Mechanism-based pharmacokinetic and pharmacodynamic modelling of tesaglitazar in type 2 diabetes patients

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Introduction

In the treatment of diabetes the primary surrogate endpoint for efficacy is HbA_{1c} (glycosylated haemoglobin). HbA_{1c} is a biomarker that correlates to long-term exposure of glucose in the body. We wanted to develop a mechanism-based pharmacokinetic (PK) and pharmacodynamic (PD) model of the interplay between exposure of tesaglitazar (a dual PPARα/γ agonist), fasting plasma glucose (FPG), haemoglobin (Hb) and HbA_{1c} over time in patients with type 2 diabetes (T2D).

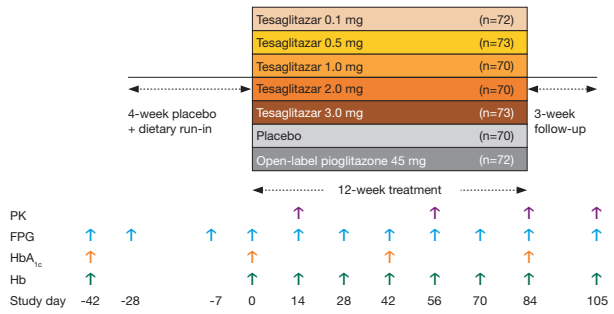
Objective

- To develop a PK/PD model of the interplay between tesaglitazar exposure, FPG, Hb and HbA_{1c} over time for patients with T2D.
- In addition, to perform an exploratory analysis to evaluate four different hypotheses for the tesaglitazar effect on Hb.

Methods

- The Glucose and Lipid Assessment in Diabetes (GLAD; SH-SBD-0001) was a 12-week, randomized, double-blind, placebo-controlled study in patients with T2D (Figure 1) with or without previous antidiabetic treatment, with five doses of tesaglitazar (0.1 to 3.0 mg). An open-label pioglitazone 45 mg arm was also included in this study, but not included in the PK/PD analysis.
- Venous blood samples for PK and FPG, Hb and HbA_{1c} analysis were taken at the times indicated in Figure 1.

Figure 1. GLAD study design



- Non-linear mixed-effects modelling using NONMEM V[1] (FOCE interaction) was used for the PK/PD analysis.
- First the PK of tesaglitazar was characterized, then FPG and lastly the integrated model for FPG, Hb and HbA_{1c} was developed.
- We also tested four different hypotheses for the tesaglitazar-induced effect on Hb. These were:
  1. Inhibition of the production of red blood cells (RBC)
  2. Shortening of the lifespan of RBC
  3. Non-selective elimination of RBC
  4. Haemodilution or redistribution of RBC.
- Covariates evaluated were prior antidiabetic therapy, gender, age, body weight and renal function.
- Covariates were investigated using a stepwise forward inclusion ($P<0.05$) and backwards deletion procedure ($P<0.01$).

Results

Demographics

- In total, 412 patients were included in the analysis (242 men and 170 women). Of the 412 patients, 130 were naïve to antidiabetic treatment. Patient demographics and baseline characteristics are presented in Table 1.
- PK data were available from 342 patients receiving tesaglitazar (1283 PK, 4035 FPG, 1548 HbA_{1c} and 3115 Hb observations, respectively).

Table 1. Demographics and baseline patient characteristics

	Age (years)	Body weight (kg)	CrCL* (mL/min)	FPG (mmol/L)	HbA_{1c} (%)	Hb (g/L)
Median	58	88	68	9	7	146
(range)	(32–80)	(46–140)	(29–163)	(5.5–16)	(5.2–11)	(103–181)

*Calculated creatinine clearance (CrCL),[2] using lean body weight[3] as a measure of body weight

Pharmacokinetics

- The PK results have been presented earlier,[4] and are only summarized here.
- The PKs of tesaglitazar were well described by a one-compartment model with first-order absorption and elimination.
- Tesaglitazar oral clearance (CL/F) was correlated with creatinine clearance (CrCL) and no significant effects of gender, age, or body weight on the CL/F of tesaglitazar after accounting for differences in renal function. Overall, between-patient variability in CL/F was moderate (37%).

PK/PD

FPG model

- An indirect-response model, with a stimulatory drug effect on the elimination of FPG best described the FPG response (Table 2, Figure 2).
- The time to new FPG steady state was approximately 10 weeks.
- Previously treated patients (other antidiabetic therapy) had an increase in FPG upon discontinuation of prior antidiabetic treatment compared to drug-naïve patients.
- A small decrease in $FPG_{baseline}$ was found with increasing age.
- A gender difference in EC_{50} was found.
- None of the other covariates affected the PD parameters.

Table 2. Population PK/PD parameters for FPG (relative SE, %)

Parameter (unit)	Estimate	Between-patient variability, CV† %	Comment
$FPG_{baseline}$ (mmol/L) Previously treated patient	8.39 (1.0)	14 (7.9)	Mean $FPG_{baseline}$ for a previously treated individual of 58 years
$FPG_{baseline}$ (mmol/L) Drug-naïve patient	8.69 (1.2)	14 (7.9)	Mean $FPG_{baseline}$ for a drug-naïve individual of 58 years
$FPG_{baseline}$ ~ age	-0.3 (27)	n.e.	Percentage change in $FPG_{baseline}$ per year change in age
E_{max} (%)	66.2 (7.2)	n.e.	
EC_{50} males (µmol/L)	1.42 (18)	99 (23)	Mean EC_{50} for a male patient
EC_{50} female (µmol/L)	0.85 (25)	n.e.	Mean EC_{50} for a female patient
k_{out} ($days^{-1}$)	0.037 (6.5)	n.e.	First-order rate constant for the natural removal of FPG
Placebo response for previously treated patients (%)	13.6 (9.2)	72 (12)	Patients discontinuing prior antidiabetic treatment at start of study

Residual variability in FPG plasma concentration was 9.7% (2.4%); †coefficient of variation; n.e.: not estimated

FPG-Hb-HbA_{1c} model

- The model was based on the following basic principles:
  - the lifespan of RBC are known to be in the range of 120–140 days
  - when Hb is released from the bone marrow into circulation it is not glycosylated
  - the glycosylation of Hb is a function of blood glucose
  - the proportion of Hb that is glycosylated increases continuously with RBC age.
- The model included (Figure 3, Table 3):
  - release of RBC into the circulation (K_{in})
  - ageing of the RBC through four transit compartments (K_{tr})
  - glycosylation of Hb to HbA_{1c} as a function of FPG (power model, $K_{glucose}$: Figure 4).
- The covariate analysis showed that:
  - females had lower RBC release (about 7%)
  - RBC release decreased somewhat with increasing age.
- Of the four different hypotheses tested for a plausible mechanism of the tesaglitazar-induced effect on Hb, the model for haemodilution or redistribution of RBC produced the lowest Objective Function Value, in combination with reasonable parameter estimates.
- This model will be reevaluated with data from tesaglitazar Phase III studies, for further refinement.

Figure 2. Observations and mean model predictions (red line) versus time for FPG, HbA_{1c} and Hb (placebo and tesaglitazar 1 mg for previously treated patients is shown)

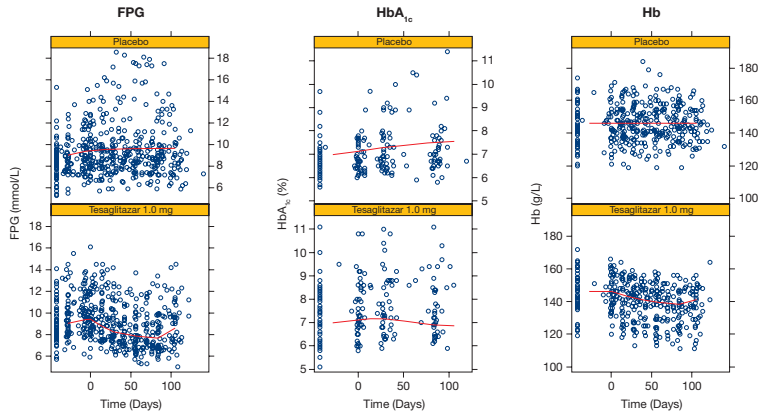


Figure 3. Model overview

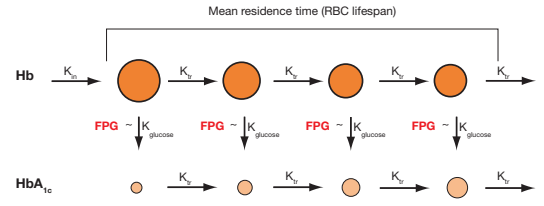
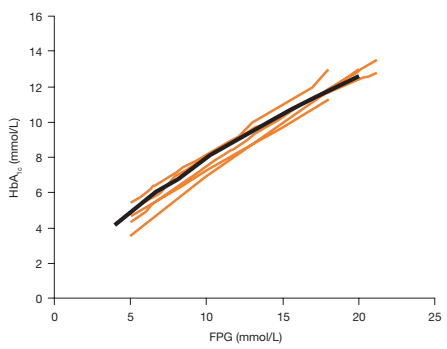


Table 3. Population PK/PD parameters for the mechanism-based FPG, Hb and HbA_{1c} model (relative SE, %)

Parameter (unit)	Estimate	Between-patient variability, CV† %	Comment
RBC lifespan (days)	136 (6.4)	n.e.	Mean residence time
K_{in} males (g/L/days)	1.10 (6.4)	7.1 (9.3)	Rate of RBC into the blood for males with an age of 55 years
K_{in} females (g/L/days)	1.02 (6.4)	7.1 (9.3)	Rate of RBC into the blood for females with an age of 55 years
K_{in} ~ age (%)	-0.08 (51)	n.e.	Percent change in K_{in} per year change in age
$K_{glucose}$ (1/day/10 mmol/L)	0.0019 (12)	n.e.	Rate constant for the glucosylation of Hb to HbA_{1c} at 10 mmol/L FPG
FPG ~ HbA_{1c}	0.722 (4.9)	6.3 (13)	Power slope for the interaction between FPG and HbA_{1c}
Haemodilution model			
K_{out} ($days^{-1}$)	0.057 (6.5)	n.e.	Rate constant describing the time to new Hb steady state
E_{max} (%)	- 36.6 (36)	n.e.	Maximal effect for the decrease in Hb
EC_{50} males (µmol/L)	8.52 (46)	47 (20)	EC_{50} for males
EC_{50} females (µmol/L)	6.32 (49)	47 (20)	EC_{50} for females
EC_{50} ~ age (%)	-2.1 (18)	n.e.	Percent change in EC_{50} for every year change
Residual error in Hb (%)	5.0 (3.9)	33 (24)	Additive error on log transformed Hb
Residual error in HbA_{1c} (%)	3.0 (1.9)	18 (32)	Additive error on log transformed HbA_{1c}

†Coefficient of variation; n.e.: not estimated

Figure 4. Model qualification, estimated relationship between FPG and HbA_{1c} (black line) compared with literature data (orange lines)[5–8]



Conclusions

- This mechanism-based PK/PD model could qualitatively and quantitatively describe the PD interactions between FPG, Hb and HbA_{1c} during tesaglitazar treatment in patients with T2D.
- The model indicated that a plausible explanation for the tesaglitazar effect on Hb is caused by haemodilution of RBC, but further studies are needed to better understand this PPAR-mediated effect.

References

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