SUSTAIN-6: cardiovascular safety of a once-weekly GLP-1 receptor agonist

Ruth Cordiner, Miles Fisher, and Russell Drummond

To establish cardiovascular safety prior to regulatory approval, pharmaceutical sponsors are mandated to demonstrate that any new antidiabetic drug does not result in an unacceptable increase in cardiovascular risk.\(^1,2\) This can be done either by including patients at high vascular risk in the phase 3 development programme, or by performing a cardiovascular safety trial, or both. This may be followed by a dedicated cardiovascular outcomes trial following approval.

Two recent trials have had a potentially important influence upon the management of people with type 2 diabetes (T2DM) by not simply demonstrating non-inferiority but statistically significant benefits in major adverse coronary events (MACE) when compared to placebo. The EMPA-REG OUTCOME trial from 2015 of the SGLT2 inhibitor empagliflozin demonstrated a 14% reduction in the primary MACE endpoint,\(^3\) and more recently the LEADER trial of the GLP-1 receptor agonist liraglutide demonstrated a 13% reduction in the primary MACE endpoint.\(^4\)

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was simultaneously presented in September 2016 at EASD’s 52nd Annual Meeting in Munich and published in the New England Journal of Medicine. This was intended as a non-inferiority study for regulatory approval; this was confirmed by a 26% reduction in the primary MACE endpoint.\(^5\) Confusingly, as this was entirely a pre-approval study, testing for superiority for the primary outcome was not pre-specified or adjusted for multiplicity. So from a purist statistical perspective this cannot be described as demonstrating superiority.

**SUSTAIN-6 trial design**

Semaglutide is a GLP-1 receptor agonist which permits once-weekly subcutaneous administration due to its extended half-life. The peptide backbone of semaglutide is similar to that of liraglutide and, like liraglutide, has a 94% homology with native GLP-1. Where liraglutide is acylated with a palmitic acid and has an extra amino acid as a spacer between the palmitic acid and the Lys26, semaglutide is acylated with a stearic diacid at Lys26 and has a much larger synthetic spacer.\(^6\) In addition, the amino acid sequence has been further modified in position 8 to reduce degradation by dipeptidyl peptidase-4 (DPP-4).

SUSTAIN-6 was part of the global phase 3a trial programme for semaglutide, which included six separate clinical trials of over 7000 patients. SUSTAIN-6 was a randomised, double-blind, placebo-controlled, parallel-group trial of 3297 patients at 230 sites in 20 countries, which studied effects of once-weekly semaglutide 0.5mg or 1.0mg (n=1648), or placebo which was volume matched to maintain dose-binding (n=1649). Subjects were randomised in 1:1:1:1 ratio, with treatment added to standard-of-care, including lifestyle modification, glucose-lowering therapy, or cardiovascular medications. The median observation time was 109 weeks (104 weeks on treatment; five weeks follow up).

The entry criteria included patients with T2DM and an HbA\(_{\text{1c}}\) of \(\geq 7\%\) (\(\geq 53.0\text{mmol} /\text{mol}\)) who were treatment-naive to antidiabetic drugs, or had prior treatment with no more than two oral antidiabetic agents, with/without basal or premixed insulin. Key inclusion criteria were age over 50 years with established cardiovascular disease, chronic heart failure, or at least stage 3 chronic kidney disease, or age over 60 years with at least one cardiovascular risk factor.

Exclusion criteria included treatment with a DPP-4 inhibitor within 30 days before screening, a GLP-1 receptor agonist or insulin other than basal or premixed within 90 days before screening, a history of acute coronary or cerebrovascular event within 90 days before randomisation, planned revascularisation, or patients who were dialysis-dependent.

SUSTAIN-6 aimed to assess non-inferiority when added to standard of care, not superiority. The primary endpoint was the composite outcome of first occurrence of death from cardiovascular causes, non-fatal myocardial infarction (MI), or non-fatal stroke, i.e. MACE. Secondary endpoints included first occurrence of an expanded composite cardiovascular outcome, an additional composite outcome, retinopathy complications, and new or worsening nephropathy.

**Cardiovascular outcomes**

Figure 1 and Table 1 summarise the main cardiovascular outcomes of the SUSTAIN-6 trial. The primary composite MACE outcome was observed in 108 of 1648 patients (6.6%) and 146 of 1649 (8.9%) patients in the semaglutide and placebo groups respectively (hazard ratio [HR] 0.74; 95% CI 0.58–0.95; p=0.001 for non-inferiority; p=0.02 for superiority). Non-fatal MI occurred in 47 patients on semaglutide (2.9%) vs 64 (3.9%) in the placebo group; a non-statistically significant difference. However, statistical significance was observed in events of non-fatal stroke; 27 patients (1.6%) in the semaglutide group vs 44 (2.7%) in the placebo group (HR 0.61; 95% CI 0.38–0.99; p=0.04). The risk of cardiovascular death was similar for semaglutide vs placebo; 44 patients (2.7%) on semaglutide, 46 patients (2.8%) on placebo (NS). Thus, the SUSTAIN-6 trial confirmed the primary hypothesis of non-inferiority of semaglutide compared to placebo with a meaningful 26% reduction in the primary outcome of cardiovascular death, non-fatal MI or non-fatal stroke. Strikingly, the number needed-to-treat (NNT) to prevent one cardiovascular death, non-fatal MI or non-fatal stroke was 45 subjects for two years.
Glycaemic control and body weight
In SUSTAIN-6, HbA1c was reduced by 1.1% and 1.4% in those on 0.5mg and 1.0mg of semaglutide respectively at week 104 (mean baseline of 8.7%). A 0.4% reduction was observed with placebo. There was increased use of sulphonylureas and insulin in the placebo group, but frequency of hypoglycaemia was not different. Reductions in mean body weight of 3.6kg and 4.9kg were observed with 0.5mg and 1.0mg semaglutide respectively, and once corrected for changes in the placebo groups body weight on semaglutide was 2.9kg lower in those on 0.5mg and 4.3kg lower in the 1.0mg group (p<0.001 for both).

Microvascular outcomes
Outcomes were positive for nephropathy, with a lower risk of new or worsening nephropathy with semaglutide, which was observed early in the trial and sustained until week 104. In contrast to the positive cardiovascular and nephropathy outcomes in the trial, diabetic retinopathy events were increased and occurred in 50 patients on semaglutide (3.0%) vs 29 (1.8%) with placebo (HR, 1.76; 95% CI 1.11–2.78; p=0.02). Retinopathy events, however, were few, but included: the requirement for photoocoagulation or the use of an intravitreal agent; vitreous haemorrhage; or blindness. Most strikingly, the difference between the two groups was observed less than four months from randomisation, and was sustained until week 104. The authors note an association has been acknowledged between rapid glucose lowering and worsening of retinopathy in patients with type 1 diabetes.7 This slight but significant increase in retinopathy is worrying and will require further analysis and investigation.

Side effects and safety
As would be expected, there was increased occurrence of gastrointestinal disorders in the semaglutide group vs placebo, with the majority occurring during the first 30 weeks with mild-to-moderate severity. Patients on 1.0mg semaglutide discontinued treatment earlier, and at higher proportions (%) compared with 0.5mg or placebo. With regard to pancreatic safety, nine patients on semaglutide developed acute pancreatitis, vs 12 with placebo. Lipase and amylase levels were noted to be significantly higher in those on semaglutide. A proportion of patients on semaglutide (n=30) developed antibodies towards the drug, with almost half (n=14) developing positive antibody titres by week 44; however, this was transient with only four patients remaining positive during follow up.

Discussion
Several similarities can be observed comparing EMPA-REG OUTCOME, LEADER and SUSTAIN-6. All three included patients with T2DM with either existing cardiovascular disease, or high cardiovascular risk (LEADER and SUSTAIN), with evaluation of MACE as the primary endpoint. All the trials had similar average age in the trial (63–65 years) and study patients had diabetes of over 10 years. SUSTAIN-6 was a shorter study with 2.1 years of follow up vs 3.8 years and 3.1 years for LEADER and EMPA-REG OUTCOME respectively.

All three trials showed reduction in the primary endpoint, but analysis of the components of the primary

endpoint showed differences, with SUSTAIN-6 showing statistically significant reductions in non-fatal stroke, whereas in LEADER and EMPA-REG OUTCOME there were differences in cardiovascular death and total mortality that were not observed in SUSTAIN-6. The mechanism by which semaglutide produces this beneficial effect is contentious. Within the LEADER trial, thus potentially attributable to semaglutide, there are putative associations with modification of progression of atherosclerotic vascular disease.8

In terms of NNT to prevent one cardiovascular death, non-fatal MI or non-fatal stroke, SUSTAIN-6 declared NNT=45 for 2 years, which is similar when compared with LEADER (NNT=55 for 3.8 years) or EMPA-REG (NNT=62 for 3.1 years). Like LEADER, more patients in the placebo group received intensification of their antidiabetic treatment than in the semaglutide group; therefore a potential confounder is whether the observed benefit can be entirely attributable to semaglutide itself or to adverse effects of the other therapies that were used in the placebo groups. Importantly, reductions in heart failure were observed in EMPA-REG OUTCOME that were not seen in LEADER or SUSTAIN-6, suggesting a different mechanism of benefit with empagliflozin. The slow separation of events in LEADER and SUSTAIN-6 suggests effects on the progression of atheroma. Although the relative contributions of the different components to the primary outcome were different (stroke for SUSTAIN-6, cardiovascular death for LEADER) all components were reduced, and a longer, larger trial with semaglutide might give significant reductions in other components.

As a non-inferiority trial with a positive benefit, it seems likely that semaglutide will be approved by the FDA on the grounds of cardiovascular safety. However, for a definitive conclusion on the macromolecular endpoints described above, a larger, longer dedicated cardiovascular outcome trial will be required. It is the stated intention of Novo Nordisk to perform such a study after approval in order to obtain endorsement of cardiovascular risk reduction in the licence. There is also an oral formulation of semaglutide which is taken on a daily basis and which is associated with similar reductions in HbA1c and weight to those of the subcutaneous weekly injection, and this will also be studied in a large cardiovascular outcomes trial.9

Finally, the addition of a third major trial reporting reductions in cardiovascular outcomes augurs benefit for people with T2DM but also ratifies and confirms the FDA mandate for cardiovascular safety as a crucial and timely requirement that is likely to lead to a paradigm shift in the management of T2DM.

As with all novel agents, and class as a whole, the position within the guidelines for T2DM management is a subject of debate. The issue, which will only be resolved with certainty following further focused studies, is whether semaglutide would not only be appropriate for second-line use following metformin in patients with the cardiovascular profile present in almost those included in SUSTAIN-6, but also as primary therapy patients with T2DM with known cardiovascular disease.

Ruth Cordiner,1 MRCP
Miles Fisher,1 MD, FRCP
Russell S Drummond,1 MD, FRCP
1Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, UK

Declaration of interests
Dr Cordiner has no conflicts of interest to declare.
Prof Fisher and Dr Drummond have done advisory boards and lectures for Novo Nordisk.

References
References are available in Practical Diabetes online at www.practicaldiabetes.com.


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Semaglutide</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No./100 person-yr</td>
<td>No. (%)</td>
<td>No./100 person-yr</td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>108 (6.6)</td>
<td>3.24</td>
<td>146 (8.9)</td>
<td>4.44</td>
</tr>
<tr>
<td>All-cause death, non-fatal myocardial infarction, or non-fatal stroke</td>
<td>122 (7.4)</td>
<td>3.66</td>
<td>158 (9.6)</td>
<td>4.81</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>44 (2.7)</td>
<td>1.29</td>
<td>46 (2.8)</td>
<td>1.35</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>47 (2.9)</td>
<td>1.4</td>
<td>64 (3.9)</td>
<td>1.92</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>27 (1.6)</td>
<td>0.8</td>
<td>44 (2.7)</td>
<td>1.31</td>
</tr>
<tr>
<td>Hospitalisation for unstable angina</td>
<td>22 (1.3)</td>
<td>0.65</td>
<td>27 (1.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>83 (5.0)</td>
<td>2.5</td>
<td>126 (7.6)</td>
<td>3.85</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>59 (3.6)</td>
<td>1.76</td>
<td>54 (3.3)</td>
<td>1.61</td>
</tr>
</tbody>
</table>
References