MODEL-BASED META-ANALYSIS OF THE EFFECT ON BODY WEIGHT OF PF-04971729, A SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITOR (SGLT2i), IN COMPARISON TO OTHER SGLT2i AND ANTI-DIABETIC AGENTS (ADA)

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ABSTRACT

PF-04971729 is a potent, selective SGLT2i in development for treatment of type 2 diabetes mellitus (T2DM). Since there is growing recognition of the need for comparative effectiveness of various ADA, a model was developed to quantify the time course of dose vs body weight change for PF-04971729 relative to other ADA including SGLT2i, DPP4 inhibitors (DPP4i), GLP-1 agonists (GLP1), sulfonylureas (SU), thiazolidinediones (TZD), and metformin. A systematic literature review yielded 120 randomized controlled trials representing >52000 T2DM patients and 21 drugs. Data for PF-04971729 were obtained from a 12-week, randomized, placebo-controlled study in T2DM patients on metformin background. A dose response was observed for weight effect of SGLT2i, TZD, DPP4i and GLP-1 whereas a dose-independent treatment effect was estimated for metformin and SU. The treatment effect was significantly dependent on baseline weight. The model predicted a statistically significant weight loss for 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 (0.5 to 1.1 kg), TZD (3.1 to 3.3 kg) and SU (2.8 to 4.3 kg) at 24 weeks. Figure 2 illustrates model-estimated and observed dose response for various SGLT2i. Estimated differences in weight loss between PF-04971729-25 mg and top doses of other SGLT2i were small (-0.20 to -0.34 kg). This analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel drugs with existing treatments.

INTRODUCTION

The emergence of new drugs for the treatment of T2DM over the last decade has resulted in a need to demonstrate differentiation in efficacy and/or safety (and potentially other beneficial effects such as weight loss) relative to existing therapies. In this challenging drug development environment, the availability of objective tools to guide go-no go decisions, dose selection, and trial strategy has become critically important. Model-based meta-analysis is a tool that explicitly incorporates the effect of dose and duration using standard pharmacology models and assumptions. The methodology utilizes and leverages data from internal and external sources and can strengthen the knowledge of a particular drug and its comparative efficacy and safety to other treatment options.

METHODS

A systematic literature review (using PubMed, conference abstracts and posters, other sources) yielded a database comprising 120 randomized controlled trials representing >52000 T2DM patients and 21 anti-diabetic agents. PF-04971729 data were obtained from a 12-week, randomized, placebo-controlled study in T2DM patients on metformin background and combined with the database of body weight changes after treatment with SGLT2i, GLP1, DPP4i, SU, TZD, and metformin.

The dose response relationship was described using the following model:

$$Effect_{ijk} = Eo_{i,k} + \frac{E_{max,class,k}(t) \cdot Dose_{ij}}{Dose_{ij} + ED_{50,drug}} + \varepsilon_{ijk}$$

- $Effect_{ijk}$ is the mean change from baseline for the k^{th} time point in the j^{th} arm in the i^{th} trial
- $Eo_{i,k}$ is the placebo response for the k^{th} time point in the i^{th} trial
- E_{max} is the maximal drug effect at time t, reflecting the maximal difference in response between placebo and active treatment
- Dose is the dose normalized to a certain frequency (daily / weekly) for each treatment
- ED_{50} is the dose to achieve 50% of Emax for each drug
- ε_{ijk} is the residual variability with variance σ^2_{ik}/N_{ij} σ^2_{ik} is the SD of the change from baseline.
- Correlation between means over time was estimated

The onset of weight change was described by an exponential relationship of E_{max} with time

$$E_{\max}(t) = E_{\max,class} \cdot (1 - \exp(-kt_{class} \cdot time))$$

For SGLT2i, the onset of weight change was best described by a model that assumed an immediate initial effect ($E_{max,0}$) followed by a slow additional effect ($E_{max,SS}$)

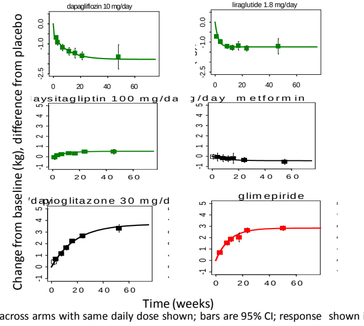
$$E_{\max}(t) = E_{\max,o} + (E_{\max,ss} - E_{\max,o}) \cdot (1 - \exp(-kt \cdot time))$$

- kt is the rate constant for the speed of onset

RESULTS

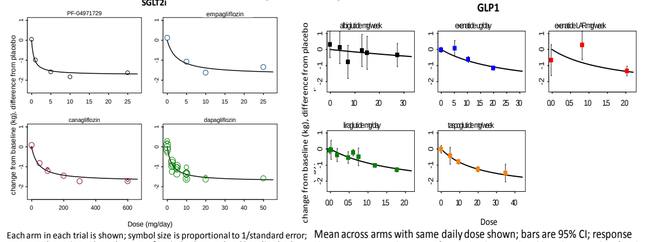
- For all drug classes, the change in body weight over time was well described by an exponential onset model (Figure 1 shows body weight changes for representative drugs in each class)
  - For SGLT2i, there was an immediate weight loss ($E_{max,0}$~0.7 kg observed within 1 week) in addition to a slowly developing weight loss
  - There was a 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 13 weeks for TZD
- Dose response was well described by an E_{max} model for SGLT2i, TZD, DPP4i and GLP1 while a dose-independent treatment effect was estimated for metformin and SU (Figures 2 and 3)
  - A significant weight loss was estimated for SGLT2i (range 1.5 to 2 kg) and GLP1 (range 0.7 to 1.5 kg)
  - A significant weight gain was estimated for SU (range 2.8 to 4.3 kg), TZD (range 3.1 to 3.3 kg), and DPP4i (range 0.5 to 1.1 kg)
  - A very small weight loss was estimated for metformin (0.4 kg)
- There was no significant difference in Emax across anti-diabetic agents within a class
- Emax was dependent on baseline body weight (Figure 4)
  - Emax was 70% smaller in a patient population with mean weight of 60 kg and 136% greater in a patient population with mean weight of 120 kg vs. a patient population with typical weight of 90 kg.
  - The baseline effect was consistent across all drug classes
- Estimated differences in weight loss between 25 mg dose of PF-04971729 and top doses of other SGLT2i were small (range -0.20 to -0.34 kg)

Figure 1. Model-estimated and observed time-course of body weight changes for dapagliflozin, liraglutide, sitagliptin, pioglitazone, glimepiride and metformin



Mean across arms with same daily dose shown; bars are 95% CI; response shown is for baseline body weight of 90 kg and on metformin background for dapagliflozin, liraglutide, sitagliptin, pioglitazone and glimepiride

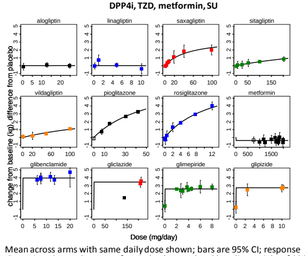
Figure 2. Model-estimated and observed dose vs body weight changes for anti-diabetic agents that cause significant weight loss



Each arm in each trial is shown; symbol size is proportional to 1/standard error; response shown is at 12 weeks on metformin background and baseline body weight of 90 kg

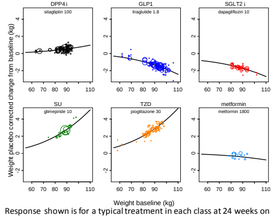
Mean across arms with same daily dose shown; bars are 95% CI; response shown is at 24 weeks on metformin background and baseline weight of 90 kg

Figure 3. Model-estimated and observed dose vs body weight changes for anti-diabetic agents that cause significant weight gain or are weight-neutral



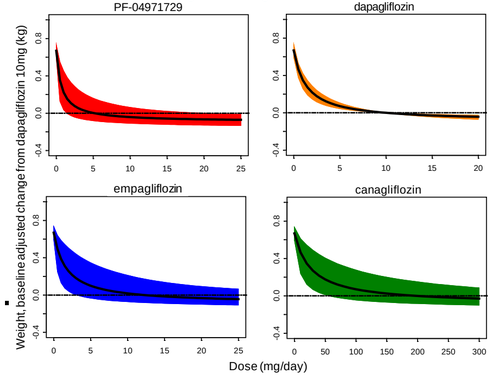
Mean across arms with same daily dose shown; bars are 95% CI; response shown is at 24 weeks on metformin background and baseline weight of 90 kg

Figure 4. Impact of baseline body weight on treatment response



Response shown is for a typical treatment in each class at 24 weeks on metformin background

Figure 5. Estimated dose response for difference in body weight changes of SGLT2i from dapagliflozin 10 mg



Response shown is at 24 weeks on metformin background and baseline body weight of 90 kg; reference line = difference from dapagliflozin 10 mg; shaded area represent 90%CI

CONCLUSIONS

- A model-based meta-analysis was used to quantify the time course of body weight response vs 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 21 anti-diabetic agents, and quantified:
  - Impact of time: 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 anti-diabetic agents with existing treatments

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