#       | -6.50*#       | -7.21*        | -8.81*        | <0.0001              |
| % of patients losing ≥5% of baseline body weight  | 29.7           | 50.4*#        | 56.1*#        | 58.1*#        | 78.1*†        | 0.0004               |
| % of patients losing >10% of baseline body weight | 9.7            | 17.6*#        | 26.7*         | 29.1*         | 35.9*         | 0.0085               |

\*Indicates significantly better than placebo. #Indicates 3.0 mg was significantly better. †Achieved FDA benchmark for weight loss.

Data are estimated means from a *post hoc* ANCOVA (mean data) or logistic regression (categorical data) with last observation carried forward imputation.

**Table 4–2 Change from baseline in secondary endpoints by liraglutide dose: Trial 1807**

| <b>Trial 1807 (obese patients without T2DM)</b> | <b>Placebo<br/>N=98</b> | <b>1.2 mg<br/>N=89</b> | <b>1.8 mg<br/>N=89</b> | <b>2.4 mg<br/>N=85</b> | <b>3.0 mg<br/>N=88</b> | <b>p-value for<br/>dose response</b> |
|---|-------------------------|------------------------|------------------------|------------------------|------------------------|--------------------------------------|
| <b>20 weeks</b>                                 |                         |                        |                        |                        |                        |                                      |
| HbA <sub>1c</sub> (%)                           | 0.02                    | -0.14*#                | -0.20*                 | -0.23*                 | -0.25*                 | <b>0.0005</b>                        |
| Fasting plasma glucose (mg/dL)                  | -1.32                   | -7.28*                 | -7.06*                 | -7.14*                 | -8.07*                 | 0.4892                               |
| Systolic blood pressure (mmHg)                  | -3.61                   | -5.30                  | -5.19                  | -8.41*                 | -6.42                  | 0.2077                               |
| Diastolic blood pressure (mmHg)                 | -0.80                   | -0.92                  | -1.45                  | -1.05                  | -2.63                  | 0.1644                               |
| HDL cholesterol (%)                             | 5.7                     | 7.4                    | 6.5                    | 4.8                    | 6.1                    | 0.4121                               |
| LDL cholesterol (%)                             | -2.7                    | -1.0                   | -0.4                   | -0.9                   | -2.6                   | 0.4001                               |
| VLDL cholesterol (%)                            | 7.0                     | -8.1                   | -4.8                   | -15.9                  | -6.6                   | 0.8679                               |
| Triglycerides (%)                               | 0.4                     | -0.3                   | -1.2                   | -7.5                   | -7.7                   | 0.0537                               |
| Total cholesterol (%)                           | 0.2                     | 1.7                    | 2.2                    | 0.8                    | -0.5                   | 0.1568                               |
| Free fatty acids (%)                            | -18.4                   | -19.7                  | -21.3                  | -13.7                  | -19.7                  | 0.6221                               |
| IWQoL-Lite total score                          | 5.06                    | 7.29#                  | 5.45#                  | 5.79#                  | 10.21*                 | 0.0538                               |
| physical function score                         | 7.02                    | 9.23#                  | 7.21#                  | 8.24#                  | 12.88*                 | <b>0.0370</b>                        |
| public distress score                           | 2.50                    | 4.10                   | 2.87                   | 2.57                   | 5.23                   | 0.5595                               |
| self-esteem score                               | 4.27                    | 6.91#                  | 6.01#                  | 7.30#                  | 12.87*                 | <b>0.0058</b>                        |
| sexual life score                               | 7.21                    | 8.84                   | 5.74                   | 2.70*#                 | 9.27                   | 0.7765                               |
| work score                                      | 1.20                    | 5.32*                  | 3.60                   | 3.72                   | 6.74*                  | 0.4966                               |

| <b>Trial 1807 (obese patients without T2DM)</b> | <b>Placebo<br/>N=98</b> | <b>1.2 mg<br/>N=89</b> | <b>1.8 mg<br/>N=89</b> | <b>2.4 mg<br/>N=85</b> | <b>3.0 mg<br/>N=88</b> | <b>p-value for<br/>dose response</b> |
|---|-------------------------|------------------------|------------------------|------------------------|------------------------|--------------------------------------|
| <b>52 weeks</b>                                 | <b>N=98</b>             | <b>N=89</b>            | <b>N=89</b>            | <b>N=85</b>            | <b>N=88</b>            |                                      |
| HbA <sub>1c</sub> (%)                           | -0.01                   | -0.13*#                | -0.22*                 | -0.23*                 | -0.27*                 | <b>0.0001</b>                        |
| Fasting plasma glucose (mg/dL)                  | 1.53                    | -3.55*#                | -6.24*                 | -5.45*                 | -7.04*                 | <b>0.0073</b>                        |
| Systolic blood pressure (mmHg)                  | -1.69                   | -4.23                  | -4.01                  | -7.05*                 | -5.12*                 | 0.2609                               |
| Diastolic blood pressure (mmHg)                 | 0.27                    | -1.17                  | -0.67                  | -0.99                  | -2.28*                 | 0.3076                               |
| HDL cholesterol (%)                             | 5.2                     | 6.1                    | 5.2                    | 6.1                    | 6.7                    | 0.7575                               |
| LDL cholesterol (%)                             | -8.7                    | -7.5                   | -6.6#                  | -8.6                   | -12.2                  | <b>0.0380</b>                        |
| VLDL cholesterol (%)†                           | 196.5                   | 149.4                  | 147.2                  | 161.5                  | 177.4                  | 0.4022                               |
| Triglycerides (%)                               | -1.9                    | -1.4#                  | -1.5#                  | -8.9                   | -12.6*                 | <b>0.0062</b>                        |
| Total cholesterol (%)                           | 2.1                     | 2.6                    | 3.8                    | 2.5                    | -0.8                   | 0.0547                               |
| Free fatty acids (%)                            | -27.3                   | -32.3                  | -26.3                  | -28.1                  | -26.8                  | 0.3606                               |
| IWQoL-Lite total score                          | 7.05                    | 8.14                   | 6.90#                  | 7.71#                  | 10.88*                 | 0.0755                               |
| physical function score                         | 7.84                    | 8.99                   | 8.73                   | 8.89                   | 12.29*                 | 0.1055                               |
| public distress score                           | 4.18                    | 5.30                   | 3.57                   | 3.60                   | 6.61                   | 0.4454                               |
| self-esteem score                               | 7.85                    | 7.60#                  | 7.82#                  | 9.84                   | 14.12*                 | <b>0.0048</b>                        |
| sexual life score                               | 8.83                    | 10.22                  | 6.68                   | 6.74                   | 8.70                   | 0.5505                               |
| work score                                      | 4.39                    | 7.78                   | 5.30                   | 4.67#                  | 8.61*                  | 0.7823                               |

\*Indicates significantly better than placebo. #Indicates 3.0 mg was significantly better. †Data for VLDL cholesterol at 52 weeks are based on estimates that are consistently elevated across groups.

Data are estimated means from a *post hoc* ANCOVA (mean data) or logistic regression (categorical data) with last observation carried forward imputation.

HDL: high-density lipoprotein. IWQoL-Lite: Impact of Weight on Quality of Life-Lite version. LDL: low-density lipoprotein. VLDL: very low density lipoprotein.

**Table 4-3 Change from baseline in secondary endpoints by liraglutide dose: Trial 1922**

|  | <b>Lira 3.0 mg, N=412 /<br/>Placebo, N=211</b> | <b>Lira 1.8 mg, N=204 /<br/>Placebo, N=211</b> | <b>Lira 3.0 mg, N=412 /<br/>Lira 1.8 mg, N=204</b> |
|--|--|--|--|
| HbA <sub>1c</sub> (%)                          | -1.32 / -0.38                                  | -1.13 / -0.38                                  | -1.32 / -1.13                                      |
| Treatment difference [95% CI]                  | -0.93 [-1.08 ; -0.78]                          | -0.74 [-0.91 ; -0.57]                          | -0.19 [-0.34 ; -0.04]                              |
| p-value  | p<0.0001                                       | p<0.0001                                       | p=0.01   |
| % of patients reaching HbA <sub>1c</sub> <7%   | 72.3 / 22.9                                    | 69.6 / 22.9                                    | 72.3 / 69.6  |
| Treatment odds ratio [95% CI]                  | 8.8 [ 5.7 ; 13.4]                              | 7.7 [ 4.8 ; 12.5]                              | 1.1 [0.76; 1.71]                                   |
| p-value  | p<0.0001                                       | p<0.0001                                       | p=0.53   |
| % of patients reaching HbA <sub>1c</sub> <6.5% | 56.7 / 12.0                                    | 44.9 / 12.0                                    | 56.7 / 44.9  |
| Treatment odds ratio [95% CI]                  | 9.6 [ 6.1 ; 15.3]                              | 6.0 [ 3.6 ; 10.0]                              | 1.6 [1.1; 2.3]                                     |
| p-value  | p<0.0001                                       | p<0.0001                                       | p=0.01   |
| Fasting plasma glucose (mg/dL)                 | -34.1 / -2.2                                   | -25.2 / -2.2                                   | -34.1 / -25.2                                      |
| Treatment difference [95% CI]                  | -31.9 [-38.1 ; -25.6]                          | -23.0 [-30.27 ; -15.8]                         | -8.8 [-15.1; -2.5]                                 |
| p-value  | p<0.0001                                       | p<0.0001                                       | p=0.0061   |
| Fasting pro-insulin to insulin ratio (%)       | -38.4 / -2.2                                   | -31.6 / -2.2                                   | -38.4 / -31.6                                      |
| Treatment difference [95% CI]                  | -37 [-42; -31]                                 | -28 [-36; -21]                                 | -12 [-19; -3]                                      |
| p-value  | p<0.0001                                       | p<0.0001                                       | p=0.0067   |
| HOMA-B (%)                                     | 94.3 / 9.1                                     | 71.3 / 9.1                                     | 94.3 / 71.3  |
| Treatment difference [95% CI]                  | 71 [52; 92]                                    | 53 [34; 74]                                    | 12 [0; 25]   |
| p-value  | p<0.0001                                       | p<0.0001                                       | p<0.0424   |
| HOMA-IR (%)                                    | -20.0 / -3.3                                   | -10.5 / -3.3                                   | -20.0 / -10.5                                      |
| Treatment difference [95% CI]                  | -16 [-25; -6]                                  | -7 [-18; 7]                                    | -10 [-20; 0]                                       |
| p-value  | p=0.0031                                       | p=0.3202                                       | p<0.0496   |
| HDL cholesterol (%)                            | 4.70 / 1.93                                    | 4.45 / 1.93                                    | 4.70 / 4.45  |
| Treatment difference [95% CI]                  | 3 [0; 5]                                       | 2 [-1; 5]                                      | 1 [-2; 3]  |
| p-value  | p=0.0255                                       | p=0.1569                                       | p=0.5352   |
| LDL cholesterol (%)                            | 0.58 / 5.02                                    | -3.07 / 5.02                                   | 0.58 / -3.07                                       |
| Treatment difference [95% CI]                  | -2 [-7; 3]                                     | -5 [-10; 1]                                    | 3 [-2; 8]  |
| p-value  | p=0.3563                                       | p=0.0957                                       | p<0.3123   |
| VLDL cholesterol (%)                           | -14.10 / 0.53                                  | -8.14 / 0.53                                   | -14.10 / -8.14                                     |
| Treatment difference [95% CI]                  | -13 [-19; -7]                                  | -6 [-13; 1]                                    | -7 [-13; -1]                                       |
| p-value  | p<0.0001                                       | p=0.0853                                       | p=0.0232   |
| Triglycerides (%)                              | -14.68 / 0.41                                  | -9.45 / 0.41                                   | -14.68 / -9.45                                     |
| Treatment difference [95% CI]                  | -14 [-20; -8]                                  | -7 [-14; 1]                                    | -7 [-13; 0]  |
| p-value  | p<0.0001                                       | p=0.0685                                       | p=0.0380   |
| Total cholesterol (%)                          | -1.46 / 3.80                                   | -2.20 / 3.80                                   | -1.46 / -2.20                                      |
| Treatment difference [95% CI]                  | -4 [-6; -1]                                    | -3 [-6; 0]                                     | -1 [-3; 2]   |
| p-value  | p=0.0116                                       | p=0.0610                                       | p=0.7097   |
| Free fatty acids (%)                           | -13.57 / -9.02                                 | -11.66 / -9.02                                 | -13.57 / -11.66                                    |
| Treatment difference [95% CI]                  | -6 [-12; 1]                                    | -5 [-12; 3]                                    | -1 [-7; 6]   |
| p-value  | p=0.0994                                       | p=0.2201                                       | p=0.8073   |

|                                      | Lira 3.0 mg, N=412 /<br>Placebo, N=211  | Lira 1.8 mg, N=204 /<br>Placebo, N=211 | Lira 3.0 mg, N=412 /<br>Lira 1.8 mg, N=204 |
|--------------------------------------|---|--|--|
| hsCRP (%)                            | -33.51 / -10.45   | -33.34 / -10.45                        | -33.51 / -10.45                            |
| Treatment difference [95% CI]        | -27 [-36; -17]  | -25 [-35; -12]                         | -3 [-15; 10]                               |
| p-value                              | p<0.0001  | p=0.0002                               | p=0.6439                                   |
| Adiponectin (%)                      | 6.6 / 1.3   | 3.5 / 1.3                              | 6.6 / 3.5                                  |
| Treatment difference [95% CI]        | 6 [-2; 15]  | 7 [-3; 18]                             | -1 [-9; 8]                                 |
| p-value                              | p=0.1685  | p=0.1779                               | p=0.8600                                   |
| Fibrinogen (%)                       | 4.54 / -3.11  | 1.68 / -3.11                           | 4.54 / 1.68                                |
| Treatment difference [95% CI]        | 5 [0; 9]  | 4 [-2; 9]                              | 1 [-3; 6]                                  |
| p-value                              | p=0.0464  | p=0.1789                               | p=0.6530                                   |
| PAI-1 (%)                            | CTR, page 177: Due to the different assay methods used at baseline and week 56, baseline values could not be compared with end of trial values, and PAI-1 is not presented in Table 11–43 and the relative change from baseline has not been estimated. |  |  |
| Urinary albumin/creatinine ratio (%) | -18.36 / -2.34  | -10.79 / -2.34                         | -18.36 / -10.79                            |
| Treatment difference [95% CI]        | -20 [-32; -6]   | -8 [-24; 12]                           | -14 [-27; 2]                               |
| p-value                              | p=0.0086  | p=0.4203                               | p=0.0840                                   |
| IWQoL-Lite total score               | 11.68 / 7.58  | 9.07 / 7.58                            | 11.68 / 9.07                               |
| Treatment difference [95% CI]        | 2.75 [0.57; 4.93]   | 0.78 [-1.74; 3.31]                     | 1.96 [-0.23; 4.16]                         |
| p-value                              | p=0.0136  | p=0.5424                               | p=0.0793                                   |
| physical function score              | 15.16 / 8.92  | 12.50 / 8.92                           | 15.16 / 12.50                              |
| Treatment difference [95% CI]        | 4.92 [2.12; 7.71]   | 2.64 [-0.59; 5.88]                     | 2.27 [-0.53; 5.08]                         |
| p-value                              | p=0.0006  | p=0.1089                               | p=0.1122                                   |
| public distress score                | 7.06 / 4.11   | 4.84 / 4.11                            | 7.06 / 4.84                                |
| Treatment difference [95% CI]        | 1.64 [-0.61; 3.89]  | 0.00 [-2.60; 2.60]                     | 1.64 [-0.62; 3.89]                         |
| p-value                              | p=0.1520  | p=0.9986                               | p=0.1546                                   |
| self-esteem score                    | 12.48 / 9.61  | 9.80 / 9.61                            | 12.48 / 9.80                               |
| Treatment difference [95% CI]        | 1.51 [-1.37; 4.39]  | 0.01 [-3.32; 3.34]                     | 1.50 [-1.39; 4.39]                         |
| p-value                              | p=0.3030  | p=0.9952                               | p=0.3088                                   |
| sexual life score                    | 9.22 / 7.78   | 6.90 / 7.78                            | 9.22 / 6.90                                |
| Treatment difference [95% CI]        | -0.70 [-4.27; 2.88]   | -2.03 [-6.16; 2.11]                    | 1.33 [-2.25; 4.91]                         |
| p-value                              | p=0.7016  | p=0.3360                               | p=0.4655                                   |
| work score                           | 8.80 / 5.45   | 5.48 / 5.45                            | 8.80 / 5.48                                |
| Treatment difference [95% CI]        | 1.54 [-0.76; 3.85]  | -1.06 [-3.73; 1.61]                    | 2.60 [0.29; 4.92]                          |
| p-value                              | p=0.1887  | p=0.4367                               | p=0.0275                                   |

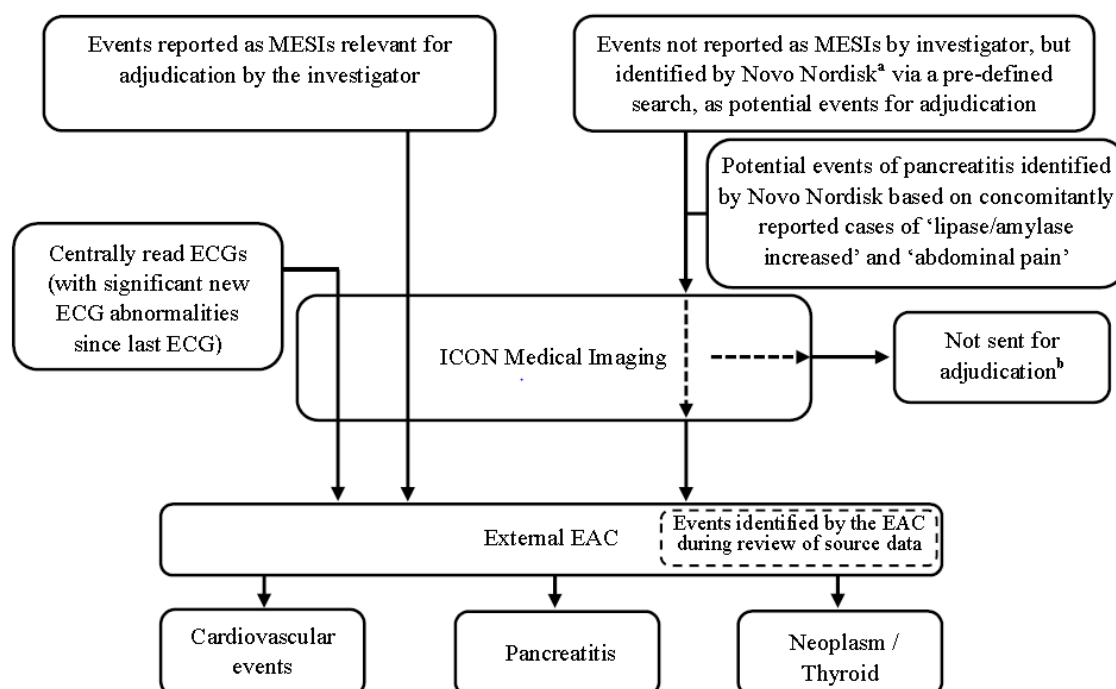
\*Indicates significantly different to placebo. # and shading indicates significantly better than 1.8 mg. Data are from an ANCOVA, except for HbA<sub>1c</sub> target endpoints, which are from a logistic regression analysis.

HDL: high-density lipoprotein. HOMA: homeostasis model assessment. HOMA-B: a measure of beta-cell function.

HOMA-IR: a measure of insulin resistance. hsCRP: high sensitivity C-reactive protein. IWQoL-Lite: Impact of Weight on Quality of Life-Lite version. LDL: low-density lipoprotein. PAI-1: plasminogen activator inhibitor-1. VLDL: very low density lipoprotein

## 5 Safety

### 5.1 Adjudication Process



a. The Novo Nordisk Event Adjudication Group (NN-EAG); events identified by pre-defined PTQ search

b. Events not relevant for adjudication as judged by ICON based on their independent pre-evaluation

**Figure 5–1 Pathways for selection of events of special interest for adjudication**



## 5.2 Pre-defined MedDRA Search Criteria

For coding of Adverse Events (AEs) the current version of MedDRA at the time of reporting of the weight management submission documents and version 15.1 was used for the analysis of AEs. The search was conducted at Preferred Term (PT) level based on the below listed individual PTs, High Level Terms (HLTs), High Level Group Terms (HLGT), System Organ Class (SOC) and Standard MedDRA Queries (SMQs)

### 1. Cardiovascular disorders

A general overview of cardiovascular events was provided based on tabulation of reported events captured by the following SMQs:

- SMQ Cerebrovascular disorders (20000060)
- SMQ Ischaemic heart disease (20000043)
- SMQ Cardiac arrhythmias (20000049)
- SMQ Cardiac failure (20000004)
- SMQ Embolic and thrombotic events (20000081)
- SMQ Shock (20000066)
- SMQ Cardiomyopathy (20000150)
- SMQ Torsade de pointes/QT prolongation (20000001)
- SMQ Vasculitis (20000174)

Separate tabulations were made of reported “Heart Failure” and “Cardiac arrhythmia” events captured by the following SMQs:

#### *Heart Failure:*

- SMQ Cardiac failure (20000004)

#### *Cardiac arrhythmia:*

- SMQ Arrhythmia related investigations, signs and symptoms (20000051)
- SMQ Bradyarrhythmia terms, nonspecific (20000053)
- SMQ Conduction defects (20000056)
- SMQ Disorders of sinus node function (20000055)
- SMQ Cardiac arrhythmia terms, nonspecific (20000162)
- SMQ Supraventricular tachyarrhythmias (20000057)
- SMQ Tachyarrhythmia terms, nonspecific (20000164)
- SMQ Ventricular tachyarrhythmias (20000058)

For cardiovascular events subject to adjudication ('Acute Coronary Syndrome', 'Cerebrovascular Event', 'Heart Failure leading to Hospitalization', 'Stent Thrombosis', and 'Coronary Revascularization Procedure'), listings of events submitted for adjudication and adjudication outcomes were provided.

## 2. Pancreatitis

- SMQ Acute pancreatitis (20000022) (narrow scope)
- HLT: Acute and chronic pancreatitis (10033646)

## 3. Gallbladder-related disorders

- SMQ Bile duct related disorders (20000125)
- SMQ Biliary system related disorders and investigations, signs and symptoms (20000123)
- SMQ Gallstone related disorders (20000127)
- SMQ Infectious biliary disorders (20000120)
- SMQ Site unspecified biliary disorders (20000126)
- SMQ Gallbladder related disorders (20000124)

## 4. Neoplasm

SOC neoplasms and the following SMQs were used:

- SMQ Biliary neoplasms malignant and unspecified (20000128)
- SMQ Biliary malignant tumours (20000196)
- SMQ Biliary tumours of unspecified malignancy (20000197)
- SMQ Breast neoplasms, malignant and unspecified (20000149)
- SMQ Breast malignant tumours (20000198)
- SMQ Breast tumours of unspecified malignancy (20000199)
- SMQ Liver neoplasms, malignant and unspecified (20000011)
- SMQ Liver malignant tumours (20000208)
- SMQ Liver tumours of unspecified malignancy (20000209)
- SMQ Malignant or unspecified tumours (20000091)
- SMQ Malignant tumours (SMQ) (20000194)
- SMQ Tumours of unspecified malignancy (20000195)
- SMQ Ovarian neoplasms, malignant and unspecified (20000151)
- SMQ Ovarian malignant tumours (20000200)
- SMQ Ovarian tumours of unspecified malignancy (20000201)
- SMQ Oropharyngeal neoplasms (20000110)
- SMQ Premalignant disorders (20000085)
- SMQ Blood premalignant disorders (20000086)

- SMQ Gastrointestinal premalignant disorders (20000087)
- SMQ Premalignant disorders, general conditions and other site specific disorders (20000169)
- SMQ Reproductive premalignant disorders (20000088)
- SMQ Skin premalignant disorders (20000089)
- SMQ Prostate neoplasms, malignant and unspecified (20000152)
- SMQ Prostate malignant tumours (20000202)
- SMQ Prostate tumours of unspecified malignancy (20000203)
- SMQ Skin neoplasms, malignant and unspecified (20000173)
- SMQ Skin malignant tumours (20000204)
- SMQ Skin tumours of unspecified malignancy (20000205)
- SMQ Uterine and fallopian tube neoplasms, malignant and unspecified (20000153)
- SMQ Uterine and fallopian tube malignant tumours (20000204)
- SMQ Uterine and fallopian tube tumours of unspecified malignancy (20000207)
- SMQ Tumour markers 20000094

## 5. Thyroid diseases

- SMQ Hyperthyroidism (20000161)
- SMQ Hypothyroidism (20000160)
- HLGT: Thyroid gland disorders (10043739)
- MedDRA PTs: Calcitonin secretion disorder, Ectopic calcitonin production, Hypercalcitoninaemia, Blood calcitonin abnormal, Blood calcitonin increased

## 6. Psychiatric disorders

A tabulation of reported events captured by the SOC Psychiatric disorders (incl. all primary and secondary PTs within the SOC) was provided.

### 5.3 Details on Pancreatic Neoplasms

**Table 5–1 Details on EAC confirmed pancreatic neoplasms – treatment-emergent and non-treatment emergent events: Phase 3 trials (through the 120-Day Safety Update)**

| Trial/Age/<br>Sex/BMI  | Preferred<br>term  | EAC<br>diagnosis  | EAC<br>malignancy<br>status                 | Inv<br>onset,<br>days | Medical history   | Details   |
|--|--|---|---|-----------------------|---|---|
| <b><i>Liraglutide 3.0 mg</i></b>                                 |  |   |   |                       |   |   |
| Trial 1839<br>Age: 39<br>Sex: Female<br>BMI at baseline:<br>38.2 | Neuroendocrine tumor of the pancreas (later re-classified as MEN1) | Pancreatic endocrine tumors<br><br>Parathyroid adenoma by imaging criteria however no pathology from surgical resection available | Malignant/ Stage 1: Localized<br><br>Benign | 69                    | The subject was under investigation for 'multiple endocrine neoplasia type 1' (MEN1) and diagnosed with hyperparathyroidism prior to trial enrolment. Relevant medical history includes benign pancreatic cyst and haemangioma right lobe liver. The subject's brother had been identified as a possible multiple endocrine neoplasia (MEN) syndrome patient. | <p>On trial day 70 the subject underwent an abdominal MRI which revealed cysts in the tail of the pancreas consistent with pre-study findings.</p> <p>In addition, the subject was diagnosed with a neuroendocrine tumor of the pancreas. 14 days later a parathyroid scan was performed and suggested left-sided parathyroid adenoma. Trial product was later discontinued due to this event. Following trial product discontinuation additional investigational procedures were performed. These procedures confirmed diagnosis of non-functioning neuroendocrine pancreatic cyst and revealed multiple colloid cysts in the thyroid gland.</p> <p>The subject underwent partial resection of pancreas. The subject underwent a distal pancreas and spleen resection. Multiple neuroendocrine grade 1 tumors measuring 1.5 cm, 1.4 cm, 1 cm, 0.9 cm, 0.8 cm, 0.7 cm, and 0.7 cm were found. No treatment was given for the benign thyroid neoplasms.</p> <p>The investigator evaluated the events as unlikely related to trial product.</p> |

BMI: body mass index; EAC: event adjudication committee; F: female; MRI: magnetic resonance imaging

## 5.4 Details on Thyroid Neoplasms

**Table 5–2 Details on EAC-confirmed thyroid neoplasms – treatment-emergent and non-treatment-emergent events: Phase 3 trials (through the 120-Day Safety Update)**

| Treatment                     | Trial/Age/<br>Sex | EAC diagnosis               | EAC<br>malignancy<br>status        | Inv onset,<br>day/<br>EAC onset,<br>day/Period   | Preferred term/<br>Reported term  | Details and medical history   |
|-------------------------------|-------------------|-----------------------------|------------------------------------|--|---|---|
| <i>Liraglutide<br/>3.0 mg</i> | 1839/27/M         | Papillary thyroid carcinoma | Malignant<br>Stage: not<br>done    | 212/211/<br>Main<br>treatment<br>period          | Thyroid cancer/<br>Worsening of<br>papillary<br>carcinoma   | A thyroid nodule was suspected at screening and ultrasound confirmed non-toxic multi-nodular goitre. 6 months later, a biopsy revealed thyroid papillary carcinoma. The subject was withdrawn from the trial. The subject underwent total thyroidectomy, started treatment with radioactive iodine and recovered with sequelae described as thyroid remnants. No relevant medical history. The subject recovered with sequelae. Calcitonin levels 1 ng/L at all visits  |
|                               | 1839/40/F         | Papillary thyroid carcinoma | Malignant<br>Stage: not<br>done    | 163/180 &<br>162/<br>Main<br>treatment<br>period | Thyroid cancer/<br>Left nodule<br>thyroid cancer,<br>right nodule<br>thyroid cancer,<br>Hashimoto's<br>thyroiditis,<br>Iatrogenic<br>hypothyroidism,<br>Hypo-<br>parathyroidism | A thyroid nodule was discovered by primary care physician. Ultrasound and fine needle aspiration revealed suspicion of papillary carcinoma. A thyroidectomy was performed and pathology confirmed thyroid carcinoma (papillary and follicular variant) located to right and left lobe of the thyroid (reported and confirmed as 2 separate events of thyroid cancer). The subject underwent radioiodine ablation. Hashimoto's Thyroiditis was an additional pathological finding during thyroidectomy. No treatment was required for this condition. As a consequence of the thyroidectomy, hypothyroidism and hypoparathyroidism was later reported. The subject recovered and continued on unchanged trial medication. No relevant medical history. The subject had a total of 5 EAC confirmed events, which were linked by the EAC and appear as 1 confirmed event in summary tables. Calcitonin levels 1 ng/L at all visits |
|                               | 1923/42/F         | Papillary thyroid carcinoma | Malignant/<br>Stage I<br>Localized | 24/15/<br>Main<br>treatment<br>period            | Thyroid cancer/<br>Papillary thyroid carcinoma (x2)   | History of hypothyroidism and family history of thyroid disease, as well as an enlarged thyroid at screening. She also had a history of thyromegaly and nodules. She withdrew from the trial, had a total thyroidectomy and had recovered at the end of the trial. The subject had a total of 2 EAC confirmed events, which were linked and appear as 1 confirmed event in summary tables.  |

| Treatment                      | Trial/Age/<br>Sex | EAC diagnosis                     | EAC<br>malignancy<br>status            | Inv onset,<br>day/<br>EAC onset,<br>day/Period | Preferred term/<br>Reported term  | Details and medical history  |
|--------------------------------|-------------------|-----------------------------------|--|--|---|--|
|                                | 1839-ext/<br>43/F | Papillary<br>thyroid<br>carcinoma | Malignant                              | 552 / 550                                      | Thyroid<br>cancer/Incidenta<br>l 3mm thyroid<br>papillary<br>microcarcinoma<br>(pT1a pN0<br>TNM7) | Parathyroidectomy in 2011. During explorative surgery due to persisting increased level of PTH a suspicious nodule in left thyroid lobe was identified leading to left hemi thyroidectomy. Histology showed a 3 mm thyroid papillary micro carcinoma which was completely excised. The subject recovered and continued on unchanged trial medication.  |
| <i>Placebo</i>                 | 1922/53/F         | Medullary<br>carcinoma            | Malignant/<br>Stage I/<br>Localized    | 23   | Thyroid cancer/<br>Medullary thyroid<br>carcinoma   | 23 days after start of trial product the subject presented with thyroid nodule. A thyroidectomy was later performed showing medullary thyroid carcinoma (MTC) of right thyroid lobe. Testing for RET oncogene was performed and no pathogenic mutations were detected in the RET gene. Calcitonin levels 18.5 ng/L at screening; 19.3ng/L at time of event. Relevant medical history included previous smoking. No relevant family history reported.   |
| <i>Pre-malignant Neoplasms</i> |                   |                                   |  |  |   |  |
| <i>Liraglutide<br/>3.0 mg</i>  | 1922/58/M         | C-cell<br>hyperplasia             | <i>In situ</i><br>Benign/<br>Stage: NA | -12/-11/<br>Screening                          | Thyroid cancer/<br>papillary<br>microcarcinoma<br>of<br>thyroid                                   | Approximately 3 months after discontinuation of treatment a thyroidectomy and central lymphadenectomy were performed due to elevated calcitonin levels. A thorough histological and immunohistological processing was performed and the thyroid gland resection showed diffuse, colloid-containing micro and macrofollicular goiters on both sides with a papillary microcarcinoma 1 mm in size in the isthmus and reactive C cell hyperplasia in both thyroid gland lobes. A normally structured parathyroid gland on the left side was also detected. Due to elevated blood calcitonin level at screening the EAC assigned an onset date of the C-cell hyperplasia to prior to treatment initiation. Testing for RET oncogene was performed and no pathogenic mutations were detected in the RET gene. Medical history included T2DM, diabetic complications, arterial hypertension, dyslipidemia and elevated calcitonin level. Calcitonin levels high (>45 ng/L) at all visits incl. baseline, except at week 56 |
|                                |                   | Papillary micro-<br>carcinoma     | Pre-<br>malignant/<br>Stage 0/         | 358/358/<br>Main<br>treatment<br>period        | Lymphadenopat<br>hy/<br>Lymphadenopat<br>hy   |  |

| Treatment | Trial/Age/<br>Sex | EAC diagnosis                 | EAC<br>malignancy<br>status                      | Inv onset,<br>day/<br>EAC onset,<br>day/Period | Preferred term/<br>Reported term                         | Details and medical history   |
|-----------|-------------------|-------------------------------|--|--|--|---|
|           | 1922/56/F         | Follicular adenoma            | Benign<br>Stage: NA                              | 51/51/<br>Main<br>treatment<br>period          | Thyroid<br>adenoma/<br>Adenoma of the<br>thyroid gland   | A 1.5 cm nodule was detected on left side of thyroid gland during clinical examination. The subject was withdrawn from the trial by the investigator due to the event. The subject had thyroidectomy, and the nodule was identified as benign follicular adenoma. In addition, a 0.5 mm malignant papillary microcarcinoma was noted incidentally from the removed thyroid tissue. The subject was withdrawn and recovered from both events. Calcitonin (and TSH) levels were normal at baseline and during the trial |
|           |                   | Papillary micro-<br>carcinoma | Pre-<br>malignant/<br>Stage 0/<br><i>In situ</i> | 137/137/<br>After<br>withdrawal                | Thyroid cancer/<br>Papillary<br>microcarcinoma           |   |
|           | 1839-<br>ext/61/F | micro papillary<br>carcinoma  | Pre-<br>malignant<br>Stage: pT1a<br>Nx Mx R0     | 378/378<br>After<br>withdrawal                 | Autoimmune<br>thyroiditis/<br>lymphocytic<br>thyroiditis | 237 days after discontinuing treatment with trial drug, the patient presented with multi-nodular goitre. A thyroidectomy was performed revealing diffuse thyroiditis with several nodules. Microscopy showed lymphocytic thyroiditis with several oncocyctic nodules. A single micro-site (3mm) of encapsulated papillary carcinoma, follicular variant, was located in the medial part of the right lobe, with no extension outside the thyroid. No relevant medical history reported. The subject recovered.        |

EAC: event adjudication committee (and EAC assessment of onset day); F: female; M: male; Thyroid neoplasm events identified by the thyroid MedDRA search as 'Thyroid disease requiring thyroidectomy' were not evaluated by the EAC with regards to stage of neoplasm.

One additional event of 'thyroid neoplasm' (non-treatment emergent, not-adjudicated) was reported with liraglutide 1.8/3.0 mg in year 2 of the phase 2 trial 1807

## 6 Supplementary information for the liraglutide type 2 diabetes programs

**Table 6–1 Baseline characteristics for patients in the liraglutide T2DM programs**

| Characteristic                                 | Total Liraglutide<br>(N=7037) | Total Comparator<br>(N=3677) |
|--|-------------------------------|------------------------------|
| Sex – N (%)                                    |                               |                              |
| Female   | 3132 (44.5)                   | 1627 (44.2)                  |
| Male   | 3905 (55.5)                   | 2050 (55.8)                  |
| Age (mean (SD)), years                         | 55.9 (10.1)                   | 56.4 (10.0)                  |
| Race – N (%)                                   |                               |                              |
| White  | 4115 (58.5)                   | 2332 (63.4)                  |
| Black or African American                      | 337 (4.8)                     | 138 (3.8)                    |
| Asian  | 2270 (32.3)                   | 1077 (29.3)                  |
| American Indian or Alaska Native               | 8 (0.1)                       | 5 (0.1)                      |
| Native Hawaiian or other Pacific Islander      | 5 (0.1)                       | 3 (0.1)                      |
| Other  | 302 (4.3)                     | 122 (3.3)                    |
| Ethnicity – N (%)                              |                               |                              |
| Hispanic or Latino                             | 539 (7.7)                     | 293 (8.0)                    |
| Not Hispanic or Latino                         | 2604 (37.0)                   | 1348 (36.7)                  |
| Not applicable                                 | 12 (0.2)                      | 8 (0.2)                      |
| Body mass index (mean (SD)), kg/m <sup>2</sup> | 30.1 (5.7)                    | 30.4 (5.7)                   |
| BMI categories – N (%)                         |                               |                              |
| 27-29.9 – overweight                           | 3694 (52.5)                   | 1828 (49.7)                  |
| 30-34.9 – obese class I                        | 1863 (26.5)                   | 1069 (29.1)                  |
| 35-39.9 – obese class II                       | 1120 (15.9)                   | 582 (15.8)                   |
| >40 – obese class III                          | 357 (5.1)                     | 192 (5.2)                    |
| Cardiovascular disease – n (%)                 |                               |                              |
| Based on MedDRA search terms <sup>a</sup>      | 914 (13.0)                    | 505 (13.7)                   |
| Dyslipidemia – N (%)                           | 3775 (53.6)                   | 2041 (55.5)                  |
| Hypertension – N (%)                           | 4177 (59.4)                   | 2272 (61.8)                  |
| Dyslipidemia and hypertension – N (%)          | 2612 (37.1)                   | 1426 (38.8)                  |

N: number of patients; SD: standard deviation. Includes data from controlled trials.

a: CV disease (by MedDRA search) includes the SMQs Ischemic heart disease, Cardiac failure, and Central nervous system hemorrhages and cerebrovascular conditions and embolic and thrombotic events.



**Table 6–2 Concomitant medication (at baseline) in liraglutide T2DM programs**

| Anatomical Therapeutic Chemical (ATC) Classification System, n (%) | Total Liraglutide (N=7037) | Total Comparator (N=3677) |
|--|----------------------------|---------------------------|
| Number of subjects with concomitant medication at baseline         | 551                        | 400                       |
| A10A   | 12 (0.2)                   | 13 (0.4)                  |
| A10AC, Insulins and analogues for injection, intermediate          | 2 (<0.1)                   | 2 (<0.1)                  |
| Insulin human injection, isophane                                  | 2 (<0.1)                   | 2 (<0.1)                  |
| A10AD, Insulin/anal for inj, intem.-act., comb.w/fast acting       | 1 (<0.1)                   | 0 (0.0)                   |
| Human mixtard  | 1 (<0.1)                   | 0 (0.0)                   |
| A10AE, Insulins and analogues for injection, long- acting          | 9 ( 0.1)                   | 11 (0.3)                  |
| Insulin detemir  | 3 (<0.1)                   | 5 (0.1)                   |
| Insulin glargine   | 6 (<0.1)                   | 6 (0.2)                   |
| A10B   | 550 (7.8)                  | 400 (10.9)                |
| A10BA, Biguanides  | 358 (5.1)                  | 308 (8.4)                 |
| Metformin  | 229 (3.3)                  | 237 (6.4)                 |
| Metformin embonate   | 0 (0.0)                    | 1 (<0.1)                  |
| Metformin hydrochloride  | 129 (1.8)                  | 70 (1.9)                  |
| A10BB AND A10BC, Sulfonamides, urea derivatives                    | 7 (<0.1)                   | 4 (0.1)                   |
| Glibenclamide  | 0 (0.0)                    | 1 (<0.1)                  |
| Gliclazide   | 1 (<0.1)                   | 0 (0.0)                   |
| Glimepiride  | 4 (<0.1)                   | 0 (0.0)                   |
| Glipizide  | 2 (<0.1)                   | 2 (<0.1)                  |
| A10BD, Combinations of oral blood glucose lowering drugs           | 2 (<0.1)                   | 1 (<0.1)                  |
| Diapride forte   | 1 (<0.1)                   | 0 ( 0.0)                  |
| Glibomet   | 0 (0.0)                    | 1 (<0.1)                  |
| Mopaday  | 1 (<0.1)                   | 0 (0.0)                   |
| A10BF, Alpha glucosidase inhibitors                                | 63 ( 0.9)                  | 30 (0.8)                  |
| Acarbose   | 10 (0.1)                   | 2 (<0.1)                  |
| Miglitol   | 25 (0.4)                   | 10 (0.3)                  |
| Voglibose  | 28 (0.4)                   | 18 (0.5)                  |
| A10BG, Thiazolidinediones  | 71 (1.0)                   | 30 (0.8)                  |
| Pioglitazone   | 2 (<0.1)                   | 1 (<0.1)                  |
| Pioglitazone hydrochloride   | 69 (1.0)                   | 29 (0.8)                  |
| A10BX, Other blood glucose lowering drugs, excluding insulins      | 59 (0.8)                   | 31 (0.8)                  |
| Liraglutide  | 1 (<0.1)                   | 0 (0.0)                   |
| Mitiglinide calcium  | 24 (0.3)                   | 13 (0.4)                  |
| Nateglinide  | 28 (0.4)                   | 15 (0.4)                  |
| Repaglinide  | 6 (<0.1)                   | 3 (<0.1)                  |

N: total number of patients; n: number of patients in each category. Includes data from controlled trials.

**Table 6–3 Comparators in liraglutide T2DM programs**

| <b>N (%)</b>      | <b>Total Comparator<br/>(N=3677)</b> |
|-------------------|--------------------------------------|
| Alpha GI          | 16 (0.4)                             |
| DPP-IV Inhibitors | 270 (7.3)                            |
| DPP-IV            | 51 (1.4)                             |
| Sitagliptin       | 55.9 (10.1)                          |
| Exenatide         | 232 (6.3)                            |
| Insulin           | 929 (25.3)                           |
| Degludec          | 611 (16.6)                           |
| Glargine          | 232 (6.3)                            |
| Insulin aspart    | 86 (2.3)                             |
| Metformin         | 64 (1.7)                             |
| Placebo           | 899 (24.4)                           |
| Sulphonylurea     | 1031 (28.0)                          |
| Glibenclamide     | 132 (3.6)                            |
| Glimepiride       | 881 (24.0)                           |
| Glinide           | 4 (0.1)                              |
| SU                | 14 (0.4)                             |
| Thiazolidinedione | 236 (6.4)                            |
| Rosiglitazone     | 231 (6.3)                            |
| Thiazolidinedione | 5 (0.1)                              |

N: number of patients; Includes data from controlled trials.

**Table 6–4 Breast cancer in the liraglutide T2DM programs**

|  | Total<br>Liraglutide |      |        |      | Total<br>Comparator |      |        |      |
|--|----------------------|------|--------|------|---------------------|------|--------|------|
|  | N                    | %    | E      | R    | N                   | %    | E      | R    |
| <b>Total number of patients</b>  |                      |      | 3703   |      |                     |      | 1624   |      |
| <b>Total PYR</b>   |                      |      | 3028.6 |      |                     |      | 1097.3 |      |
| <b>Total breast cancer</b>   | 7                    | 0.19 | 7      | 0.23 | 1                   | 0.06 | 1      | 0.09 |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                      |      |        |      |                     |      |        |      |
| <b>Breast neoplasms malignant and unspecified (incl nipple)</b>            | 7                    | 0.19 | 7      | 0.23 | 1                   | 0.06 | 1      | 0.09 |
| Breast cancer  | 6                    | 0.16 | 6      | 0.20 | 1                   | 0.06 | 1      | 0.09 |
| Inflammatory carcinoma of breast stage III                                 | 1                    | 0.03 | 1      | 0.03 | 0                   | 0    | 0      | 0    |

N=Number of patients, PYR=person years of exposure defined as time at risk. E: Number of events R: Event rate per 100 years. Includes data from controlled and uncontrolled trials.

**Table 6–5 Pancreatic cancer in the liraglutide T2DM programs**

|  | Total<br>Liraglutide |      |        |      | Total<br>Comparator |      |        |      |
|--|----------------------|------|--------|------|---------------------|------|--------|------|
|  | N                    | %    | E      | R    | N                   | %    | E      | R    |
| <b>Total number of patients</b>  |                      |      | 8344   |      |                     |      | 3671   |      |
| <b>Total PYR</b>   |                      |      | 6747.6 |      |                     |      | 2525.3 |      |
| <b>Total pancreatic cancer</b>   | 3                    | 0.04 | 3      | 0.04 | 1                   | 0.03 | 1      | 0.04 |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                      |      |        |      |                     |      |        |      |
| <b>Gastrointestinal neoplasms malignant and unspecified</b>                |                      |      |        |      |                     |      |        |      |
| Adenocarcinoma pancreas  | 1                    | 0.01 | 1      | 0.01 | 0                   | 0    | 0      | 0    |
| Pancreatic carcinoma   | 1                    | 0.01 | 1      | 0.01 | 0                   | 0    | 0      | 0    |
| Pancreatic carcinoma stage IV  | 1                    | 0.01 | 1      | 0.01 | 0                   | 0    | 0      | 0    |
| Pancreatic carcinoma metastatic  | 0                    | 0    | 0      | 0    | 1                   | 0.03 | 1      | 0.04 |

N=Number of patients, PYR=person years of exposure defined as time at risk. E: Number of events R: Event rate per 100 years. Includes data from controlled and uncontrolled trials.

**Table 6–6 Thyroid neoplasms in the liraglutide T2DM programs**

|   | Total Liraglutide |      |        |      | Total Comparator |      |        |      |
|---|-------------------|------|--------|------|------------------|------|--------|------|
|   | N                 | %    | E      | R    | N                | %    | E      | R    |
| Total number of patients  |                   |      | 8344   |      |                  |      | 3671   |      |
| Total PYR   |                   |      | 6747.6 |      |                  |      | 2525.3 |      |
| Total thyroid cancer  | 9                 | 0.11 | 9      | 0.13 | 2                | 0.05 | 2      | 0.08 |
| Total thyroid neoplasm  | 36                | 0.43 | 37     | 0.55 | 4                | 0.11 | 4      | 0.16 |
| Endocrine disorders   |                   |      |        |      |                  |      |        |      |
| Thyroid gland disorders   |                   |      |        |      |                  |      |        |      |
| Thyroid C-cell hyperplasia  | 1                 | 0.01 | 1      | 0.01 | 0                | 0    | 0      | 0    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |      |        |      |                  |      |        |      |
| Endocrine neoplasms malignant and unspecified                       |                   |      |        |      |                  |      |        |      |
| Thyroid neoplasm  | 36                | 0.43 | 37     | 0.55 | 4                | 0.11 | 4      | 0.16 |
| Thyroid cancer  | 9                 | 0.11 | 9      | 0.13 | 2                | 0.05 | 2      | 0.08 |

N=Number of patients, PYR=person years of exposure defined as time at risk. E: Number of events R: Event rate per 100 years. Includes data from controlled and uncontrolled trials.

**Table 6–7 Colorectal neoplasms in the liraglutide T2DM programs**

|  | Total Liraglutide |      |    |      | Total Comparator |      |    |      |
|--|-------------------|------|----|------|------------------|------|----|------|
|  | N                 | %    | E  | R    | N                | %    | E  | R    |
| <b>Total number of patients</b>  | 8344              |      |    |      | 3671             |      |    |      |
| <b>Total PYR</b>   | 6747.6            |      |    |      | 2525.3           |      |    |      |
| <b>Total colorectal cancer</b>   | 8                 | 0.10 | 8  | 0.12 | 3                | 0.08 | 3  | 0.12 |
| <b>Total benign colon neoplasm</b>   | 3                 | 0.04 | 3  | 0.04 | 2                | 0.05 | 2  | 0.08 |
| <b>Total benign colorectal polyps</b>                                      | 26                | 0.31 | 27 | 0.40 | 13               | 0.35 | 14 | 0.55 |
| <b>Gastrointestinal disorders</b>  |                   |      |    |      |                  |      |    |      |
| <b>Benign neoplasms gastrointestinal</b>                                   |                   |      |    |      |                  |      |    |      |
| Colonic polyp  | 20                | 0.24 | 20 | 0.30 | 12               | 0.33 | 13 | 0.51 |
| Rectal polyp   | 5                 | 0.06 | 6  | 0.09 | 1                | 0.03 | 1  | 0.04 |
| Polyp colorectal   | 1                 | 0.01 | 1  | 0.01 | 0                | 0    | 0  | 0    |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                   |      |    |      |                  |      |    |      |
| <b>Gastrointestinal neoplasms malignant and unspecified</b>                |                   |      |    |      |                  |      |    |      |
| Colon cancer   | 3                 | 0.04 | 3  | 0.04 | 1                | 0.03 | 1  | 0.04 |
| Rectal cancer  | 3                 | 0.04 | 3  | 0.04 | 0                | 0    | 0  | 0    |
| Colon cancer stage 0   | 1                 | 0.01 | 1  | 0.01 | 0                | 0    | 0  | 0    |
| Colorectal carcinoma stage 0   | 1                 | 0.01 | 1  | 0.01 | 0                | 0    | 0  | 0    |
| Colorectal cancer  | 0                 | 0    | 0  | 0    | 1                | 0.03 | 1  | 0.04 |
| Large intestine carcinoma  | 0                 | 0    | 0  | 0    | 1                | 0.03 | 1  | 0.04 |
| <b>Gastrointestinal neoplasms benign</b>                                   |                   |      |    |      |                  |      |    |      |
| Colon adenoma  | 2                 | 0.02 | 2  | 0.03 | 2                | 0.05 | 2  | 0.08 |
| Benign colonic neoplasm  | 1                 | 0.01 | 1  | 0.01 | 0                | 0    | 0  | 0    |

N=Number of patients, PYR=person years of exposure defined as time at risk. E: Number of events R: Event rate per 100 years. Includes data from controlled and uncontrolled trials.