Correlation between means over time was estimated

**RESULTS**

- For all drug classes, the change in body weight over time was well described by an exponential model (Figure 2).
- For SGLT2i, there was an immediate weight loss (Emax, ~0.7 kg observed within 1 week) in addition to a slowly developing weight loss.
- There was no significant difference in the time course of weight change across the drug classes.
- The estimated half-life values ranged from 1.6 weeks for GLP1 (except exenatide) to 6.7 weeks for T2D.
- Dose response was well described by an Emax model for SGLT2i, TZD, DPP4i and GLP1.
- A high dose-independent treatment effect was estimated for metformin and SU.

**CONCLUSIONS**

- A model-based meta-analysis was used to quantify the time course of body weight response to dose of PF-04971729 relative to other anti-diabetic agents including SGLT2i, DPP4i, GLP1, SU, TZD, and metformin.
- The analysis provided insights into the relative effects across the various mechanisms of action and among the 27 anti-diabetic agents, and quantified the impact of time on onset of weight loss.
- Impact of baseline body weight.
- The analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel drugs with existing treatments.

**ACKNOWLEDGMENTS**

This research was supported by Pfizer, Inc. The authors would like to thank members of the CV/MED Research Unit, especially Neeta Amin, Gianluca Nucci, and Xin Wang for their contributions. This research was supported by Pfizer, Inc. The authors would like to thank members of the CV/MED Research Unit, especially Neeta Amin, Gianluca Nucci, and Xin Wang for their contributions.

**REFERENCES**


**ABBREVIATIONS**

- CV/MED: Cardiovascular and Metabolic Diseases
- DPP4: Dipeptidyl peptidase-4
- GLP1: Glucagon-like peptide-1
- SGLT2i: Sodium-glucose cotransporter-2 inhibitors
- SU: Sulfonylurea
- TZD: Thiazolidinedione

**TABLES**

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Dose response to body weight change for various anti-diabetic agents</th>
<th>Reference</th>
<th>Change from baseline (kg), difference from placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>A significant weight loss was estimated for SU (0.5 ± 1.1 kg) and DPP4i (2.5 ± 1.2 kg)</td>
<td>[1]</td>
<td>Decrease in body weight from baseline</td>
</tr>
<tr>
<td>50</td>
<td>There was no significant difference in Emax across anti-diabetic agents within a class and across time for each drug.</td>
<td>[2]</td>
<td>Decrease in body weight from baseline</td>
</tr>
<tr>
<td>100</td>
<td>The baseline effect was consistent across all drug classes.</td>
<td>[3]</td>
<td>Decrease in body weight from baseline</td>
</tr>
<tr>
<td>200</td>
<td>There was no significant difference in Emax across anti-diabetic agents within a class and across time for each drug.</td>
<td>[4]</td>
<td>Decrease in body weight from baseline</td>
</tr>
</tbody>
</table>

**FIGURES**

- Figure 1: Model-estimated and observed dose vs body weight changes for anti-diabetic agents that cause significant weight loss.
- Figure 2: Model-estimated and observed dose vs body weight changes for anti-diabetic agents that cause significant weight loss.
- Figure 3: Model-estimated and observed dose vs body weight changes for anti-diabetic agents that cause significant weight loss.
- Figure 4: Impact of baseline body weight on treatment response.
- Figure 5: Estimated dose response for differences in body weight changes of SGLT2i (1.5 to 2 kg), GLP1 (0.7 to 1.5 kg) and metformin (0.4 kg), and a statistically significant weight gain for DPP4i (2.5 kg).

**ANALYSIS**

- The analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel drugs with existing treatments.
- The analysis provides insights into the relative effects across the various mechanisms of action and among the 27 anti-diabetic agents, and quantifies the impact of time on onset of weight loss.
- Impact of baseline body weight.
- The analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel drugs with existing treatments.

**TECHNICAL DETAILS**

- The final model is a two-compartment model with an absorption phase and an elimination phase.
- The elimination phase is described by a first-order process.
- The absorption phase is described by a zero-order process.
- The model includes the following parameters:
  - Emax: Maximal effect
  - EC50: Half-maximal effect
  - t1/2: Half-life
  - tmax: Time to peak effect
  - AUC: Area under the curve
  - Cmax: Maximum concentration

**DATA SOURCES**

- Clinical trial data from Pfizer, Inc.
- Registry data from various pharmaceutical companies.
- Meta-analysis of published literature.

**CONTRIBUTIONS**

- Jaap Mandema: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft.
- Kevin Sweeney: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft.
- Steven Terral: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft.
- Vaishali Sahasrabudhe: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft.