**Pharmacokinetic and Pharmacodynamic Modeling of GPR40 Agonist MK-8666 Proof of Concept Data to Inform Clinical Decisions**

Pavan Vaddady\(^1\), Bharath Kumar\(^1,2\), Alexander W. Krug\(^1\), Elizabeth Migoya\(^1,3\), Menghui Chen\(^1\), Elizabeth Ommen\(^1\), Daniel Tatosian\(^1\), Prajakti Kothare\(^1\)

\(^1\)Merck & Co., Inc., Kenilworth, NJ, USA; \(^2\)Biogen Idec, Boston, MA, USA; \(^3\)Shionogi Inc., Florham Park, NJ, USA

**Objective:** MK-8666 is a partial agonist for the G-protein-coupled receptor (GPR) 40, which was being developed to improve glycemic control in patients with type 2 diabetes mellitus. Pharmacokinetic (PK) and pharmacodynamic (PD) data from the clinical phase 1 and phase 1b studies were modeled to a) predict glycemic efficacy over 12 weeks from short-term glucodynamic data, b) guide dose selection for the phase 2b study and c) compare glycemic efficacy to new or existing oral anti-diabetic agents.

**Methods:** A population PK and PK-fasting plasma glucose (FPG) model was developed based on single ascending dose (10 to 1000 mg), once-daily multiple ascending dose (50 mg to 800 mg for 10 days) studies in healthy subjects and once-daily multiple dose (placebo, 50, 150 and 500 mg for 2 weeks) phase 1b study in patients with T2DM. A previously published FPG-HbA1c relationship\(^1\) was utilized to extrapolate MK8666 FPG predictions to 12 week HbA1c response. Clinical trial simulations of plausible dose combinations were performed to evaluate the characterization of the overall dose response curve. A previously developed comparator model on dipeptidyl peptidase IV (DPP IV) inhibitors and published TAK-875 clinical results were leveraged to identify a potential clinically efficacious dose with superior glycemic efficacy.

**Results:** The PK of MK8666 was characterized by a two compartment model with dose dependent central volume of distribution and first order absorption rate constant. An indirect response model with stimulation of glucose elimination well described the PK-FPG relationship. Based on simulations utilizing the PK-FPG model and FPG-HbA1c relationship\(^1\), robust reductions in HbA1c at 12 weeks were feasible at 150 mg QD or higher, with smaller incremental benefits beyond 250-300 mg QD. Doses around 500 mg and above were predicted to be at the Emax. Based on this analysis, doses of 50, 150, 300 and 600 mg QD were predicted to provide an adequate characterization of the overall dose-response curve. A potential clinically efficacious dose of 300 mg had the highest probability for a superior glycemic efficacy in comparison to DPP IV inhibitors and TAK-875.

**Conclusion:** Integration of modeling and simulation with team strategy allowed extrapolation of two week proof of concept study results to 12 week HbA1c response. The predicted dose-HbA1c curve facilitated decisions on dose selection for a proposed Phase 2b study.

**Reference:**