Objectives: Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor developed for treatment of Type 2 diabetes mellitus. Sitagliptin is another available DPP-4 inhibitor and serves as a relevant comparator. Our objective was to estimate the magnitude of the HbA1c lowering effects of linagliptin and sitagliptin, based on a comprehensive analysis of available clinical trial data. Specifically, we sought to provide the comparison by means of a longitudinal dose-response meta-analysis based on indirect comparisons. Given appropriate covariate adjustment to account for differences in study designs and patient population, one may infer the efficacies of linagliptin and sitagliptin relative to placebo when administered to comparable patients under comparable conditions.

Methods: An analysis data set was assembled based on a systematic review of available clinical trials for sitagliptin and summary statistics computed from Boehringer Ingelheim internal data sources for linagliptin. A Bayesian hierarchical model was developed to describe HbA1c levels as a function of dose, time, and selected covariates. Covariates related to demographics and study design were evaluated and incorporated in the model where appropriate. Standard model diagnostics were applied to ensure adequate model convergence and model fit. Population simulations based on the selected model were used to evaluate the average effects of linagliptin and sitagliptin in a reference population over 24 weeks of treatment.

Results: The final model described HbA1c levels for placebo treated individuals as a nonlinear function of time. Drug effects were incorporated as multiplicative adjustments to the placebo time course, and additional multiplicative covariate adjustments were made for baseline HbA1c, washout duration and race. Population simulations assuming no washout and a mean baseline HbA1c of 8% resulted in expected HbA1c differences from placebo at 24 weeks of −0.810 percentage points for linagliptin 5 mg (90% credible interval from −0.881 to −0.740) and −0.807 percentage points for sitagliptin 100 mg (90% credible interval from −0.878 to −0.737).

Conclusion: Consistent with the common mechanism of action, this model-based meta-analysis showed that the new DPP-4 inhibitor linagliptin (5 mg qd) results in a comparable efficacy as seen with the DPP-4 inhibitor sitagliptin (100 mg qd).
A Model-based Meta-analysis Comparison of the Effects of Linagliptin and Sitagliptin on HbA1c Levels in Patients with Type 2 Diabetes Mellitus

James Rogers1, Dan Polhamus1, William Gillespie1, Christian Friedrich2, Alexander Staab2, Silke Retlich2
1Metrum Research Group, Tariffville, CT, USA; 2Boehringer Ingelheim, Biberach, Germany

INTRODUCTION

• Linagliptin and sitagliptin are dipeptidyl peptidase-4 inhibitors developed for the treatment of type 2 diabetes mellitus (T2DM).
• At present, no head-to-head trial has been conducted to support a direct comparison of the two drugs.
• Each drug has been compared separately to placebo in randomized trials, but naive comparison of placebo-adjusted results is confounded by differences in trial designs and enrolled populations.

METHODS

• Following the approach of Ahn et al.2, the equations below fully account for longitudinal correlations.
  \[
  \log (1 - \Delta HbA1c) = \beta_0 + \beta_1 \cdot \text{Drug} + \beta_2 \cdot \text{Race} + \text{Random Effects} 
  \]
  where \( \text{Drug} \) and \( \text{Race} \) represent treatment and race, respectively.
• Both drugs reduced mean HbA1c by approximately 0.8%.

RESULTS

• The final model included race as a covariate on baseline, drug,
  and \( \sigma^2 \), and attempts to include other covariates resulted in poor convergence diagnostics, so those covariates were excluded from the final model. All modelled covariates were examined for potential association with model-random effects and none were observed.
• Convergence diagnostics for the final model were consistent with adequate mixing and converge to a well-defined posterior.
• Posterior predictive checks for both unexplained means (not shown) and placebo-adjusted means (Figure 2) suggest that the model adequately characterizes the observed data, with no systematic over- or under-prediction.
• Treatment effect estimates based on population simulations suggest nearly identical treatment effects for linagliptin and sitagliptin within each racial group as well as by country in racially mixed populations. A reference simulation in a population with an HbA1c baseline of 8.0%, consisting of 0.13 white, 0.25 black, and 0.62 Asian patients, showed placebo-adjusted treatment effects of 0.0% (95% credible interval: 0.7, 0.8) for linagliptin 5 mg and 0.1% (95% credible interval: 0.7, 0.8) for sitagliptin 100 mg (Figure 3).

Figure 2: Difference from placebo values (percentage points) of the 21 studies and an average treatment effect was computed for each posterior sample, resulting in a total of \( \times 50,000 / 50 = 4000 \) samples.

• Both drugs reduced mean HbA1c by approximately 0.8% following 4 weeks of treatment in patients with T2DM and a baseline HbA1c of 8.0%.

CONCLUSIONS

• The proposed model permits a valid synthesis of the total available relevant data for comparing the treatment effects of linagliptin and sitagliptin.
• Both drugs reduced mean HbA1c by approximately 0.8% following 4 weeks of treatment in patients with T2DM and a baseline HbA1c of 8.0%.

REFERENCES

5. Boehringer Ingelheim Study 212620B. Available at http://www.cheminformatics.com/xref/ NC2861294/212620B.