Efficacy and safety of semaglutide by baseline BMI in SUSTAIN 1–5 and 7

**Aim**

- Semaglutide (Riso Nordisk, Denmark) is a glucagon-like peptide 1 (GLP-1) analogue approved for the once-weekly subcutaneous treatment of type 2 diabetes (T2D).
- The efficacy and safety of semaglutide were evaluated in the SUSTAIN clinical trial programme, which covered the continuum of care in T2D, including drug-naive subjects and those on background medication with or without additional drugs.
- Across the SUSTAIN trials, semaglutide showed superior reductions in HbA1c, and body weight in placebo and active comparator subgroups, reversible extended injection, insulin, glargine, and dulaglutide, and enabled a greater proportion of subjects to achieve clinically meaningful (15%) weight loss improvements.
- A higher body mass index (BMI) at baseline was generally associated with greater weight loss during semaglutide therapy.
- As exposure to a drug may be affected by body weight, the aim of this post hoc analysis was to assess if reductions in HbA1c were affected by baseline BMI in the SUSTAIN trials.

**Methods**

**SUSTAIN 1–5 and 7 trial designs**

- In SUSTAIN 1–5 and 7, adults with T2D (HbA1c >7%) were randomised to semaglutide 0.5 mg or 1.0 mg, placebo or active comparator (Figure 1).

**Figure 1: SUSTAIN 1–5 and 7 trials**

**Results**

- **Baseline characteristics and demographics**
  - Baseline characteristics were broadly consistent across SUSTAIN 1–5 and 7, with more baseline HbA1c and body weight values ranging from 8.1% to 8.4% and 68 kg to 96 kg, respectively (Table 1).
  - Diabetes duration at baseline ranged from 4.2 years to 13.3 years, reflecting the continuum of T2D care covered by the SUSTAIN trials (Table 1).

**Table 1: Baseline characteristics and demographics by trial**

<table>
<thead>
<tr>
<th>Trial</th>
<th>HbA1c (%)</th>
<th>BMI &gt;25</th>
<th>BMI 25 to &lt;30</th>
<th>BMI 30 to &lt;35</th>
<th>BMI ≥35</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN 1</td>
<td>8.1</td>
<td>50.1</td>
<td>52.9</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>SUSTAIN 2</td>
<td>8.2</td>
<td>51.2</td>
<td>51.8</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>SUSTAIN 3</td>
<td>8.2</td>
<td>51.8</td>
<td>51.2</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>SUSTAIN 4</td>
<td>8.2</td>
<td>51.8</td>
<td>51.2</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>SUSTAIN 5</td>
<td>8.2</td>
<td>51.8</td>
<td>51.2</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>8.2</td>
<td>51.8</td>
<td>51.2</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>SUSTAIN 7</td>
<td>8.2</td>
<td>51.8</td>
<td>51.2</td>
<td>11.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Glucose control**

- Reductions in mean HbA1c (%) from baseline were generally greater with semaglutide vs placebo or active comparator in all BMI subgroups.
- The only exception was in the ≥35 kg/m² BMI subgroup, for semaglutide 0.5 mg vs insulin glargine (−1.7% vs −0.9%, respectively) and for semaglutide 0.5 mg vs dulaglutide (−1.5% vs −1.0%, respectively).
- There were no significant interactions between treatment and BMI, with the exception of semaglutide 0.5 mg in SUSTAIN 7.

**Safety**

- In all treatment arms, adverse events (AEs) occurred in similar proportions of subjects across BMI subgroups.
- The proportion of subjects with gastrointestinal AEs was higher with semaglutide vs placebo or active comparators; however, this event generally decreased with increasing baseline BMI.
- Premature treatment discontinuations due to AEs:
  - Decreased with increasing baseline BMI, potentially reflecting the trend in gastrointestinal AEs.
  - Varies higher in BMI subgroup with semaglutide vs placebo or active comparators.

**Discussion**

- A higher BMI in T2D is challenging, and approaches to therapy are important.
- In the post hoc analysis of the SUSTAIN 1–5 and 7 trials, the estimated treatment differences in mean HbA1c for semaglutide vs placebo or active comparator did not appear to be influenced by baseline BMI, indicating a consistent effect of semaglutide.
- A previous analysis of SUSTAIN 1–5 data, showing change in HbA1c vs placebo, suggests change in body weight with semaglutide, resulting in similar findings.
- Reductions in mean HbA1c from baseline were generally greater with semaglutide vs placebo or active comparators in all BMI subgroups.
- All AEs occurred in a similar proportion of subjects in all treatment arms and across BMI subgroups.
- Gastrointestinal AEs generally decreased with increasing BMI in subjects receiving semaglutide.

**Conclusion**

- Semaglutide consistently reduced HbA1c vs placebo or active comparators in subjects with T2D regardless of their baseline BMI.
- Semaglutide had an acceptable safety profile in all BMI subgroups.