Liraglutide 3,0mg: A Novel Pharmaceutical Approach in Obesity Management

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Note: Age- and gender-adjusted rates of obesity and overweight, 2005 OECD standard population. Measured height and weight in Australia, England, Korea, Mexico and the United States; self-reported in other countries. No projections were produced in 2010 for Australia, Mexico and Switzerland.
Παγκόσμιος πληθυσμός

7.579.331.787 Τρέχων παγκόσμιος πληθυσμός

Τροφή

728.710.670 Υποσιτιζόμενοι άνθρωποι στον κόσμο

1.650.402.152 Υπέρβαροι άνθρωποι στον κόσμο

690.680.498 Παχύσαρκοι άνθρωποι στον κόσμο
Obesity is one of the top three global social burdens generated by human beings

Estimated annual global direct economic impact and investment to mitigate selected global burdens, 2012

GDP, $ trillion

<table>
<thead>
<tr>
<th>Selected global social burdens</th>
<th>Share of global GDP</th>
<th>Historical trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Armed violence, war, and terrorism</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td><strong>2.0</strong></td>
<td><strong>2.8</strong></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Illiteracy</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Climate change</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Outdoor air pollution</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Drug use</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Road accidents</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Workplace risks</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Household air pollution</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Child and maternal undernutrition</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Unsafe sex</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Poor water and sanitation</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

2. Source: World Health Organization
4. Source: UNESCO
5. Source: World Health Organization
6. Source: UNAIDS
7. Source: World Health Organization
Projected obesity for 2030

WHO Modelling obesity Project 2013 – submitted
As per NOPA II
Obesity is associated with multiple complications

Health Effects of Overweight and Obesity in 195 Countries over 25 Years

The GBD 2015 Obesity Collaborators

Disabilità

Mortalità

1990

2015

MAINTENANCE OF WEIGHT LOSS IS CHALLENGING

*Diets Are Not the Answer?*

Follow up range from 4 to 7 years

- Mean change from baseline to end of diet (kg)
- Mean change from baseline to follow-up (kg)

*Mann et al. Am Psychol 2007*
Weight Loss at 1 Year with High-Intensity Lifestyle Interventions or Pharmacotherapy Combined with Low-to- Moderate-Intensity Lifestyle Counseling

Heymsfield and Wadden, N Engl J Med, 2017
WEIGHT LOSS MAINTENANCE

CV EFFECTS OF INTENSIVE LIFESTYLE INTERVENTION IN T2D
THE LOOK AHEAD STUDY

Main effect, -4 (95% CI, -5 to -3)
P<0.001

10-YEAR FOLLOW-UP OF DIABETES INCIDENCE AND WEIGHT LOSS IN THE DPP OUTCOMES STUDY

PHYSIOLOGICAL RESPONSES TO WEIGHT LOSS FAVOR WEIGHT REGAIN

- Hunger
- Desire to eat

- Energy intake
- Resting energy expenditure

- Insulin
- Leptin
- GLP-1, CCK, PYY, Ghrelin

Pancreas
Adipose tissue
Gut

2 yr re-randomisation trial shows need for continued drug use

(X. Pi-Sunyer, Circulation 2005:111(13);1727)
“A treatment gap exists for those patients who do not respond sufficiently to behavioural and lifestyle interventions and who are not viable candidates for, or do not wish to undergo, bariatric surgery. Such patients need additional options for treatment. Used appropriately, effective prescription drugs could potentially help fill that gap”.

GLP-1 secretion and receptor expression

GLP-1 is secreted by:
- Nucleus tractus solitarius
- L-cells of the gut

GLP-1R is expressed in:
- Brain
- Endothelium
- Myocardium
- Pancreas
- Kidney
- Gastrointestinal tract
AgRP, Agouti-related protein; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; α-MSH, α-melanocyte stimulating hormone; GLP-1R, glucagon-like peptide-1 receptor; OXM, oxyntomodulin

Liraglutide 3.0 mg
LIRAGLUTIDE EFFECTS ON HYPOTHALAMIC NEURONS INVOLVED IN APPETITE REGULATION

AgRP, Agouti-related protein
CART, cocaine and amphetamine-regulated transcript
NPY, Neuropeptide Y
POMC, pro-opiomelanocortin

THE ARCUATE NUCLEUS MEDIATES GLP-1 RECEPTOR AGONIST LIRAGLUTIDE-DEPENDENT WEIGHT LOSS

Fluorescently labeled liraglutide in the mouse brain

Normal mice

GLP-1R⁻/⁻ mice

GLP-1 caused membrane depolarization and increased firing rate of spontaneous action potentials in POMC/CART cells

Secher et al, J Clin Invest, 2014
**Inclusion criteria:**
- ≥30 BMI ≤40 kg/m²
- Age 18–65 years
- Stable body weight
- FPG <7 mmol/L at Week −2

Lifestyle intervention: −500 kcal/day hypocaloric diet + increased physical activity

*From 20–52 weeks, participants/investigators remained blinded to liraglutide/placebo treatment but the sponsor was unblinded; after 1 year, all were unblinded. FPG, fasting plasma glucose; s.c., subcutaneous

Change in body weight
Screening to 104 weeks

Mean (±SE). Observed means with no imputation for individuals completing each scheduled visit. ITT, intention-to-treat; LOCF, last observation carried forward; SE, standard error

**SCALE Phase 3a Clinical Trial Program**

**SCALE, Satiety and Clinical Adiposity Liraglutide Evidence in non-diabetic and diabetic individuals**

**SCALE Obesity and Prediabetes (1839)**
- Weight management & delayed onset of diabetes
  - Liraglutide 3.0 mg n=2487
  - Placebo n=1244

**SCALE Diabetes (1922)**
- Weight management in type 2 diabetes
  - Liraglutide 3.0 mg n=423
  - Liraglutide 1.8 mg n=211
  - Placebo n=212

**SCALE Maintenance (1923)**
- Prevention of weight regain
  - Liraglutide 3.0 mg n=212
  - Placebo n=210

**SCALE Sleep Apnea (3970)**
- Effect of liraglutide in subjects with obesity and moderate to severe OSA
  - Liraglutide 3.0 mg n=180
  - Placebo n=179

OSA, Obstructive Sleep Apnea

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SCALE Obesity and Prediabetes

Baseline Characteristics of the Patients

**Table 1. Baseline Characteristics of the Patients.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liraglutide (N = 2487)</th>
<th>Placebo (N = 1244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body-mass index‡</td>
<td>38.3±6.4</td>
<td>38.3±6.3</td>
</tr>
<tr>
<td>Body-mass index categories — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27–29.9: overweight</td>
<td>66 (2.7)</td>
<td>44 (3.5)</td>
</tr>
<tr>
<td>30–34.9: obese class I</td>
<td>806 (32.4)</td>
<td>388 (31.2)</td>
</tr>
<tr>
<td>35–39.9: obese class II</td>
<td>787 (31.6)</td>
<td>398 (32.0)</td>
</tr>
<tr>
<td>≥40: obese class III</td>
<td>828 (33.3)</td>
<td>414 (33.3)</td>
</tr>
</tbody>
</table>

61.2% had prediabetes

Pi-Sunyer et al., New Engl J Med, 2015
Inclusion criteria:
• BMI: ≥30 kg/m², or ≥27 kg/m² + comorbidities*
• Stable body weight, and preceding failed dietary effort

Without prediabetes
Randomisation 2:1 (lira:pbo)

With Prediabetes
Screening

Dose escalation

Liraglutide 3.0 mg/day

Placebo

Liraglutide 3.0 mg/day

Placebo

Re-randomisation 1:1

EOS**

EOT

EOS

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min./week increased physical activity

* Treated or untreated hypertension or dyslipidaemia according to ATP-III; ** Treatment ends at week 68 for the population without prediabetes and is followed by an off-treatment follow-up period of 2 weeks. EOS end of study; EOT, end of treatment. NN8022-1839 3yr data. ClinicalTrials.gov Identifier: NCT01272219. Pi-Sunyer et al. NEJM 2015;373:11–22
SCALE Obesity and Prediabetes

Mean weight loss (%) from baseline to week 56

FAS, fasting visit data only. Line graphs are observed means (±SE). Circles are observed means LOCF. Statistical analysis is ANCOVA. FAS, full analysis set; LOCF, last observation carried forward; SE, standard error.

Pi-Sunyer et al., New Engl J Med, 2015
SCALE Obesity and Prediabetes

Weight loss responders
0–56 weeks

FAS, fasting visit data only, LOCF. Graphs are observed proportions LOCF. Statistical analysis is logistic regression. FAS, full analysis set; LOCF, last observation carried forward.

Pi-Sunyer et al., New Engl J Med, 2015
Cumulative distribution of changes in body weight after 56 weeks of treatment

Pi-Sunyer X, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *NEJM* 2015;373:11-22
Liraglutide 3.0 mg: WL and progression to T2D
SCALE Obesity and Prediabetes: 3 years

Trial design

Inclusion criteria:
• BMI: ≥30 kg/m², or ≥27 kg/m² + comorbidities*
• Stable body weight, and preceding failed dietary effort

Trial design

Screening
Dose escalation
Randomisation 2:1 (lira:pbo)
With Prediabetes
Placebo
Re-randomisation 1:1
EOS**
Liraglutide 3.0 mg/day
0.6 mg
1.2 mg
1.8 mg
2.4 mg

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min./week increased physical activity

Week
−2 0 4

EMO
With Prediabetes
Observational follow-up
Liraglutide 3.0 mg/day

Liraglutide 3.0 mg: WL and progression to T2D
SCALE Obesity and Prediabetes: 3 years

Full analysis set, fasting-visit data only. Line graphs are observed means (±SE).

*Derived from the primary Weibull analysis. ETD, estimated treatment difference; LOCF, last observation carried forward; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes; SE, standard error; T2D, type 2 diabetes; WL, weight loss.

Adverse events reported in ≥5% of participants
0–56 weeks

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Liraglutide 3.0 mg %</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>40.2</td>
<td>14.7</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>20.9</td>
<td>9.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>20.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>5.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17.2</td>
<td>18.8</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Influenza</td>
<td>5.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Headache</td>
<td>13.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>11.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.9</td>
<td>8.5</td>
</tr>
<tr>
<td>Injection site haematoma</td>
<td>5.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Safety analysis set

Pi-Sunyer et al., New Engl J Med, 2015
Overall summary and conclusions (2/2)

SCALE Obesity and Prediabetes

- Safety profile was generally consistent with that of previous clinical trials with liraglutide 3.0 mg\(^1,2\) and liraglutide 1.8 mg in individuals with T2D\(^3\)
- Liraglutide 3.0 mg was generally well tolerated; nausea, diarrhoea and constipation were the most commonly reported adverse events
- Incidence of gallbladder disorders and acute pancreatitis was low, but more frequent with liraglutide 3.0 mg:
  - Gallbladder disorders: 2.5 vs. 1.0 events/100 PYE (n=54 vs. 9)*
  - Acute pancreatitis: 0.3 vs. 0.1 events/100 PYE (n=7 vs. 1)\(^\dagger\)
  - Acute pancreatitis: no consistent mode of presentation or latency period, majority mild according to revised Atlanta criteria

Pi-Sunyer et al., New Engl J Med, 2015
Gallbladder and pancreatic safety

- Gallbladder-related adverse events and events of confirmed acute pancreatitis were low, but more frequent with liraglutide 3.0 mg vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 3.0 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder-related events</td>
<td>2.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Acute pancreatitis events</td>
<td>0.29</td>
<td>0.13</td>
</tr>
</tbody>
</table>

PYO, patient years of observation

le Roux et al. Obesity Week 2015, 2–6 November 2015, Poster T-P-LB-3843
Pancreatitis (confirmed by adjudication)

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>18</td>
<td>0.4</td>
<td>23</td>
<td>0.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>0.0</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Full analysis set. The occurrence of pancreatitis was adjudicated by the event adjudication committee. P-values were calculated by means of Pearson’s chi-square test. %: proportion of patients; N: number of patients.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
Inclusion criteria:
- Type 2 diabetes
- BMI ≥27 kg/m²
- HbA₁c 7.0–10.0%
- Diet and exercise and/or 1–3 OADs (met, SU*, TZD)

*proportion of subjects treated with SU mono- or combination therapy at screening was restricted to a maximum of 30% of randomised subjects.

met, metformin; OAD, oral antidiabetic drug; SU, sulphonylurea; TZD, thiazolidinedione

Davies et al., JAMA 2015
## SCALE Diabetes – Trial design

Table 1. Baseline Demographic Characteristics and Secondary Efficacy End Points

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>No. (%)</th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3.0 mg</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>Patients, No.</td>
<td></td>
<td>423</td>
<td>211</td>
</tr>
<tr>
<td>Body mass index group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0-29.9 (preobese)</td>
<td></td>
<td>52 (12.3)</td>
<td>34 (16.1)</td>
</tr>
<tr>
<td>30.0-34.9 (obese class I)</td>
<td></td>
<td>139 (32.9)</td>
<td>62 (29.4)</td>
</tr>
<tr>
<td>35.0-39.9 (obese class II)</td>
<td></td>
<td>108 (25.5)</td>
<td>50 (23.7)</td>
</tr>
<tr>
<td>&gt;40.0 (obese class III)</td>
<td></td>
<td>124 (29.3)</td>
<td>65 (30.8)</td>
</tr>
<tr>
<td>Background diabetes treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and exercise only</td>
<td></td>
<td>46 (11.2)</td>
<td>29 (14.2)</td>
</tr>
<tr>
<td>Metformin only</td>
<td></td>
<td>237 (57.5)</td>
<td>111 (54.4)</td>
</tr>
<tr>
<td>Metformin + glitazone</td>
<td></td>
<td>22 (5.3)</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>Metformin + sulfonylurea</td>
<td></td>
<td>86 (20.9)</td>
<td>44 (21.6)</td>
</tr>
<tr>
<td>Metformin + sulfonylurea + glitazone</td>
<td></td>
<td>10 (2.4)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td></td>
<td>7 (1.7)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Sulfonylurea + glitazone</td>
<td></td>
<td>4 (1.0)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>
Liraglutide is not approved for weight management outside Canada, EU -8 -7 -6 -5 -4 -3 -2 0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 Change in body weight (%)

0–56 weeks

FAS, fasting visit data only. Line graphs are observed means (±SE). Circles are observed means LOCF. Statistical analysis is ANCOVA.

Mean baseline body weight: 106.0 kg

Liraglutide 3.0 mg

Liraglutide 1.8 mg

Placebo

FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

SCALE Diabetes
Change in body weight (%)

Davies et al., JAMA 2015
Liraglutide is not approved for weight management outside Canada, EU -2 -1.6 -1.2 -0.8 -0.4 0 Time (weeks) Change in HbA1c (%) Mean baseline HbA1c: 8.0% FAS LOCF. Line graphs are observed means (±SE). Circles are observed means LOCF FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Davies et al., JAMA 2015
Individuals achieving ≥5% and >10% weight loss
0-56 weeks (co-primary endpoint)

Proportions are observed means, FAS-LOCF. Estimates are from a logistic regression model using FAS-LOCF. *p<0.05; **p<0.001; ***p<0.0001. LS mean values: 49.9%, 35.0% and 12.7% of individuals on liraglutide 3.0 mg, 1.8 mg and placebo, respectively, lost ≥5% body weight, while 22.1%, 13.3% and 3.8% lost >10% body weight, respectively. FAS, full analysis set; LOCF, last observation carried forward; LS, least square; OR, odds ratio.
Liraglutide is not approved for weight management outside Canada, EU.

Baseline FPG: $8.8 \text{ mmol/L}$

Observed mean change in FPG 0-68 weeks

Baseline FPG: **8.8 mmol/L**

\[
\begin{array}{c|c|c}
& \text{Week 0} & \text{Week 68} \\
\hline
\text{Placebo} & 8.8 & 8.6 \\
\text{Liraglutide 1.8 mg} & 8.8 & 8.7 \\
\text{Liraglutide 3.0 mg} & 8.8 & 8.9 \\
\end{array}
\]

**Estimated differences at week 68 (mmol/L):**
- Liraglutide 3.0 mg vs. placebo: $-0.09 (p=NS)$
- Liraglutide 1.8 mg vs. placebo: $0.12 (p=NS)$
- Liraglutide 3.0 vs. 1.8 mg: $-0.20 (p=NS)$

FAS. Data are observed means ($\pm$SE), no imputation. Statistical analysis is ANCOVA.

*p* $<0.05$, *****p* $<0.0001$ vs. placebo; ††*p* $<0.001$ vs. liraglutide 1.8 mg. LS mean change at week 68: $-0.21$, $-0.01$ and $-0.12$ mmol/L for liraglutide 3.0 mg, 1.8 mg and placebo, respectively. FPG Fasting Plasma Glucose

Davies et al., *JAMA 2015*
Liraglutide is not approved for weight management outside Canada, EU -8 -6 -4 -2 0 2 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 0 2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 Change in SBP (mmHg) Baseline SBP: 129 mmHg Observed mean change in SBP 0-68 weeks Estimated differences at week 68 (mmHg):
- Liraglutide 3.0 mg vs. placebo −1.36 (p=NS)
- Liraglutide 1.8 mg vs. placebo −1.72 (p=NS)
- Liraglutide 3.0 vs. 1.8 mg 0.37 (p=NS)
FAS. Data are observed means (±SE), no imputation. Statistical analysis is ANCOVA.
*p<0.05 vs. placebo. LS mean change at week 68: 0.06, -0.31 and 1.42 mmHg for liraglutide 3.0 mg, 1.8 mg and placebo, respectively.
SBP, systolic blood pressure

Davies et al., JAMA 2015
LS mean change at week 68: −1.38, −0.39 and 0.54 bpm for liraglutide 3.0 mg, 1.8 mg and placebo, respectively.

bpm, beats per minute

Estimated differences at week 68 (bpm):
- Liraglutide 3.0 mg vs. placebo: −1.92 (p=0.0419)
- Liraglutide 1.8 mg vs. placebo: −0.92 (p=NS)
- Liraglutide 3.0 vs. 1.8 mg: −1.00 (p=NS)

Baseline pulse: 74.2 bpm

SAS. Data are observed means (±SE), no imputation. Statistical analysis is ANCOVA (specified post-hoc).

***p<0.0001 vs. placebo. LS mean change at week 68: −1.38, −0.39 and 0.54 bpm for liraglutide 3.0 mg, 1.8 mg and placebo, respectively.
Primary outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.
Liraglutide is not approved for weight management outside Canada, EU and US.

Early responders, individuals who achieved ≥5% weight loss from baseline at 16 weeks; early non-responders, individuals who achieved <5% weight loss from baseline at 16 weeks.

Week 56 completers, FAS, fasting visit data only. Line graphs are observed means (±95% CI). CI, confidence interval; FAS, full analysis set.

Blüher et al. IDF 2015. 30 November–4 December 2015, Vancouver, Canada. Poster 0208-P.
SCALE Maintenance
Change in body weight (%)

Wadden et al., Int J Obes, 2013
Liraglutide is not approved for weight management outside Canada, EU

Change in body weight (%)
0–32 weeks

Mean baseline weight:
118 kg

FAS. Line graphs are observed means (±SE). Circles are observed means LOCF. Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Blackman et al., Int J Obes, 2016
Liraglutide is not approved for weight management outside Canada, EU and US.

**SCALE Sleep Apnoea**

**Change in AHI (events/h)**

0–32 weeks

FAS. Line graphs are observed means (±SE). Circles are observed means LOCF. Statistical analysis is ANCOVA. AHI, apnoea–hypopnoea index, FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Blackman et al., *Int J Obes*, 2016
Weight loss across SCALE trials

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Duration</th>
<th>N</th>
<th>Liraglutide 3.0 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCALE Obesity &amp; Prediabetes¹</td>
<td>56 weeks</td>
<td>3,731</td>
<td>8.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>SCALE Diabetes²</td>
<td>56 weeks</td>
<td>844</td>
<td>5.9%</td>
<td>2.0%</td>
</tr>
<tr>
<td>SCALE Sleep Apnoea³</td>
<td>32 weeks</td>
<td>308</td>
<td>5.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>SCALE Maintenance⁴</td>
<td>12-week run-in, 56 weeks</td>
<td>420</td>
<td>6.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Weight loss at end of trial
% subjects achieving ≥5% weight loss

Data are observed means; LOCF at end of trial

1. Pi-Sunyer et al. *NEJM*, 2015
2. Davies et al. *JAMA*, 2015
Dose escalation schedule

<table>
<thead>
<tr>
<th>Week</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>2</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>3</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>4</td>
<td>2.4 mg</td>
</tr>
<tr>
<td>5 and onward</td>
<td>3 mg</td>
</tr>
</tbody>
</table>
Treatment options for people with obesity

“A treatment gap exists for those patients who do not respond sufficiently to behavioural and lifestyle interventions and who are not viable candidates for, or do not wish to undergo, bariatric surgery. Such patients need additional options for treatment. Used appropriately, effective prescription drugs could potentially help fill that gap”