Treatment Efficacy of Combination-Therapy based on a Mechanistic Characterisation of Disease Processes in Type 2 Diabetes Mellitus over a two-year period

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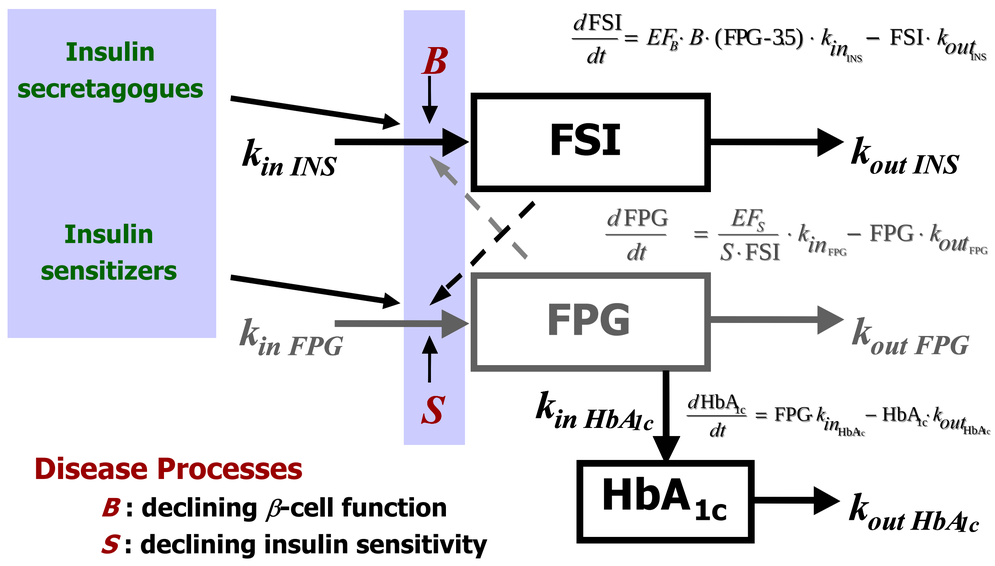
Introduction

In the current analysis a mechanism-based T2DM disease progression model (W. DeWinter, *et al*) was applied to evaluate combination therapy effects on their ability to modify disease processes in a patient population of 1269 T2DM patients during a treatment period of two-years.

Type 2 Diabetes Mellitus (T2DM) is a chronic progressive disease in which specific disease processes (i.e. progressive decline in β-cell function and insulin sensitivity) result in loss of glycaemic control. Information regarding these processes facilitates differentiation between drug efficacies on a mechanistic basis. By modelling the homeostatic feedback relationship between fasting serum insulin (FSI) and fasting plasma glucose (FPG) such process-information on the time-course of the β-cell function and insulin sensitivity can be derived.

Model Structure: FSI-FPG Homeostasis

The core of the mechanistic model consists of the homeostatic feedback between FSI and FPG for glycaemic control as described in Matthews, *et al* (1985), integrated with the FPG-HbA_{1c} cascade:



Disease Processes

***B*: declining β-cell function**

***S*: declining insulin sensitivity**

→ *Time-dependent changes in system-specific variables*

Short-term treatment effects (specific target-sites)

→ Insulin secretagogues (short-term: EF_B)

→ Insulin sensitizers (short-term: EF_S)

Long-term treatment effects

→ Modification time-course *B* and/or *S*

Discrimination between short-term effectiveness (EF_B, EF_S) and disease modifying effects (modification time-course *B* and/or *S*) requires long-term information on the time-course of the specific disease processes under influence of treatment. The data on FSI and FPG contain specific information regarding these processes which ultimately lead to loss of glycaemic control in T2DM, and they reflect the qualitative (e.g. short-term effectiveness *versus* disease modifying properties) and quantitative influence of various treatments on these processes. One comprehensive system enables the derivation of this disease process information and the qualitative treatment effects on the processes from the observed dynamics in FSI, FPG and the resulting HbA_{1c} levels.

Materials and methods

The mechanistic T2DM disease progression model was implemented as a population pharmacodynamic model in NONMEM® V.1, FOCE INTERACTION. Two Phase III, two-year clinical studies were analysed, comparing:

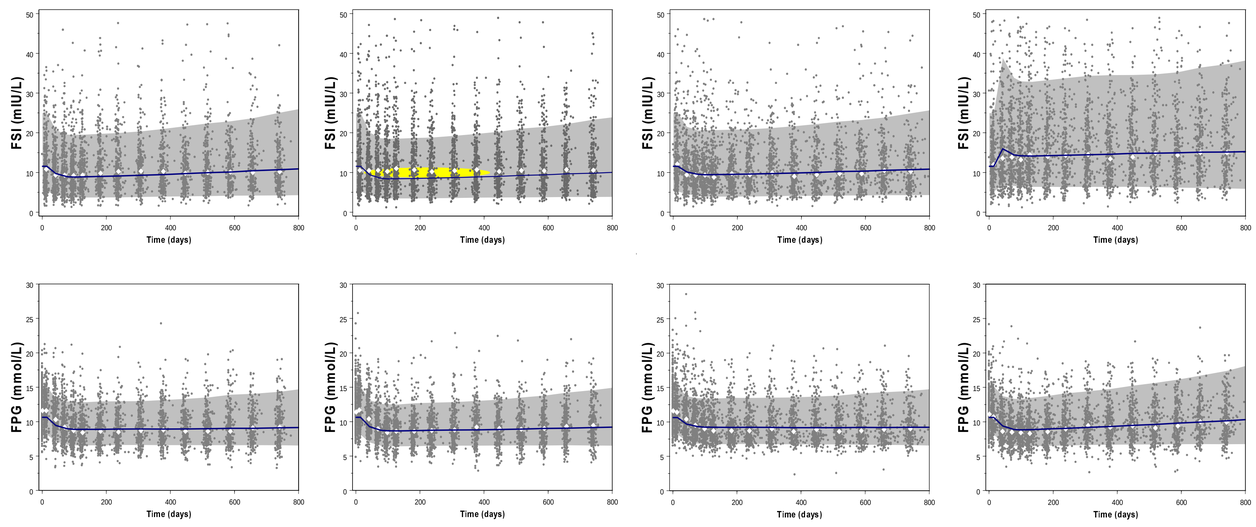
1. ***pioglitazone to metformin in combination-therapy of patients inadequately controlled by sulphonylurea*** (EC409, su+pio, su+met)
2. ***pioglitazone to gliclazide in combination-therapy of patients inadequately controlled by metformin*** (EC410, met+pio, met+gli)

Both studies were multicenter, randomised, double-blind, double-dummy, parallel-group studies on the long-term safety and efficacy of combination therapy. Glycaemic control was evaluated with change in HbA_{1c} (%), fasting plasma glucose (FPG) and fasting serum insulin (FSI). The study was preceded by a ***2-week screening period***, and consisted of a ***12-week*** (1.) forced titration period ***or a 16-week titration period*** (2) followed by a ***maintenance period*** at the individual optimal dose ***up to two years***.

Model Results

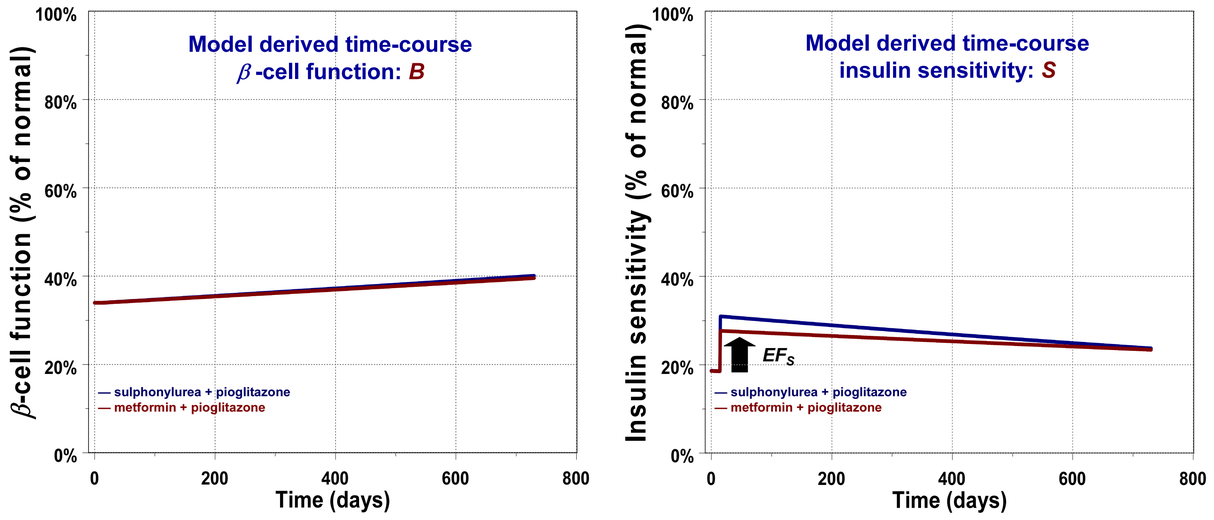
The figures below present the Predictive Check (PC) for the FSI and FPG measurements per treatment arm. The shaded area presents the 90% interquantile range (5^{th} – 95^{th} percentiles) and the solid blue line depicts the median trend predicted by the mechanism-based disease progression model. The white diamonds present the median of the observations per visit.

The trend and skewed variability of the observed data are adequately predicted by the model. In all treatment groups a greater (short-term) effect in FPG at the end of the titration period is observed than predicted by the model, and as a result, the FPG observations at screening are slightly underpredicted. However, this bias in the model prediction has no effect on the prediction of the long-term effects on FSI and FPG. Interestingly, the FSI observations resulting from addition of metformin to sulphonylurea remain almost unchanged during the treatment period. This is not expected as metformin mostly acts as an insulin sensitizer that indirectly lowers FSI observations, such as predicted by the model.

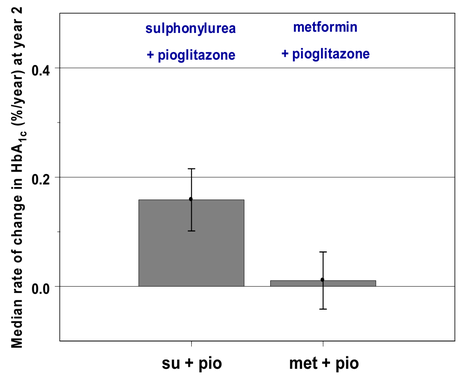


Disease Processes and Treatment Effects

The figures below visualise the model derived time-course of both disease processes (β-cell function: *B* and insulin sensitivity: *S*) under influence of short- and long-term treatment effects of pioglitazone addition to failing monotherapy over a treatment period of two years. The black arrow depicts the short-term effectiveness on insulin sensitivity (EF_S). The time-trends in both the β-cell function and the insulin sensitivity are modified by the addition of pioglitazone.



The figure on the right depicts the resulting model based rate of change (1^{st} derivative) in HbA_{1c} levels at two years. This illustrates the net effect of disease processes and treatment efficacy after two years of combination-therapy. (UKPDS indicates ~ 0.2 % p•y^{-1}; not including thiazolidinediones). **NONMEM**: DADT(HbA_{1c})



References

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DR Matthews, JP Hosker, AS Rudenski, BA Naylor and RC Turner. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985: 412-419.

UKPDS 33 and 34. UK Prospective Diabetes Study Group. *Lancet* 1998; 352: 837-853 and 854-865.

Charbonnel B *et al. Diabetologia* 2005, May 12.

Discussion

In all treatment groups a greater (short-term) effect in FPG at the end of the titration period is observed than predicted by the model, indicating that this short-term effect is reached more slowly. However, this bias in the model prediction has no effect on the prediction of the long-term effects on FSI and FPG.

The time-course of the FSI observations for the treatment arm with metformin added to sulphonylurea remains almost unchanged during the treatment period, which is not expected based on *a priori* information that metformin acts as an insulin sensitizer that indirectly lowers the FSI observations.

Conclusion

The time-course of relevant biomarkers (FSI, FPG) for glycaemic control in T2DM patients on combination-therapy over a period of two-years can be adequately characterised with a comprehensive mechanism-based disease progression model. As a result, the model allows for the evaluation of combination-therapy efficacies (long-term) based on the influence of various treatments on the time-course of the specific disease processes, e.g. β-cell function and insulin sensitivity.