MODEL-BASED META-ANALYSIS OF THE HbA1c LOWERING EFFECT 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 time course of dose vs HbA1c response of 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 153 randomized controlled trials representing >67000 T2DM patients and 21 drugs. PF-04971729 data were obtained from a 12-week, randomized, placebo-controlled study in T2DM patients on metformin background. The model indicated that SGLT2i have the fastest onset time for HbA1c lowering followed by DPP4i, metformin, SU, TZD and GLP1. A significant loss of effect over time was predicted for all drug classes except SGLT2i and TZD. There was no significant difference in maximal effect (Emax) across ADA within a class; however, Emax was dependent on baseline HbA1c and time (Emax = -0.70% [95% CI -0.62 to -0.78] for SGLT2i at 12 weeks at baseline HbA1c of 8%). Figure 2 illustrates model-estimated and observed dose response for various SGLT2i and other classes of ADA. Estimated differences in HbA1c lowering between PF-04971729 25 mg and top doses of other SGLT2i ranged from -0.01 to -0.13%. This analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of novel ADA 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.

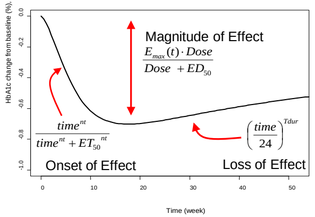
METHODS

A systematic literature review (using PubMed, conference abstracts and posters, other sources) yielded a database comprising 153 randomized controlled trials representing >67000 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 HbA1c changes after treatment with SGLT2i, GLP1, DPP4i, SU, TZD, and metformin.

The dose response relationship was described using the following model:

$$Effect_{ijt} = Eo_{it} + \frac{E_{max,class} \cdot Dose_{ijt}}{Dose_{ijt} + ED_{50,drug}} \cdot \frac{time^{nt}}{time^{nt} + ET_{50}{}^{nt}} \cdot \left(\frac{time}{24}\right)^{Tdur} + \varepsilon_{ijt}$$

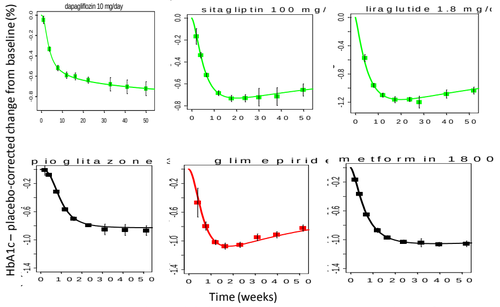
- $Effect_{ijt}$ is the mean change from baseline HbA1c in the j^{th} arm in the i^{th} trial at time t
- Eo_{it} is the placebo response for the i^{th} trial (non-parametric placebo model) at time t
- $E_{max,class}(t)$ is the time course of maximal drug effect, reflecting maximal difference in response 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
- ET_{50} is the median onset time for HbA1c lowering
- nt and Tdur are the slopes for onset and offset, respectively
- ε_{ijt} is the residual variability with variance σ^2_{it}/N_{ij}



RESULTS

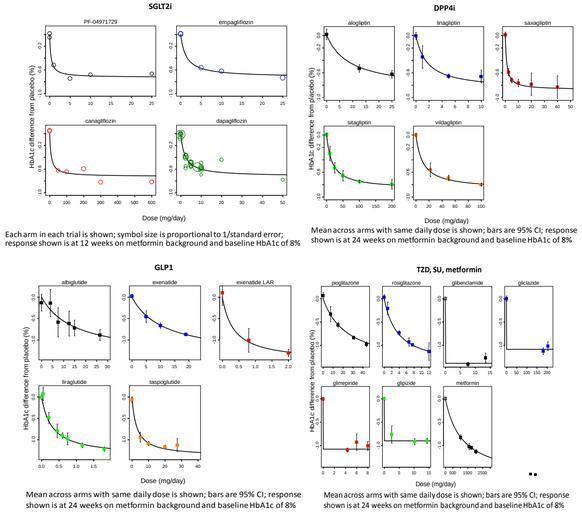
- The model estimated a significant difference in rate of onset for the various classes (Figure 1)
  - SGLT2i had the fastest onset time for HbA1c lowering (ET_{50} = 3 weeks) followed by DPP4i, metformin, SU, GLP1 (ET_{50} = 7.2-8.7 weeks), and TZD (ET_{50} = 9.6 weeks)
  - Relatively fast onset for SGLT2i could be explained by their immediate effect on glucose excretion
- Significant loss of effect was estimated for all drug classes apart from SGLT2i and TZD (Figure 1)
  - SU show steepest decline in glycemic control between 24 and 52 weeks followed by GLP1, DPP4i, and metformin
- There was no significant difference in Emax across anti-diabetic agents within a class (Figure 2)
- Emax was dependent on baseline HbA1c (Figure 3)
  - Patient populations with a baseline HbA1c of 6 had a 41% smaller response than patient populations with a median baseline of 8
  - Patient populations with a baseline HbA1c of 10 had a 51% greater response than patient populations with a median baseline of 8
- The model-estimated Emax was -0.70% [95% CI -0.62 to -0.78] for SGLT2i at 12 weeks at baseline HbA1c of 8%
- Estimated differences in HbA1c lowering between 25 mg dose of PF-04971729 and top doses of other SGLT2i ranged from -0.01 to -0.13%

Figure 1. Model-estimated and observed time-course of HbA1c lowering for dapagliflozin, sitagliptin, liraglutide, pioglitazone, glimepiride and metformin



Mean across arms with same daily dose shown; bars are 95% CI; response shown is for baseline HbA1c of 8% and on metformin background for dapagliflozin, sitagliptin, liraglutide, pioglitazone and glimepiride

Figure 2. Model-estimated and observed dose vs HbA1c lowering for SGLT2i, DPP4i, GLP1, TZD, SU and metformin



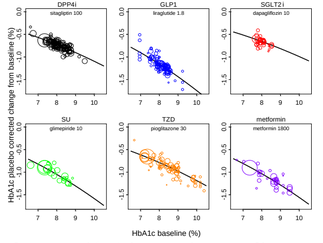
Each arm in each trial is shown; symbol size is proportional to 1/standard error; response shown is at 12 weeks on metformin background and baseline HbA1c of 8%

Mean across arms with same daily dose is shown; bars are 95% CI; response shown is at 24 weeks on metformin background and baseline HbA1c of 8%

Mean across arms with same daily dose is shown; bars are 95% CI; response shown is at 24 weeks on metformin background and baseline HbA1c of 8%

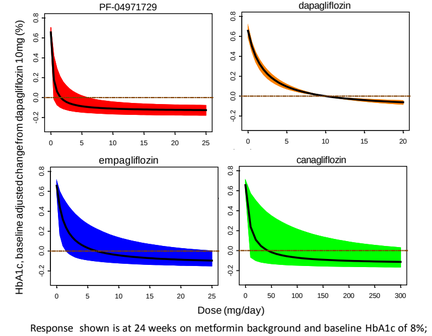
Mean across arms with same daily dose is shown; bars are 95% CI; response shown is at 24 weeks on metformin background and baseline HbA1c of 8%

Figure 3. Impact of baseline HbA1c on treatment response



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

Figure 4. Estimated dose response for difference in HbA1c lowering of SGLT2i from dapagliflozin 10 mg



Response shown is at 24 weeks on metformin background and baseline HbA1c of 8%; reference line = dapagliflozin 10 mg; shaded area represent 90%CI

- Specific background treatments impacted specific randomized treatments
  - SU, TZD or Insulin background significantly diminished DPP4i response
  - Any background treatment significantly diminished GLP1 response, with a greater decrease on TZD background therapy when compared to SU or metformin
  - Insulin background treatment significantly diminished SGLT2i response
  - There was no significant impact of background treatment on SU, TZD or metformin response

CONCLUSIONS

- A model-based meta-analysis was used to quantify the time course of HbA1c 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 efficacy across the various mechanisms of action and among the 21 anti-diabetic agents, and quantified:
  - Impact of time: onset and loss of drug effect
  - Impact of baseline HbA1c
  - Impact of background treatment
- 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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