**Background and Objectives**

Lixisenatide, a new glucagon-like-peptide receptor agonist, is known to act on the fasting plasma glucose (FPG) and on postprandial glucose concentrations [1]. The aim of this work was to investigate different PK/PD models to describe the effect of lixisenatide on glycated haemoglobin (HbA1c) in type 2 diabetes (T2D) patients. Secondly, a more mechanistic understanding of the mode of action of lixisenatide on HbA1c values was to be assessed.

**Methods**

**Patients/Study**

The PK/PD model development was based on HbA1c measurements of 162 patients from 2 randomised, double-blind, placebo-controlled, parallel-group studies sponsored by Sanofi in T2D patients inadequately controlled on metformin and treated with s.c. doses of 5, 10, 20 or 30 μg lixisenatide (LIX) once or twice daily. The characteristics of the study population are summarised in Tab. 1 and are in accordance with those expected from typical T2D patient.

**Population PK/PD modelling**

Three PK/PD models were investigated: (i) a turnover model (Fig. 2) with an inhibitory drug effect (E) on the production rate of HbA1c, (ii) the FP dependent lifespan model by Hamrein et al [2] (Fig. 3, blue) and, (iii) an extended version of this model with an additional, FP independent glycation rate (KGL2) which was linked to lixisenatide concentrations via E_aeq model (Fig. 3, green). Bayesian parameter estimates for PK [3] and FP [4] from previously developed population models (see Tab. 2, model depicted in Fig. 1) were used as input into the 3 models following a sequential PK/PD modelling approach. Model comparison was guided by AIC, DOF plots and precision of parameter estimates. All modelling and simulation activities were performed in NONMEM® VII, statistical and graphical analysis in R (version 2.15.1).

**Results**

**Turnover model**

![Fig. 2: Structural model for the turnover model. HbA1c before therapy and the degradation rate kKGL were estimated. The production rate kKGL was expressed as the product of both.](image)

**Lifespan model / Extended lifespan model**

![Fig. 3: Structural model for the lifespan model and the extended lifespan model. NRTE: Liberation of the erythrocytes; transition rate krin=4MRTE; kKGL: Release rate for erythrocytes into circulation; FPG: Fasting plasma glucose; γ: Exponent of power function describing the FPG and Hb interaction; KGL: glycation rate for the FP dependent pathway (present in both models); KGL2: additional glycation rate for the FP-independent glycation pathway; I: inhibitory drug effect on KGL2 in 1/(1+α/(E_aeq+EC50)).](image)

**Model comparison**

HbA1c values were not sufficiently described when taking only FP as a predictor (lifespan model) into account whereas the introduction of KGL2 to the model (extended lifespan model) improved the fit considerably (compare Fig. 4 and Fig. 5 B,C).

The IC50 of KGL2 was estimated to be 62.8 ng/L with an IIV of 108%, possibly representing the varying remaining ability of insulin secretion of the patients. Additionally, the extended lifespan model enabled the separation and quantification of two glycation pathways, an FP dependent and an FP independent one. The latter, possibly being attributed to postprandial glucose concentrations, explained 50% (95% CI: 43%-59%) of the reduction in HbA1c (see Fig. 6).

**Discussion and Conclusion**

For the description of HbA1c values the turnover model and the extended lifespan model were superior compared to the lifespan model with regard to AIC and prediction of observed HbA1c values. The mechanistically more complex lifespan models, however, was more appropriate (Fig. 3) and is more meaningful with regard to physiological parameter interpretation. The lifespan model, which originally was developed for tesaglitazar, a PPAR α/γ agonist with probably no action on postprandial glucose concentrations, did not sufficiently describe the observed HbA1c. The extended lifespan model best described the data and enabled the estimation of a FP-dependent and independent glycation pathway.

**References**