INTRODUCTION
• Cardiovascular (CV) safety outcome study is routinely required in type 2 diabetes (T2DM) drug approval.
• Empagliflozin (Sodium-glucose cotransporter 2 inhibitors [SGLT2]) approval for CV indication provides an additional risk reduction option for T2DM patients with high CV risks [1].
• Presents a confounding in the CV effect assessment for future studies.
• Patients might already take SGLT2i at the study start or initiate it during the study.
• Concomitant administration of GLP-1ra increases the CV effect assessment uncertainty, especially when there is imbalanced SGLT2i addition between treatments during the study.
• A glugon-like peptide-1 receptor agonists (GLP-1ra) class drug CV outcome study as a case study to understand the impact of this co-administration.

OBJECTIVES
1. To estimate GLP-1ra, SGLT2i, GLP-1ra + SGLT2i CV effects relative to SOC using RWD data.
2. To assess the impact of this confounding and other influencing factors on the study probability of success (POS) of a GLP-1ra drug CV outcome study.

METHODS
1. Simulate patients’ HbA1c over time for GLP-1ra and SOC using PopPK and PK/HbA1c exposure-response models and planned study design.
2. Model antidiabetic medication addition, especially imbalanced addition between treatments due to differential HbA1c control using literature and internal CV outcome studies.
3. Estimate relative CV effects of GLP-1ra, SGLT2i, GLP-1ra+SGLT2i vs SOC using Truven database,
   • Assume all SGLT2i with similar CV effects.
   • GLP-1ra effect can be assessed separately if desired (not done).
   • See left for details.
4. Simulate the study and CV events with SGLT2i addition at baseline & during the study.
   • Integrate PK, PK/PD, models, study design, and assumptions etc.
   • Percentage SGLT2i patients at baseline and during the study based on SGLT2i utilization market prediction.
5. Analyze each simulated study as if observed and summarize study POS (over 1000 simulated studies).
   • To explore and identify influential factor(s) such as SGLT2i patient%, study sample size, enrollment rate, treatment initiation and discontinuation rates.

RESULTS
• Imbalanced GLP-1ra and SGLT2i addition during the blinded study phase under differential HbA1c control of SOC and GLP-1ra arms was established using an internal historical CV outcome study (not shown).

CONCLUSIONS:
• Design: 4000 patients with ~300 events to non inferiority with margin 1.3 (safety).
• The simulation indicated a small impact of differential SGLT2i addition during the blinded study phase unless there was a fairly large % SGLT2i patient usage.
• The percentage of patients on GLP-2i can be monitored during the study to mitigate the risk.

REFERENCES

ACKNOWLEDGEMENTS:
Zhaoling Meng (1), James Rogers (3), Jonathan Sidi (3), Qi Tang (1), Dimple Patel (1), Nadia Gaudel-Dedieu (2) and David Delvart (2)
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Figure 1: Simulated Power assuming no additional GLP-1ra CV benefit when on top of SGLT2i.

Figure 2: Simulated Power assuming no additional GLP-1ra CV benefit when on top of SGLT2i.

Table 1: LEADER2CV antidiabetic medication addition during the study.

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>GLP-1ra</th>
<th>SGLT2i</th>
<th>GLP-1ra + SGLT2i</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>0.93</td>
<td>0.96</td>
<td>0.94</td>
<td>0.93</td>
</tr>
<tr>
<td>2 years</td>
<td>0.94</td>
<td>0.94</td>
<td>0.93</td>
<td>0.92</td>
</tr>
</tbody>
</table>

GLP-1ra: 1st GLP-1ra CV event.
SGLT2i: 1st SGLT2i CV event.
SOC: Non-glucose cotransporter 2 inhibitors (not SGLT2i).

Table 2: MAACE: GLP-1 vs. non-GLP-1 CV effect by SGLT2i use subgroup.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>GLP-1ra</th>
<th>SGLT2i</th>
<th>GLP-1ra + SGLT2i</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.34</td>
<td>0.62</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>No SGLT2i</td>
<td>0.36</td>
<td>0.54</td>
<td>0.42</td>
<td>0.56</td>
</tr>
<tr>
<td>Prior SGLT2i</td>
<td>0.32</td>
<td>0.49</td>
<td>0.40</td>
<td>0.51</td>
</tr>
</tbody>
</table>

MAACE: MI, stroke, CV death.}

Figure 3: First GLP-1ra & first SGLT2i Patient Counts in Truven.

<table>
<thead>
<tr>
<th>Event Type</th>
<th>GLP-1ra</th>
<th>SGLT2i</th>
<th>GLP-1ra + SGLT2i</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.10</td>
<td>0.16</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.08</td>
<td>0.12</td>
<td>0.10</td>
<td>0.12</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.06</td>
<td>0.09</td>
<td>0.07</td>
<td>0.08</td>
</tr>
</tbody>
</table>

| Total | 0.32 | 0.37 | 0.33 | 0.34 |

• RWD estimated a GLP-1ra vs. SOC CV benefit ~10% and smaller GLP-1ra+SGLT2i vs. SGLT2i-2CV benefit in high CV risk population.

CONCLUSIONS:
Real world data was used to estimate the concomitant CV effects with/without empagliflozin and inform the CTS and study POS assessment.

REAL WORLD EVIDENCE AND MODEL-INFORMED DRUG DEVELOPMENT — an antidiabetic drug cardiovascular outcome case study

PAGE 2018 Montreux, Switzerland

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