Comparison of three PK/PD models for glycated haemoglobin in diabetes type 2 patients treated with lixisenatide

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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 Tab. 1. and are in accordance with those expected from typical T2D patient.

Table 1: Patients characteristics

Parameter	Unit	Median	P2.5	P97.5
Age	[year]	61	43	74
Weight	[kg]	81	51	118
Height	[cm]	167	149	187
Predicted normal weight	[kg]	72	49	106
CLCR	[L/h]	5.9	3.7	10.4
FPG before study	[mmol/L]	8.7	7.0	12.9
Race	[caucasian /black/ asian/other]		104 / 3 / 45 / 10	
Gender	[male/female]		106 / 56	

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 FPG dependent lifespan model by Hamrén et al [2] (Fig. 3, blue) and, (iii) an extended version of this model with an additional, FPG independent glycation rate (KGL2) which was linked to lixisenatide concentrations via a E_{max} model (Fig. 3,green). Bayesian parameter estimates for PK [3] and FPG [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, GOF plots and precision of parameter estimates. All modelling and simulation activities were performed in NONMEM™ VII, statistical and graphical analysis in R (version 2.12.1).

Table 2: PK & PD parameter for lixisenatide and FPG

Parameter	Unit	Median	P 0.025	P 0.975
PK Parameter (lixisenatide)				
CL/F	[L/h]	33.4	18.1	61.2
V/F	[L]	40.2	20.2	82.4
Ka	[1/h]	0.37	0.27	0.45
PD Parameter (FPG)				
Kin	[mmol/(L*h)]	0.29	0.23	0.43
Kout	[1/h]	0.03	-	-
EC_{50}	[ng/L]	12.3	0.31	115
Emax		0.44	-	-

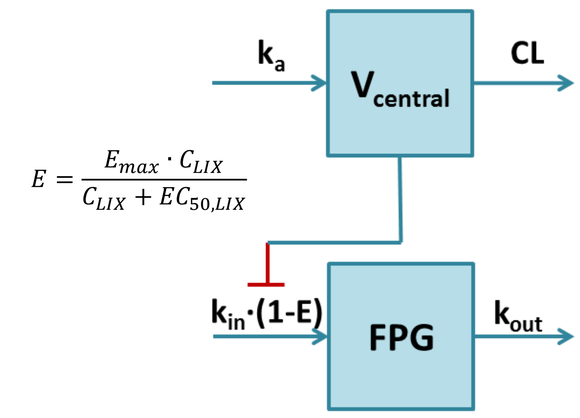


Fig. 1: PK/PD model for FPG. One compartment PK model for lixisenatide after subcutaneous (s.c.) application. Drug concentrations (C_{LIX}) are linked to a turn over model for FPG trough a sigmoidal E_{max} model with inhibtion of the zero-order production rate (k_{in}). CL: Lixisenatide clearance; $EC_{50,LIX}$: lixisenatide concentration at half maximal effect; k_a: absorption rate of lixisenatide; k_{out}: elimination rate for FPG

Results

Turnover model

$$E = \frac{E_{max} \cdot C_{LIX}}{C_{LIX} + EC_{50,LIX}}$$

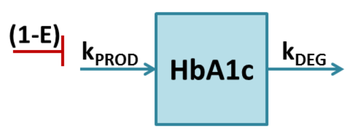
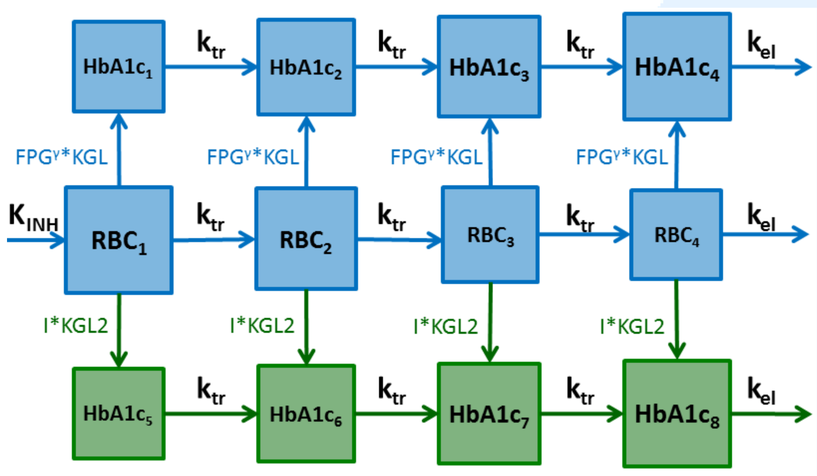


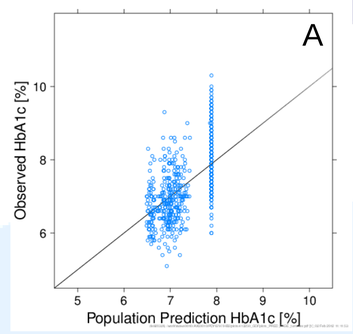
Fig. 2: Structural model for the turnover model. HbA1c before therapy and the degradation rate k_{DEG} were estimated. The production rate k_{PROD} was expressed as the product of both.

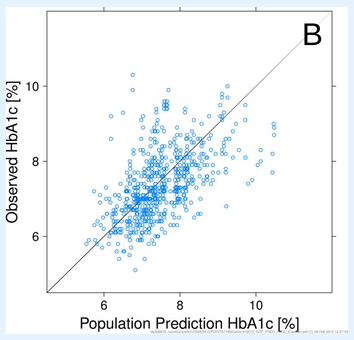
Lifespan model / Extended lifespan model



$$HbA1c = \frac{\sum HbA1c_i}{\sum RBC_i + HbA1c_i} \cdot 100\%$$

Fig. 3: Structural model for the lifespan model and the extended lifespan model. MRTE: Lifespan of the erythrocytes; transition rate ktr=4/MRTE; K_{INH}: 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 FPG dependent pathway (present in both models); KGL2: additional glycation rate for the FPG-independent glycation pathway; I: inhibitory drug effect on KGL2: $I=1/(1+IC_{50}/C_{LIX})$.





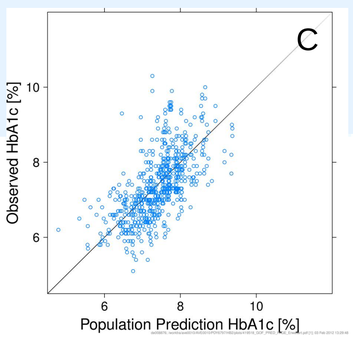


Fig. 4: GOF plots of A) the turn over model, B) the lifespan model and C) the extended lifespan model.

Table 3: Parameter estimates turn over model

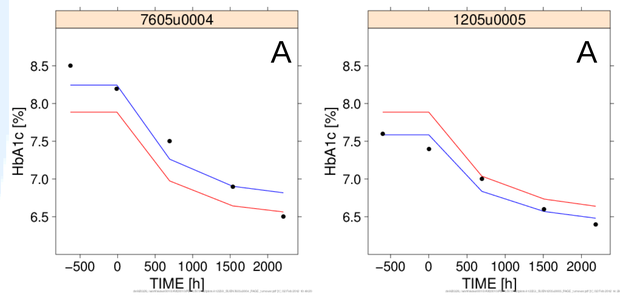
AIC	-2961.05		(412250)
Parameter	Unit	Estimate	RSE, %
Fixed-effects parameters			
K_{DEG}	[% HbA1c/h]	1.48*10^-3	10.7
HbA1c Baseline	[%]	7.89	0.74
E_{MAX}		0.19	16.2
$EC_{50,LIX}$	[ng/L]	0.61	173
Random-effects parameters			
ω_{BASE}	% CV	8.81	10.8
ω_{IC50}	% CV	78.0	52.4
Residual error			
$\sigma_{proportional}$	% CV	6.08	7.73

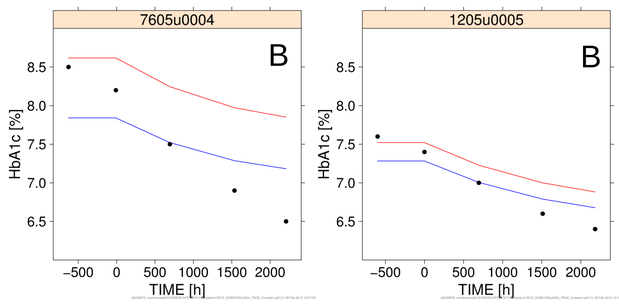
Table 4: Parameter estimates lifespan model

AIC	-2762.18		(419573)
Parameter	Unit	Estimate	RSE, %
Fixed-effects parameters			
KINH	[g/L/d]	1.16 FIX	-
MRTE	[d]	101 FIX	-
KGL	[1/d/mmol/L]	$3.01 \cdot 10^{-4}$	0.67
γ		0.67	9.66
Random-effects parameters			
ω_{γ}	% CV	100	15.2
Residual error			
$\sigma_{proportional}$	% CV	105	5.04

Table 5: Parameter estimates extended lifespan model

AIC	-2911.31		(420376)
Parameter	Unit	Estimate	RSE, %
Fixed-effects parameters			
KINH	[g/L/d]	1.10	2.98
MRTE	[d]	101 FIX	-
KGL	[1/d/mmol/L]	$1.22 \cdot 10^{-4}$	0.25
γ		0.75 FIX	-
KGL2	[1/d]	$6.74 \cdot 10^{-4}$	0.30
IC_{50}	[ng/L]	62.8	3.07
Random-effects parameters			
ω_{γ}	% CV	33.0	15.6
ω_{IC50}	% CV	108	21.5
Residual error			
$\sigma_{proportional}$	% CV	4.09	1.95





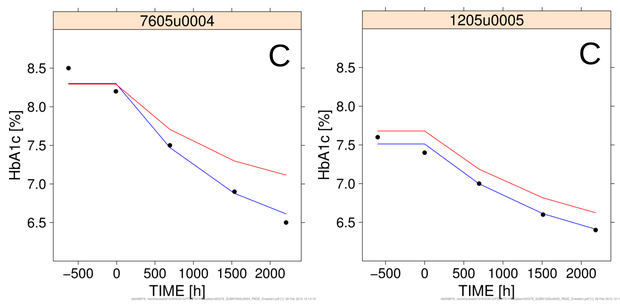


Fig. 5: Individual plots of 2 patients: PRED (red line), IPRED (blue line) and observations (black dots), of A) the turn over model, B) the lifespan model and C) the extended lifespan model.

Model comparison

HbA1c values were not sufficiently described when taking only FPG 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 IC_{50} 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 FPG dependent and an FPG 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).

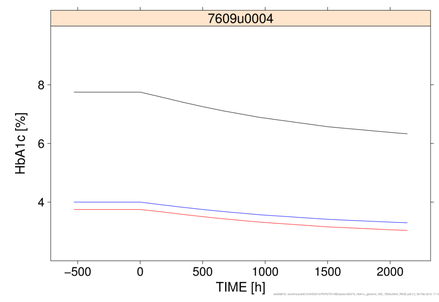


Fig. 6: Total HbA1c (black), HbA1c of the FPG dependent (blue) and the independent glycation pathway (red).

References [1] Christensen M et al. (2011), [2] Hamrén B et al. (2008), [3] Frank T et al. (in preparation.), [4] Rüppel D et al. (2010)

Discussion and Conclusion

For the description of HbA1c values the turnover model and the extended lifespan model were superior compared to the lifespan model 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 FPG dependent and independent glycation pathway.

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