Mathematical Modeling of Patient Response and Nonresponse to Therapy

Rebecca Baillie, Michael Weis, Katherine Kudrycki, Michael Reed**, Himanshu Naik, Deborah Demanno, Stephanie Moran, Majid Vakilnejad, Ananth Kadambi

1 Rosa & Co., CA, USA; 2 Takeda, IL, USA *mreed@rosaandco.com

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 healthy 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™ (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.

Sensitivity analysis identified key pathways as drivers of TAK-875 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 (DVP c, and body weight that was found to be the primary drivers of response.

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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