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 patient-selected 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 mean change in HbA1c (% of placebo) relative to ADA including SGLT2i, DPP4i, SU, TZD and GLP1. The model was built using a population PK-PD model and systematic review and meta-analysis (SRA) of 164 randomized controlled trials (RCT) in >67000 T2DM patients and 21 ADA. The study aimed to perform a meta-analysis of SGLT2i at 12 weeks at baseline HbA1c of 8%. 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 aspects) (Figure 1).

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 background treatment
- 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 Insulin background
- Insulin background treatment significantly diminished SGLT2i response
- There was no significant impact of background treatment on SU, TZD or metformin response

The analysis offers a quantitative framework to leverage external data and thus enables an indirect comparison of ADA with existing treatments.

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 (ET50 = 3 weeks) followed by DPP4i, metformin, SU, GLP1 (ET50 = 7.2-8.7 weeks), and TZD (ET50 = 9.6 weeks) (Figure 2)
- Relatively fast onset for SGLT2i could be explained by their immediate effect on renal glucose excretion (Figure 1)

CONCLUSIONS
- A model-based meta-analysis was used to quantify the time course of HbA1c response of PF-04971729 relative to other anti-diabetic agents including SGLT2i, DPP4i, 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 of dose 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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