Mathematical Modeling of Patient Response and Nonresponse to Therapy

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Introduction

- For novel type 2 diabetes (T2D) drug candidates, a major challenge lies in planning for the likelihood of Phase 2 and Phase 3 clinical trial success. Later-stage trial subjects may differ significantly in disease severity and other comorbidities and thus may respond differently than patients in earlier-stage trials.
- Also, uncertainties about the drug candidate mechanisms of action (MOA) may impact the ability to select patients most likely to respond.
- Quantitative PhysioPD™ modeling is often used to provide mechanistic insight to support decision making in early drug development stages such as target and drug candidate selection. It can also inform later drug development stages and trial design.

Objectives

- Integrate multiple novel drug targets and standards of care (SOC) therapies into quantitative PhysioPD Platform of diabetes.
- Integrate preclinical and early stage human trial data to create a cohort of T2D Virtual Patients (VPs) to be used for later-stage trial simulations.
- Provide insight into drug MOA that impacts patient response and non-response to therapy in Phase 2 and Phase 3 clinical trials.

Methods

A quantitative mechanistic T2D PhysioPD™ Research Platforms was used to assess impact of target mechanisms on late-stage clinical trial outcomes.

- Rosa and Takeda developed a T2D PhysioPD Platform, a quantitative mechanistic model of glucose, insulin, and lipid regulation together with food intake and representations of multiple drugs.
- The Platform integrated published and proprietary data for TAK-875, a first-in-class GPR40 agonist developed by Takeda, including a pharmacokinetic model for TAK-875 and mechanistic representation of TAK-875 pharmacodynamic effects.
- A cohort of heathy and diabetic Virtual Patients (VPs) was developed to be representative of the average baseline characteristics of Takeda human trial subjects.
- The Platform was qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1).
- The response of healthy VPs to 14 days of TAK-875 treatment was calibrated using Phase 1 clinical data over a range of doses.
- Subsequently, clinical trial PhysioPD simulations of Phase 2 and Phase 3 trials were conducted in the cohort of T2D VPs, and the results were compared to the clinical data.

Figure 1. The Platform was qualified according to Rosa's Model Qualification Method[1] (MQM)

Results

A Diabetes PhysioPD Platform was developed and qualified.

- Platform development and qualification included an evaluation using preclinical and clinical data including dietary and drug interventions. (Figure 2)
- Diet interventions included response to fasting, oral glucose tests, and meal tests.
- Simulated drugs included metformin, insulin, liraglutide, sitagliptin, sulfonylureas, and SGLT inhibitors. All VPs, both healthy and diabetic, were tested (not shown)

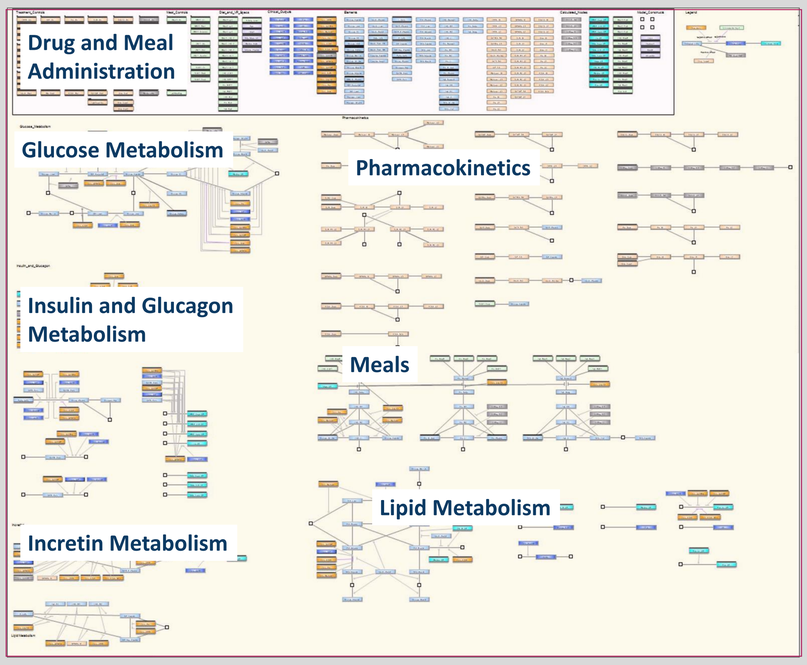

Figure 2. PhysioMap® of the Diabetes Platform is a graphical representation of the disease physiopathology and drug interventions.

Sensitivity analysis identified key pathways as drivers of TAK-875 response.

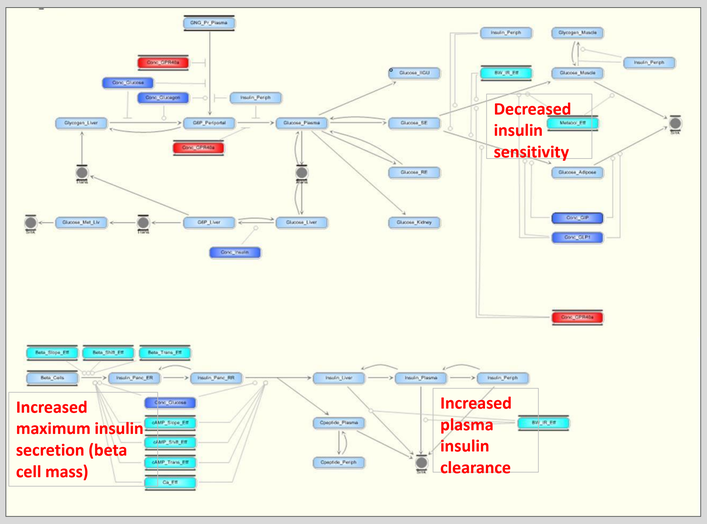

Figure 3. Sensitivity analysis was used to identify 3 pathways each with multiple parameters which tested as sensitive for drug response. Decreased insulin sensitivity, increased insulin clearance, and maximum insulin secretion were all key drivers of drug response.

Patient beta cell function and insulin resistance at baseline were found to be the primary drivers of response.

- Changing the three most sensitive pathways identified by sensitivity analysis (Figure 3) yielded different magnitudes of response:
  - Changes in maximum insulin secretion (beta cell mass) had the largest effect in select VPs (DVP6, DVP9, DVP38) (Figure 4)
    - Insulin clearance and insulin sensitivity contribute to the drug response

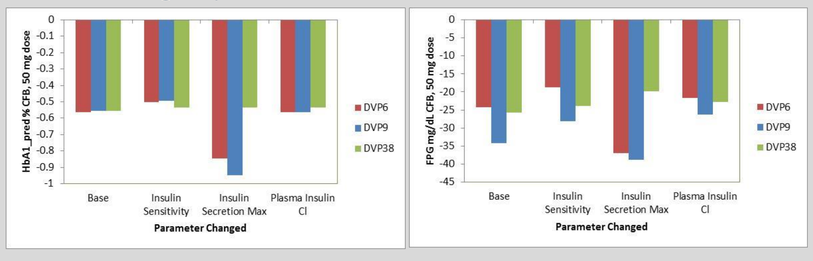

Figure 4. HbA1c and FPG response in select VPs upon parameter changes in pathways identified in a sensitivity analysis as important for drug efficacy. Results are shown as change from baseline. FPG = fasting plasma glucose, HbA1_pred = predicted HbA1c.

Results

Phase 2a and 2b trial research simulations yielded predictions of fasting glucose, HbA1c, and body weight that were consistent with clinical observations at 12 weeks across multiple TAK-875 doses.

- TAK-875 effects were calibrated based on literature and Phase 1 trial data [2,3]
- The T2D VP cohort was treated with simulated doses of 25, 50, 100, 200 mg of TAK-875 or placebo over 12 weeks or 6 month period
  - Outputs included glucose, insulin, HbA1c, body weight
- Results from the Platform simulations were compared to Phase 2 and Phase 3 trail results to prospectively predict drug efficacy and to validate the Platform (Figures 5-7)

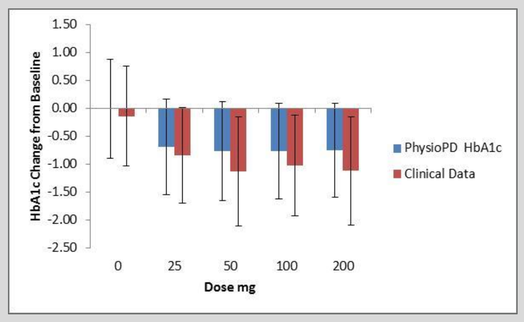

Figure 5. TAK-875-mediated changes in HbA1c in VPs at 12 weeks is consistent with Phase 2 clinical data. PhysioPD simulation data is median and range. Clinical data is mean and standard deviation.

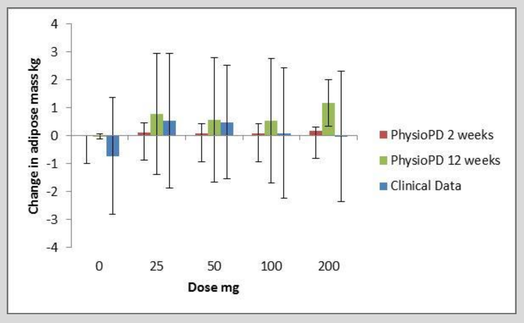

Figure 6. TAK-875-mediated change in adipose mass at 12 weeks is consistent with Phase 2 clinical data.

Phase 3 TAK-875 research simulations were consistent with clinical observations at 24 weeks when the VP cohort median was compared to trial mean results. The creation and analysis of VPs with mechanistic variability enabled exploration of potential mechanistic drivers of response to TAK-875 in the Phase 3 data.

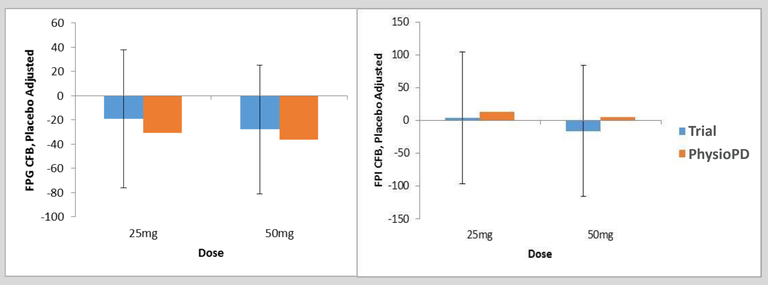

Figure 7. To validate the Platform and VPs were used to prospectively simulate 24-week results for an upcoming trial. The PhysioPD results were comparable to placebo-adjusted FPG and FPI changes from baseline trial results. PhysioPD = Median simulated results; Trial = Clinical trial results.

Conclusions

- PhysioPD Research provided an effective means of extrapolating early TAK-875 clinical trial results to predict late stage trial results in T2D patient populations with different degrees of T2D severity and other baseline characteristics.
- The T2D PhysioPD Research Platform helped provide insight into the TAK-875 MOA and patient characteristics most likely to impact efficacy

References

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