Liraglutide

Peter Kristensen, SVP
Global development
Liraglutide demonstrates higher efficacy than active comparators across phase 3 studies

Liraglutide has shown statistically significantly better HbA$_{1c}$ reductions compared to the following active comparators in large phase 3 studies:

- glimepiride (SU)*
- rosiglitazone (TZD)
- insulin glargine (basal insulin)
- exenatide (GLP-1)

Head-to-head data versus sitagliptin expected in the third quarter of 2009

*For patients previously in monotherapy
Liraglutide phase 3 programme
Exposure across type 2 diabetes disease progression

Start an oral agent

- **Phase 3B: NN 2211-1860**
  - Liraglutide+MET vs. sitagliptin+MET

- **LEAD 2**
  - Liraglutide+MET vs. SU+MET

- **LEAD 1**
  - Liraglutide+SU vs. TZD+SU

- **LEAD 4**
  - Liraglutide+MET+TZD vs. MET+TZD

- **LEAD 5**
  - Liraglutide+MET+SU vs. glargine+MET+SU

- **LEAD 6**
  - Liraglutide+MET and/or SU vs. exenatide+MET and/or SU

Add another oral agent

Add a third oral or start insulin

**Diet/exercise**

**LEAD: Liraglutide Effect and Action in Diabetes.** All studies 26 weeks’ duration (LEAD 3=52 weeks); all RCT; all with double dummy except LEAD 5 vs. glargine. Studies NN2211-1436, -1572, -1573 and -1697 presented as Marre et al. Diabetes 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. Diabetes 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Russell-Jones et al. Diabetes 2008;57(Suppl. 1):A159 (LEAD 5).
## LEAD demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>LEAD 3 Mono-therapy</th>
<th>LEAD 2 Metformin</th>
<th>LEAD 1 SU</th>
<th>LEAD 4 Metformin +TZD</th>
<th>LEAD 5 Metformin+SU</th>
<th>LEAD 6 Metformin, SU, Met+SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>746</td>
<td>1091</td>
<td>1041</td>
<td>533</td>
<td>581</td>
<td>464</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.0</td>
<td>56.8</td>
<td>56.1</td>
<td>55.1</td>
<td>57.5</td>
<td>56.7</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5.4</td>
<td>7.4</td>
<td>7.9</td>
<td>9.2</td>
<td>9.4</td>
<td>8.2</td>
</tr>
<tr>
<td>Previously on mono:combi (%)</td>
<td>(36:64)*</td>
<td>36:64</td>
<td>30:70</td>
<td>18:82</td>
<td>6:94</td>
<td>73:27</td>
</tr>
<tr>
<td>FPG (mM)</td>
<td>9.5</td>
<td>10.0</td>
<td>9.8</td>
<td>10.1</td>
<td>9.2</td>
<td>9.6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3</td>
<td>8.4</td>
<td>8.4</td>
<td>8.5</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.1</td>
<td>31.0</td>
<td>30.0</td>
<td>33.5</td>
<td>30.5</td>
<td>32.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>98.8</td>
<td>88.6</td>
<td>81.6</td>
<td>96.3</td>
<td>85.4</td>
<td>93.1</td>
</tr>
</tbody>
</table>

Source: Data originally presented as Marre et al. Diabetes 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. Diabetes 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. Diabetologia 2008;51(Suppl. 1): Poster 898 (LEAD 4); Russell-Jones et al. Diabetes 2008;57(Suppl. 1):A159 (LEAD 5).

Note: * Ratio of patients previously on diet/exercise vs monotherapy
# LEAD demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>LEAD 3 Mono-therapy</th>
<th>LEAD 2 Metformin</th>
<th>LEAD 1 SU</th>
<th>LEAD 4 Metformin +TZD</th>
<th>LEAD 5 Metformin +SU</th>
<th>LEAD 6 Metformin, SU, Met+SU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment period</strong></td>
<td>52 w</td>
<td>26 w</td>
<td>26 w</td>
<td>26 w</td>
<td>26 w</td>
<td>26 w</td>
</tr>
<tr>
<td><strong>Dosage (in mg)</strong></td>
<td>• 1.2</td>
<td>• 0.6</td>
<td>• 0.6</td>
<td>• 1.2</td>
<td>• 1.2</td>
<td>• 1.8</td>
</tr>
<tr>
<td></td>
<td>• 1.8</td>
<td>• 1.2</td>
<td>• 1.2</td>
<td>• 1.8</td>
<td>• 1.8</td>
<td>• 1.8</td>
</tr>
<tr>
<td><strong>Active comparator</strong></td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
<td>Placebo</td>
<td>Lantus</td>
<td>Exenatide</td>
</tr>
<tr>
<td><strong>Extension study</strong></td>
<td>260 w</td>
<td>104 w</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>14 + 38 w</td>
</tr>
</tbody>
</table>

Source: Data originally presented as Marre et al. Diabetes 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. Diabetes 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. Diabetologia 2008;51(Suppl. 1): Poster 898 (LEAD 4); Russell-Jones et al. Diabetes 2008;57(Suppl. 1):A159 (LEAD 5).
Changes in HbA$_{1c}$ from baseline for liraglutide 1.8 mg vs comparator and placebo

- **LEAD 3** Monotherapy
  - Baseline A1c%: 8.3
  - Change in HbA$_{1c}$ (%): -1.1$^\S$

- **LEAD 2** Metformin combination
  - Baseline A1c%: 8.4
  - Change in HbA$_{1c}$ (%): -0.9$^*$

- **LEAD 1** SU combination
  - Baseline A1c%: 8.4
  - Change in HbA$_{1c}$ (%): -1.1$^\S$

- **LEAD 4** Met + TZD combination
  - Baseline A1c%: 8.5
  - Change in HbA$_{1c}$ (%): -1.5$

- **LEAD 5** Met + SU combination
  - Baseline A1c%: 8.2
  - Change in HbA$_{1c}$ (%): -1.1$^\S$

Source: Data originally presented as Marre et al. *Diabetes* 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. *Diabetes* 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. *Diabetologia* 2008;51(Suppl. 1): Poster 898 (LEAD 4); Russell-Jones et al. *Diabetes* 2008;57(Suppl. 1):A159 (LEAD 5).

Note: *Significant vs placebo; $^\S$Significant vs active comparator
Reductions in HbA$_{1c}$ for patients previously on monotherapy

<table>
<thead>
<tr>
<th>LEAD 3</th>
<th>LEAD 2</th>
<th>LEAD 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>Metformin combination</td>
<td>SU combination</td>
</tr>
<tr>
<td>Baseline A1c %</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>#Change in HbA$_{1c}$ (%)</td>
<td>-1.2$^\S$</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

Source: Data originally presented as Marre et al. Diabetes 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. Diabetes 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. Diabetologia 2008;51(Suppl. 1)

Note: *Significant vs placebo; $^\S$Significant vs active comparator. Included patients: add-on to diet and exercise failure (LEAD 3); or add-on to previous OAD monotherapy (LEAD 2,1). LEAD 4 and 5 data excluded due to low number of patients previously on monotherapy.
Hypoglycaemia: liraglutide 1.8 mg vs comparator and placebo

Source: Data originally presented as Marre et al. Diabetes 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. Diabetes 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. Diabetologia 2008;51(Suppl. 1): Poster 898 (LEAD 4); Russell-Jones et al. Diabetes 2008;57(Suppl. 1):A159 (LEAD 5).
**Body weight change: liraglutide 1.8 mg vs comparator and placebo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline BW</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEAD 3</strong> Monotherapy</td>
<td>93.3</td>
<td>-2.5§</td>
</tr>
<tr>
<td><strong>LEAD 2</strong> Metformin combination</td>
<td>88.6</td>
<td>-2.8*§</td>
</tr>
<tr>
<td><strong>LEAD 1</strong> SU combination</td>
<td>81.6</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>LEAD 4</strong> Met + TZD combination</td>
<td>96.3</td>
<td>-2.0*</td>
</tr>
<tr>
<td><strong>LEAD 5</strong> Met + SU combination</td>
<td>85.4</td>
<td>-1.8*§</td>
</tr>
</tbody>
</table>

Source: Data originally presented as Marre et al. *Diabetes* 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. *Diabetes* 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. *Diabetologia* 2008;51(Suppl. 1): Poster 898 (LEAD 4); Russell-Jones et al. *Diabetes* 2008;57(Suppl. 1):A159 (LEAD 5).

Note: *Significant vs placebo; §Significant vs active comparator
Liraglutide reduces visceral and subcutaneous fat
86% of liraglutide induced weight loss was fat mass

**Change in body fat**

<table>
<thead>
<tr>
<th>Change in body fat, kg (%)</th>
<th>Liraglutide 1.2 mg + met</th>
<th>Liraglutide 1.8 mg + met</th>
<th>Glimepiride + met</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.6$ (-1.1%)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2.4$ (-1.2%)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+1.1 kg (+0.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Visceral vs. subcutaneous fat**

<table>
<thead>
<tr>
<th>Change in percentage fat (%)</th>
<th>Visceral</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>-17.1$</td>
<td></td>
<td>-7.8$ -8.5$</td>
</tr>
<tr>
<td>-16.4</td>
<td></td>
<td>-8.5$</td>
</tr>
<tr>
<td>-4.8</td>
<td></td>
<td>-7.8$</td>
</tr>
<tr>
<td>+3.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: LEAD 2 substudy, originally presented as Jendle et al. Diabetes 2008;57(Suppl. 1):A32.

Note: Data are mean±SEM; §Significant vs active comparator
Liraglutide consistently reduces systolic blood pressure

**Bar Chart**

- **LEAD 3**: Monotherapy
  - Liraglutide 1.2 mg: -3.6*
  - Liraglutide 1.8 mg: -2.1
  - Glimepiride: -0.7

- **LEAD 2**: Metformin combination
  - Liraglutide 1.8 mg: -2.3*
  - Liraglutide 1.2 mg: -2.8*
  - Glimepiride: -2.8

- **LEAD 1**: SU combination
  - Liraglutide 1.8 mg: -2.6
  - Liraglutide 1.2 mg: -2.8
  - Rosiglitazone: -0.9

- **LEAD 4**: Met + TZD combination
  - Liraglutide 1.8 mg: -5.5*
  - Liraglutide 1.2 mg: -6.6*
  - Rosiglitazone: -2.3*

- **LEAD 5**: Met + SU combination
  - Liraglutide 1.8 mg: -4.0*
  - Liraglutide 1.2 mg: 0.5

Source: Data originally presented as Colagiuri et al. Diabetes 2008;57(Suppl. 1):A16.

Note: *Significant vs baseline
Nausea almost at background level after 3 months
Lead 3: 5 withdrawals from liraglutide 1.8 mg arm due to nausea

Proportion of subjects with nausea by week and treatment – safety population

Source: The Lancet, accepted for publication (LEAD 3)
Few patients withdrew due to nausea

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Nausea reported at least once (%)</th>
<th>Withdrawals due to nausea (n/total patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD 3</td>
<td>Liraglutide 1.8 mg</td>
<td>29</td>
<td>5/246</td>
</tr>
<tr>
<td>Mono</td>
<td>Glimepiride</td>
<td>9</td>
<td>0/248</td>
</tr>
<tr>
<td>LEAD 2</td>
<td>Liraglutide 1.8 mg</td>
<td>19</td>
<td>15/242</td>
</tr>
<tr>
<td>Metformin</td>
<td>Glimepiride</td>
<td>3</td>
<td>0/242</td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD 1</td>
<td>Liraglutide 1.8 mg</td>
<td>7</td>
<td>2/234</td>
</tr>
<tr>
<td>SU</td>
<td>Rosiglitazone</td>
<td>3</td>
<td>0/231</td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD 4</td>
<td>Liraglutide 1.8 mg</td>
<td>40</td>
<td>16/178</td>
</tr>
<tr>
<td>Met + TZD</td>
<td>Placebo</td>
<td>9</td>
<td>0/175</td>
</tr>
<tr>
<td>combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEAD 5</td>
<td>Liraglutide 1.8 mg</td>
<td>14</td>
<td>2/230</td>
</tr>
<tr>
<td>Met + SU</td>
<td>Glargine</td>
<td>1</td>
<td>0/232</td>
</tr>
<tr>
<td>combination</td>
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</table>

Data orginally presented as Marre et al. Diabetes 2008;57(Suppl. 1):A4 (LEAD 1); Nauck et al. Diabetes 2008;57(Suppl. 1):A150 (LEAD 2); Garber et al, The Lancet, accepted for publication (LEAD 3); Zinman et al. Diabetologia 2008;51(Suppl. 1):Poster 898 (LEAD 4); Russell-Jones et al. Diabetes 2008;57(Suppl. 1):A159 (LEAD 5).
## Liraglutide profile

<table>
<thead>
<tr>
<th>Area</th>
<th>Risk / benefit profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td>• Less than 10% of patients across the LEAD trials</td>
</tr>
<tr>
<td></td>
<td>• No neutralising antibodies</td>
</tr>
<tr>
<td></td>
<td>• No impact on glycemic control</td>
</tr>
<tr>
<td>Cardiovascular profile</td>
<td>• Significant weight loss</td>
</tr>
<tr>
<td></td>
<td>• Significant reduction in systolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>• Significant HbA1c reduction</td>
</tr>
<tr>
<td></td>
<td>• Positive trend on triglycerides and cholesterol (LDL/HDL ratio)</td>
</tr>
<tr>
<td></td>
<td>• Transient heart rate increase of 2-3 beats per minute</td>
</tr>
<tr>
<td>Injection</td>
<td>• Convenient and safe injections</td>
</tr>
<tr>
<td>Acute Pancreatitis</td>
<td>• Low number of incidents observed. No cases of hemorrhagic or necrotising pancreatitis.</td>
</tr>
<tr>
<td></td>
<td>• Incidence rate in the normal range for type 2 diabetes</td>
</tr>
</tbody>
</table>
Steady state levels of GLP-1 after treatment with liraglutide and exenatide

- Modelling of plasma concentration of active drug vs maximal concentration at steady state achieved following clinically relevant doses OD or BD. Based on published exenatide data and modelled liraglutide data.

Source: Jonker et al. Diabetes 56 (Suppl. 1):A160 (Abstract 0605-P from ADA 2007)
Outline of LEAD 6 study design

- **Type 2 diabetes**
  - **HbA1c:** 7.0-11.0%

- **Screening**

- **26 weeks**
  - **Liraglutide**
    - 0.6mg qd 1 week
    - 1.2mg qd 1 week
    - 1.8mg qd 24 weeks
  - Metformin and/or sulfonylurea cont'd at pre-study dose

- **14 weeks**
  - **Exenatide**
    - 5μg bid 4 weeks
    - 10μg bid 22 weeks
LEAD 6 - headline efficacy data for the first 26 weeks

- Average baseline HbA1c level was slightly above 8%
- Patient treated with liraglutide achieved a statistically significantly larger reduction in HbA1c
  - Liraglutide: Reduction of more than 1.1%
  - Exenatide: Reduction of less than 0.8%
- The most frequently reported adverse event was nausea
  - Liraglutide: the percentage of patients reporting nausea fell to low single-digit numbers after 8–10 weeks
  - Exenatide: the percentage of patients reporting nausea was around 10% throughout the study
- The overall rate of hypoglycaemia in the study was low
  - The rate of minor hypoglycaemia was statistically significantly lower in the liraglutide group

Detailed clinical data will be presented 16 October 2008 at the annual Canadian Diabetes Association meeting in Montreal
LEAD 6 14-week extension: shift of patients to liraglutide improves control: $\text{HbA}_1\text{c}$
LEAD 6 14-week extension: shift of patients to liraglutide improves control: FPG

![Graph showing changes in Fasting Plasma Glucose (mM) over weeks before and after changing therapy from Liraglutide to Liraglutide and Exenatide to Liraglutide.](image)
LEAD 6 14-week extension: headline data

- Patients that switched from exenatide to liraglutide:
  - HbA$_{1c}$ statistically significantly decreased by 0.3 percentage points
  - FPG statistically significantly decreased by 0.9 mmol/L
  - Average body weight statistically significantly reduced by approximately 1 kg
  - Systolic blood pressure statistically significantly reduced by close to 4 mmHg

- Tolerability profile of liraglutide confirmed
### Design of phase 3b study vs. sitagliptin

**Entry criteria**
- Treatment with metformin alone for at least three months (≥1500 mg)
- HbA1c between 7.5% and 10

**Randomisation**
- Metformin + liraglutide 1.2mg
- Metformin + liraglutide 1.8mg
- Metformin + sitagliptin 100mg

**Base study**
- 26 weeks

**Extension phase I**
- 26 weeks

**Extension phase II**
- 26 weeks

Total randomised app. 650 subjects
Weight loss over time with liraglutide

- App. 75% treated with 3.0 mg liraglutide achieved a weight loss larger than 5%
- More than 35% treated with 3.0 mg liraglutide achieved a weight loss larger than 10%
- Signs of prediabetes disappeared for 80% of prediabetics treated with 3.0 mg liraglutide

Note: ANCOVA analysis of ITT population, LOCF
Design of the phase 3 programme

Phase 3 programme design

- Weight management & delayed onset of diabetes
  - Liraglutide 3.0 mg
  - Placebo
  - Pre-diabetics only
  - Blinded follow-up off drug

- Weight management in Type 2 Diabetes
  - Liraglutide 3.0 mg
  - Liraglutide 1.8 mg
  - Placebo
  - Observational follow-up off-drug

- Prevention of weight regain
  - Liraglutide 3.0 mg
  - Placebo
  - Observational follow-up off-drug

Total randomised 4500-5000 subjects

- 1 year
- 3 month follow-up
- 3 years
Timeline for phase 3 study and pursued indication in obesity

**Phase 3 timeline**

Programme planning:
- Programme expected to start before year-end 2008
- 1 year data expected early 2011

**Expected indication**

Weight Management:
- Obese subjects (BMI>30)
- ...or overweight subjects with co-morbidities (BMI > 27 + hypertension / dyslipidaemia / type 2 diabetes)
**Concluding remarks**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>Once-daily GLP-1 analogue</td>
<td>Type 2 diabetes</td>
<td>Filed in the US, EU and Japan</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Once-daily GLP-1 analogue</td>
<td>Obesity</td>
<td>Phase 2 completed</td>
</tr>
<tr>
<td>NN9535</td>
<td>Once-weekly GLP-1 analogue</td>
<td>Type 2 diabetes</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Non-invasive GLP-1 analogue</td>
<td>Type 2 diabetes</td>
<td>Pre-clinical</td>
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</table>