Population PKPD modeling of an anti-diabetic compound with a new mechanism of action in ob/ob mice to predict the human dose

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INTRODUCTION

PXL is an anti-diabetic agent with a new mechanism of action developed in Type 2 diabetes. An early readout on a likely efficacious human dose was required. In ob/ob mice, one of the disease models, a PKPD correlation was apparent from preliminary glucose data at 1h after 8 days of dosing. This initiated a programme with the design of new studies for PK and PKPD population modelling in mice, and allometry to predict the human dose.

OBJECTIVE

To predict a likely clinical efficacious dose for PXL based on *in vitro* (IVT) activity data, PKPD modeling in ob/ob mice, and a single endpoint, glucose.

Diabetes
New mechanism of action. First in class

What model & study design for PopPKPD?

Sparse sampling PD: only glucose

Phoenix®
Excel template for data entry

Human Dose Prediction
In vivo: 3 species PK; mice PD
In vitro: PD + plasma binding in man & rat

METHODS

- Exploration of early and sparse PK and glucose data justified a PKPD approach based on glucose only levels
- Specific PK and PKPD studies were designed in ob/ob mice under experimental constraints. Glucose and PXL concentrations were measured over 8h following the morning dose (0, 25, 50 or 100 mg/kg BID).
- Population PK (PopPK) models were developed in normal and ob/ob mice
- PopPKPD indirect response (IR) models were developed in ob/ob mice
- Phoenix® software was used for exploratory analysis and Phoenix® NLME™ for NLME (using FOCE algorithm). A template excel spreadsheet was designed for data entry and direct import into Phoenix®
- Simple allometry was used to predict human clearance (CL)
- A likely clinical efficacious dose range was predicted using IC50s estimated in mice, scaled to human based on IVT differences between species and plasma binding

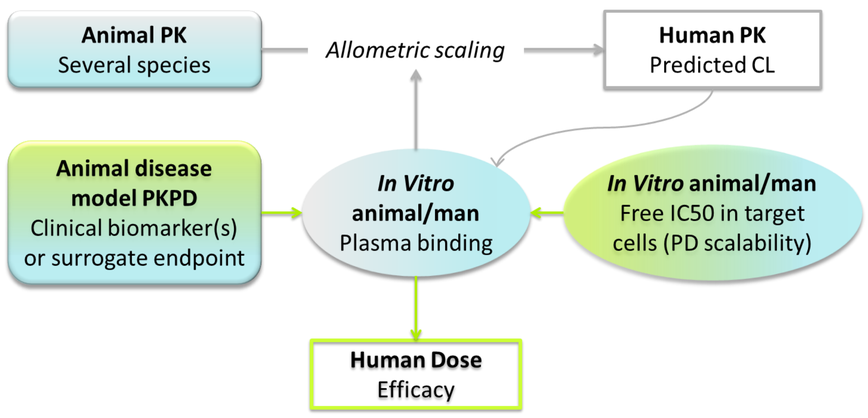
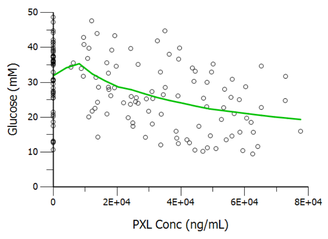


Figure 1 - Prediction of Human Therapeutic Dose from Animal PK & PKPD

RESULTS

Concept. The first pharmacological experiments showed that plasma glucose levels 1h post-dose after 8 days of treatment were correlated to PXL concentrations.

Glucose



PXL concentrations

Figure 2 – Naïve Pool of 1h Glucose vs. PXL Concentrations from Initial Experiments

A literature evaluation focused on PKPD approaches for glucose only and oral antidiabetic agents, in rat and man (no references in mouse)[1-6]. It allowed to select *a priori* the best model structure for PXL.

Table 1. Published PKPD Glucose Models for Non-Insulinic Compounds

Met formin[1]	Rosigli tazone[2]	Piogli tazone[2]	Rivogli tazone[2]	Tesagli tazar[3]	DPP4	PXL	Methyl prednisolone[4]
Inhibition of glucose production							
x		x			x	?	
Stimulation of glucose utilization							
	x		x	x	x	?	
Stimulation of glucose production							
							x

[1]Biguanides, [2]Thiazolidinediones, [3]PPAR agonists, [4]Anti-inflammatory drug: the glucose increase is a side effect

RESULTS

Study design. Doses of 25, 50, 75 and 100 mg/kg BID (semi-regular 8am/4pm) were selected. Samples taken after the morning dose were split between D1 and D8; trough samples were taken in-between. PK study: 9 mice/dose, 3 mice/time, 5 samples/mice. PD study: 30 mice/dose, 4 PD and 1 PK samples/mice.

PopPK. The objective of the model was to best represent PXL concentrations for PKPD modelling. A 1st order absorption 2-compartment model was developed, with between-subject variability (BSV) on CL, V and V2; the kinetics was proportional with dose.

Table 2. PopPK Parameters for PXL in ob/ob Mice

Parameter	Estimate	Units	SE	SE%
KA	5.27	1/h	1.849	35.1
V	0.355	L/kg	0.200	56.3
V2	3.14	L/kg	0.612	19.5
CL	0.487	L/(kg*h)	0.040	8.2
CL2	1.40	L/(kg*h)	0.149	10.6
Residual error SD	0.570		0.042	7.4

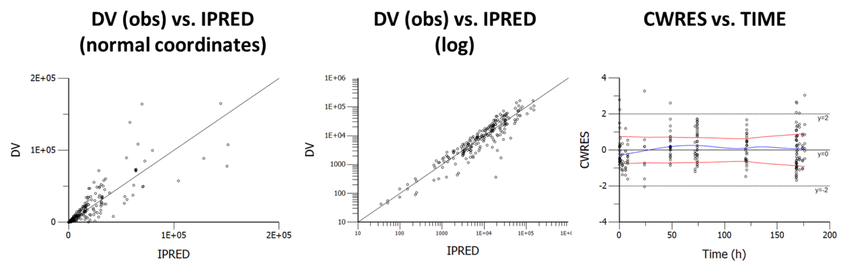


Figure 3 – Goodness of Fit Plots for the PopPK Model

PopPKPD. There was an apparent diurnal pattern for glucose; however data were not available over 24h and a constant baseline was used. The best model was an IR model with inhibition of glucose (G) production, with BSV on glucose production rate (Kin). Some model misspecification was partly due to the circadian baseline which could not be accounted for. Using individual PK parameters provided a lower estimate of IC50.

$$dG/dt = Kin * \{ 1 - Imax * C / (C + IC50) \} - Kout * G$$

Table 3. PopPKPD Parameters for the Effect of PXL on Glucose in ob/ob Mice

Parameter	Estimate	Units	SE	SE%
Kin	2.93	mM/h	1.13	39
Kout	0.182	1/h	0.0667	37
Imax	0.613		0.221	36
IC50	6529	ng/mL	5223	80
Residual error SD	3.66		0.170	5

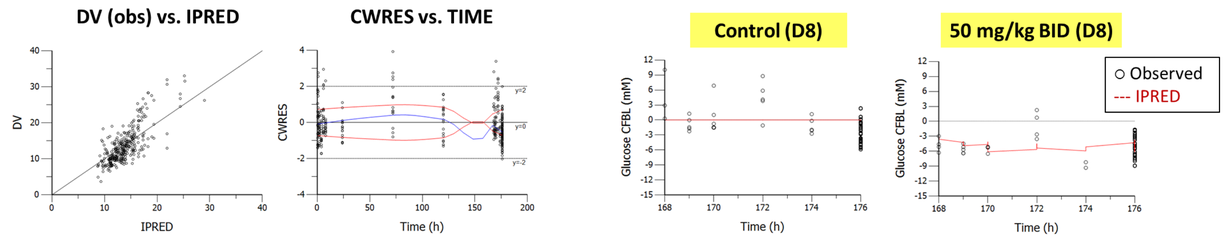


Figure 4 – Goodness of Fit Plots for the PopPKPD Glucose Model (Left: DV vs. IPRED and CWRES vs. time. Right: change from baseline in glucose on D8)

Allometric Scaling. Scaling with unbound concentrations led to lower and tighter predictions of human CL. For oral F in man, the average of animal values was used.

Table 5. Allometric Scaling Using Unbound Concentrations

Human Clearance (L/h)	Range*		
CL scaling *(iv scaling)*	*	0.6	0.9
CL/F from iv scaling, assuming $F_{man} = F_{avg} = 0.48$		1.3	1.9
CL/F assuming $F_{man} = F_{avg} = 0.48$ *(po scaling)*	*	1.1	1.3

* Using best methods[7]

Human Dose. The IVT difference in sensitivity between man and rat was 8 fold. The same sensitivity was assumed in rats and mice. The human dose providing, on average, 50 and 80% of maximal effect was predicted at 25 (range 21-26) and 100 (85-102) mg/d, respectively.

CONCLUSION

- Integrating early sparse data and literature information allowed designing studies which led to successful modeling for a compound with a new mechanism of action, using glucose as the only endpoint and population PK and PKPD modelling in mice
- Using *in vitro* data in animal and man, human doses likely to produce a defined lowering effect on glucose were predicted, which should guide the FTIM study
- Phoenix® software allowed flexibility and rapidity in exploratory plots and in testing several PK and PKPD models

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