**Disease progression model to describe longitudinal change in hemoglobin A1C in response to Gliclazide therapy in type2 diabetic patients**

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## Abstract

Diabetes is a global health issue that affects more than 425 million people and is expected to affect over 690 million people by 2045. The objectives of the present project are: 1) Develop a disease progression model for the effect of Glibenclamide on FPG and Hb1Ac levels in type 2 diabetic patients. 2) Explore association between various patients' characteristics and Glibenclamide response.

This analysis is a secondary analysis for the result of clinical study number GSK-BRL49653/231 sponsored by GlaxoSmithKline. We conducted a population pharmacodynamic analysis with covariate screening analysis. Nonlinear mixed effects modeling approach was implemented. First, we described the longitudinal change in

hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) without including patients' characteristics as covariates. This was followed by multiple linear regression between individual pharmacodynamic parameters and various covariates. Finally, significant covariates identified with multiple linear regression were included in the final pharmacodynamic model using backward deletion approach.

We quantified longitudinal change in HbA1c and FPG levels in response to Glibenclamide therapy in type 2 diabetic patients using population pharmacodynamic modeling. We also identified Alanine aminotransferase, White Blood Cell count, and peripheral Pulse Pressure as significant determinants of glycemic response to Glibenclamide therapy.

Longitudinal change in HbA1c and FPG following Glibenclamide therapy was described using a mechanistic pharmacodynamic model. Patients with an Alanine aminotransferase< 25 iu/L have reduced response to Glibenclamide therapy. Additionally, White blood cell count was identified as a predictor of negative response to Glibenclamide therapy. Finally, Patients with increased Peripheral Pulse Pressure are expected to have reduced FPG production rate.