

Support of phase II dose selection of a novel dual GIP/GLP-1 agonist using a population PKPD model developed on phase I data



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Background and Objective

RG7696 is a dual GIP/GLP-1 agonist which is currently being developed as a treatment for type 2 diabetes.

The objective of the current analysis was to support the Phase II dose selection through

- Characterization of the non-linear properties of RG7696 PK
- Identification of the reduction in mean plasma glucose (MPG) as a function of exposure
- Prediction of 12-week HbA1c reduction from 2-week MPG decrease

Material and Method

- Data from 92 individuals (healthy volunteers and T2D patients) which were treated with at least one dose of RG7697 were included in the PK analysis. Doses ranged between 0.03-5 mg (s.c. injection) once daily. Rich sampling was performed on day 1 and 14 with additional sparse sampling in between.
- In 54 type 2 diabetics (T2D) patients receiving 2-week treatment, the pharmacological effect of RG7697 was assessed with repeated meal tolerance tests (MTT). 24-hour glucose profiles were collected on days -1, 1, 7 and 14 (20 samples). MPG was calculated as the average of the collected samples over 24 hours.
- PK and PKPD (AUC-MPG) models were developed based on 2-week data.
- 12-week HbA1c extrapolations were generated based on the 2-week PKPD model, coupled with a life-span model of HbA1c [1]. The results were compared to literature data of GLP-1 compounds through a model-based meta analysis from which liraglutide was the main comparator.
- Analysis and simulations were performed using NONMEM 7.2.

PK Results

- The PK of RG7697 was described using a 2-compartment model with 0- and 1st-order absorption, see figure 1 and table 1.
- A complex absorption pattern is observed with dose and time dependent effects on bioavailability and duration of absorption leading to a greater than proportional accumulation with dose and a delayed T_{max} at later doses, see equations in figure 1b and model predictions in figure 3.
- Steady-state was reached after approximately 1 week of treatment and model diagnostics confirmed the performance of the model, see figure 2.

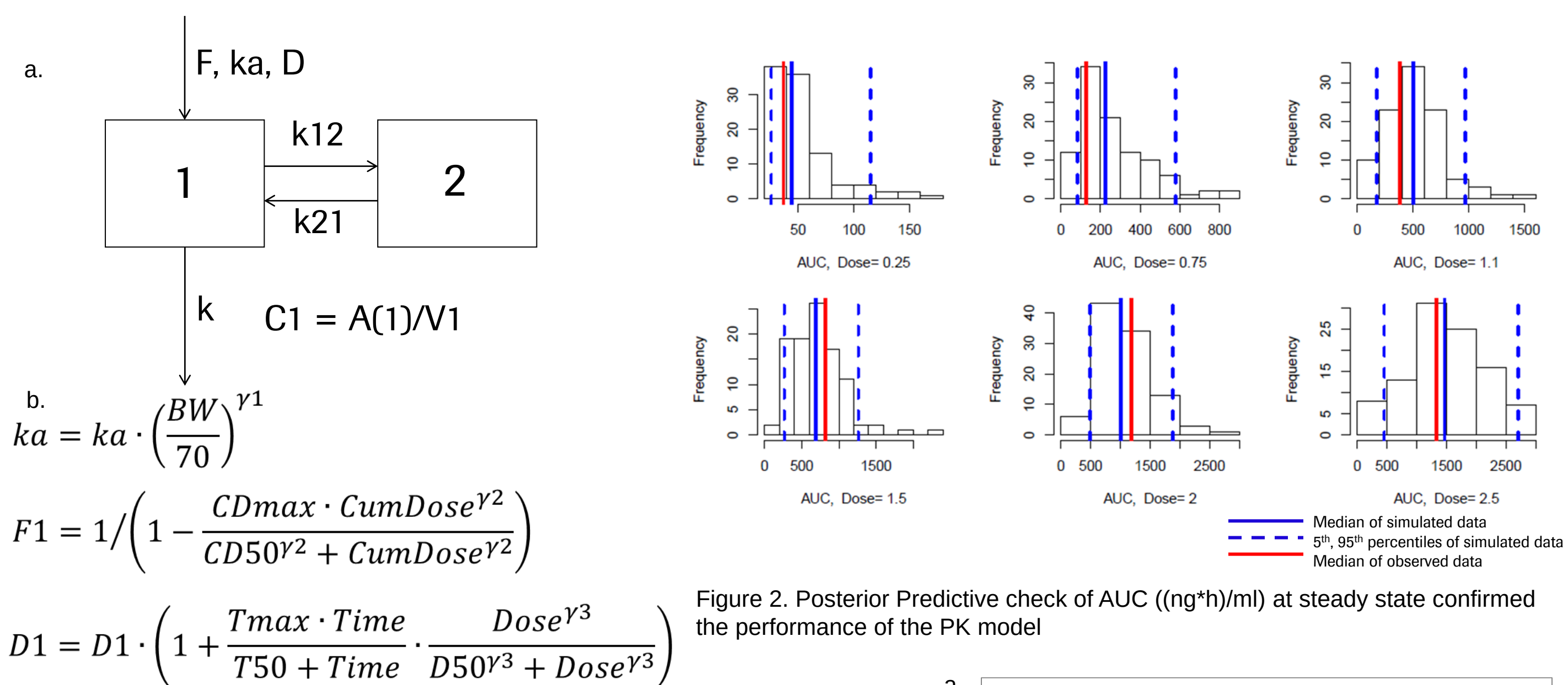


Figure 1. a. Schematic representation of PK model, the corresponding parameter estimates are included in Table 1. b. equations detailing the non-linearities of ka, relative bioavailability and duration which are further illustrated in figure 3.

Table 1. Final parameter estimates of the PK model

Parameter	Typical value (SE%)	IIV % (SE %) [shrinkage, %]
Basic PK parameters		
ka (h ⁻¹) (absorption rate)	0.529 (13)	51 (21) [9]
D1 (h) (absorption duration)	0.737 (6)	42 (27) [18]
k (h ⁻¹) (elimination rate)	0.142 (9)	29 (37) [18]
k12 (h ⁻¹) (distribution rate)	0.0728 (18)	75 (31) [8]
k21 (h ⁻¹) (distribution rate)	0.0356 (12)	84 (27) [10]
V1 (L) (central volume of distribution)	47.4 (8)	20 (39) [28]
γ1 (BW on ka)	-2.38 (14)	-
Parameters for non-linearity on Central volume		
CDmax (-) (maximum effect)	0.758 (5)	-
CD50 (mg) (cumulative dose giving half the maximum effect)	8.49 (13)	79 (31) [35]
γ2 (-) (sigmoidicity factor)	2.96 (15)	-
Parameters for non-linearity on D1		
Tmax (-) (maximum effect)	10 FIX	-
T50 (h) (time at which half the maximum effect is reached)	12.1 (90)	-
D50 (mg) (Dose giving half the maximum effect)	1.4 FIX	-
γ3 (-)	10 FIX	-
Residual Error		
Proportional Error (%)	15.2 (5)	-

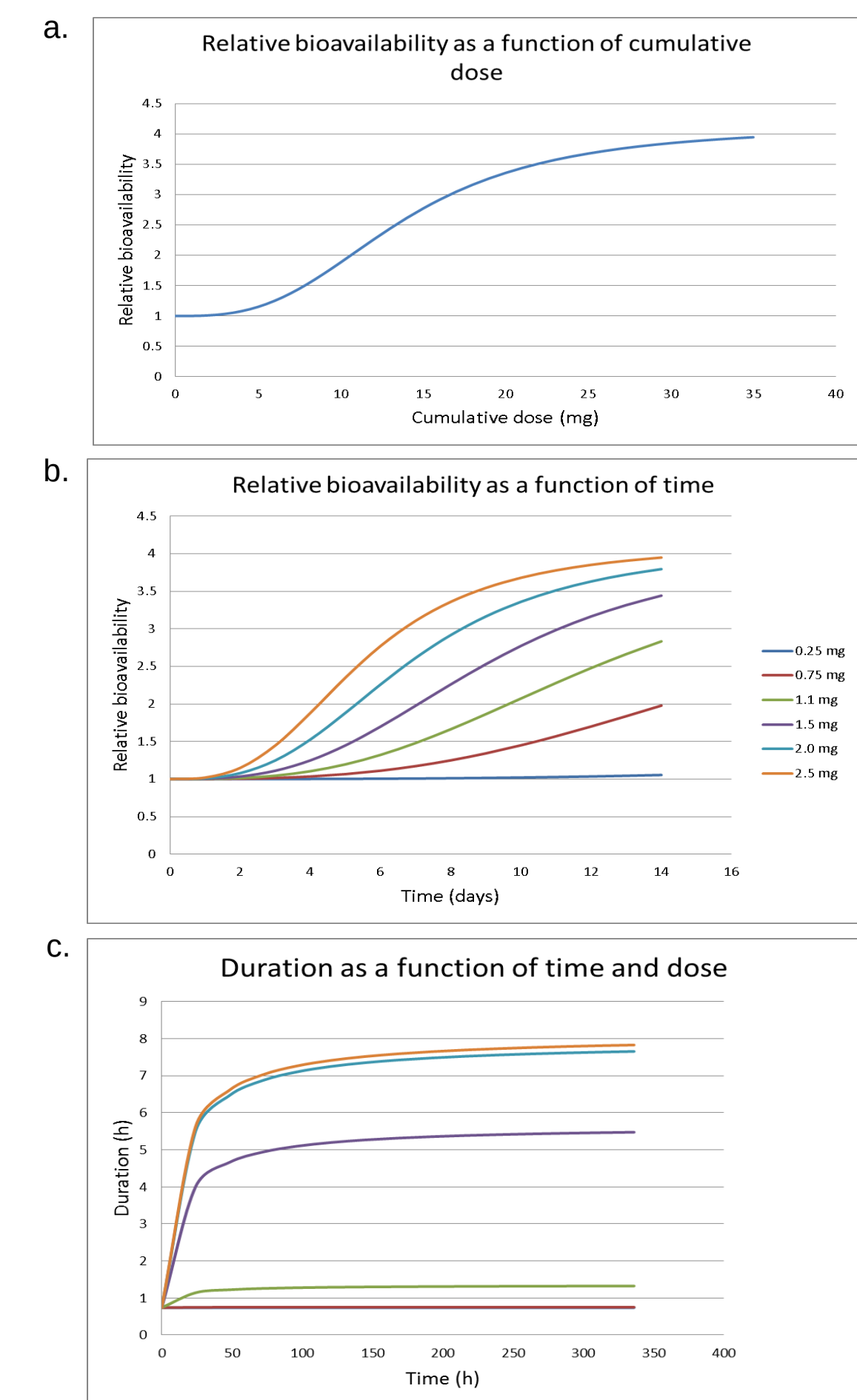


Figure 3. Impact of dose (a) and time (b) on bioavailability and infusion duration (c).

PD Results – 2-week MPG reduction

- The majority of the effect was reached after two weeks of treatment, see figure 4.
- The time course of MPG over 2 weeks was captured using an indirect response model (IDR) with a stimulatory effect of RG7697 on K_{out} in accordance with the hypothesized mechanism of action, see figure 5.
- Fasting plasma glucose was included as a covariate on the baseline MPG and the placebo effect was expressed as the difference between the MPG_{BASE} and MPG_{SS}
- Model diagnostics confirmed the performance of the model, see figure 6.

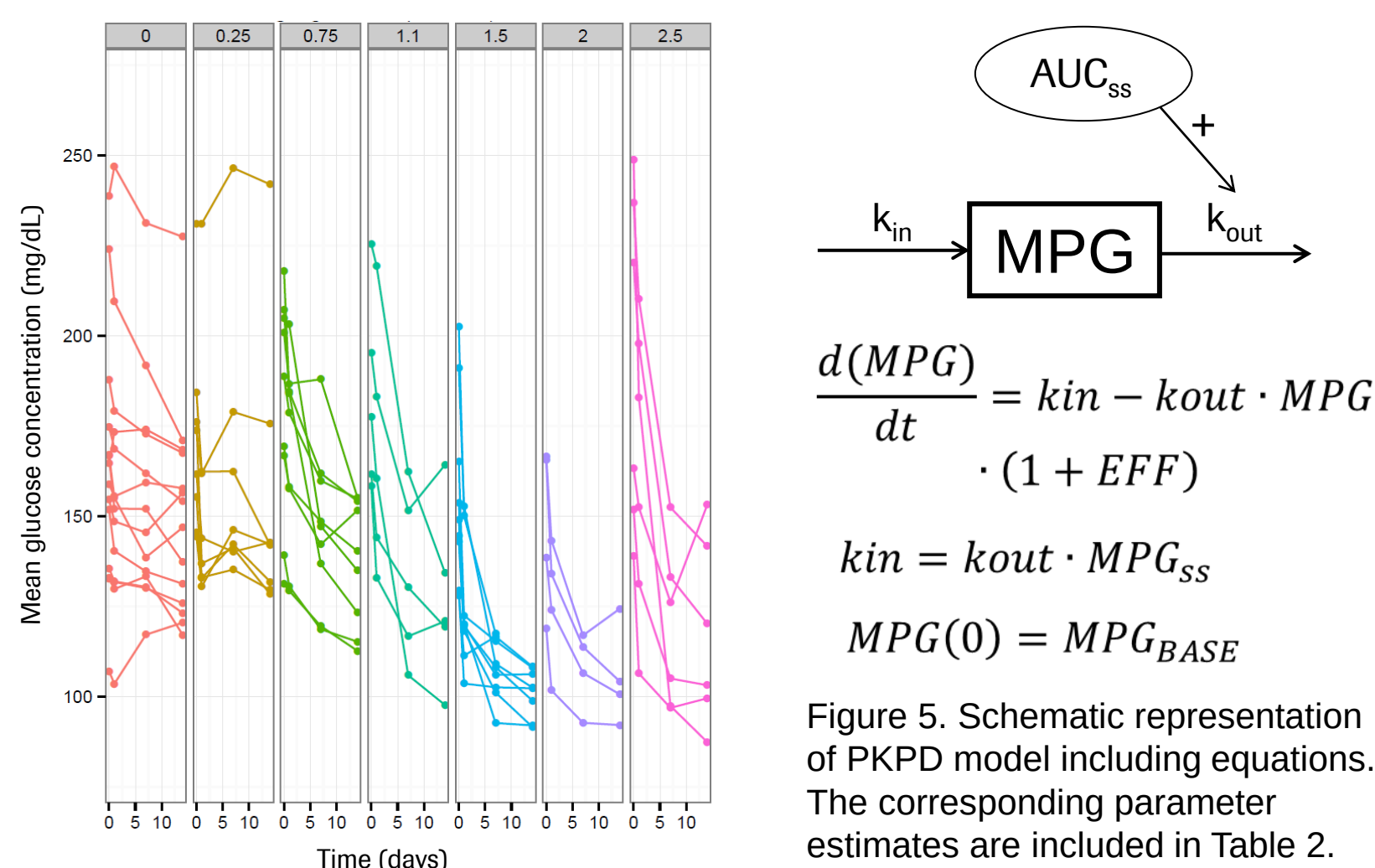


Figure 4. Observed MPG by dose level

Table 2. Final parameter estimates of the PKPD model

Parameter	Typical value (SE%)	IIV, % (SE%) [shrinkage, %]
Base model		
MPG _{BASE} (mg/dL)	171 (1)	9.7 (13) [5]*
MPG _{SS} (mg/dL)	158 (3)	13 (12) [3]*
K _{out} (day ⁻¹)	0.35 (22)	-
FPG on MPG _{BASE}	0.917 (9)	-
FPG on MPG _{SS}	0.521 (23)	-
Drug effect parameters		
Emax	0.572 (22)	-
AUC50 (ng*day/mL)	361 (56.2)	-
HbA1c at baseline on Emax	3.25 (21)	-
Time component for onset of effect (day ⁻¹)	0.071 (76)	-
Residual Error		
Proportional Error (%)	5 (7)	-
* Correlation = 55%		

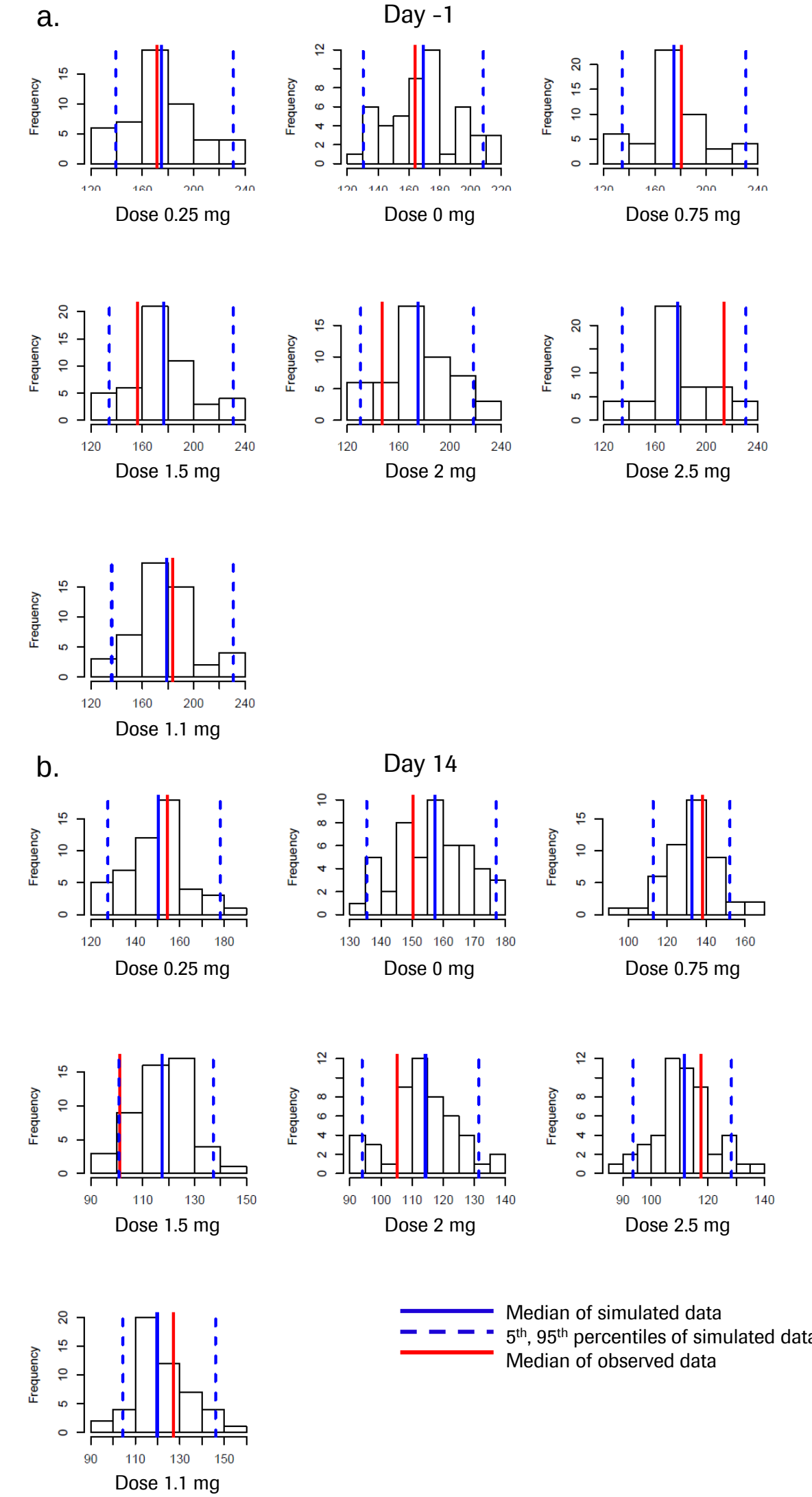


Figure 6. Posterior Predictive check of MPG (mg/dL) confirmed the performance of the PKPD model for prediction of MPG over time. Included here are Day -1 (a) and Day 14 (b).

PD Results – 12-week HbA1c prediction

- The appropriateness of HbA1c predictions was confirmed by comparing the simulated data to available HbA1c from the 2-week trial, see figure 7.
- Predicted 12-week HbA1c reduction across a range of RG7697 doses was compared to the liraglutide prediction from a meta-analysis model of GLP-1 compounds, see figure 8.
- The results predict that the 12-week HbA1c reduction following RG7697 treatment at well tolerated doses would follow a faster onset and would be larger than liraglutide at the recommended dose of 1.8 mg.

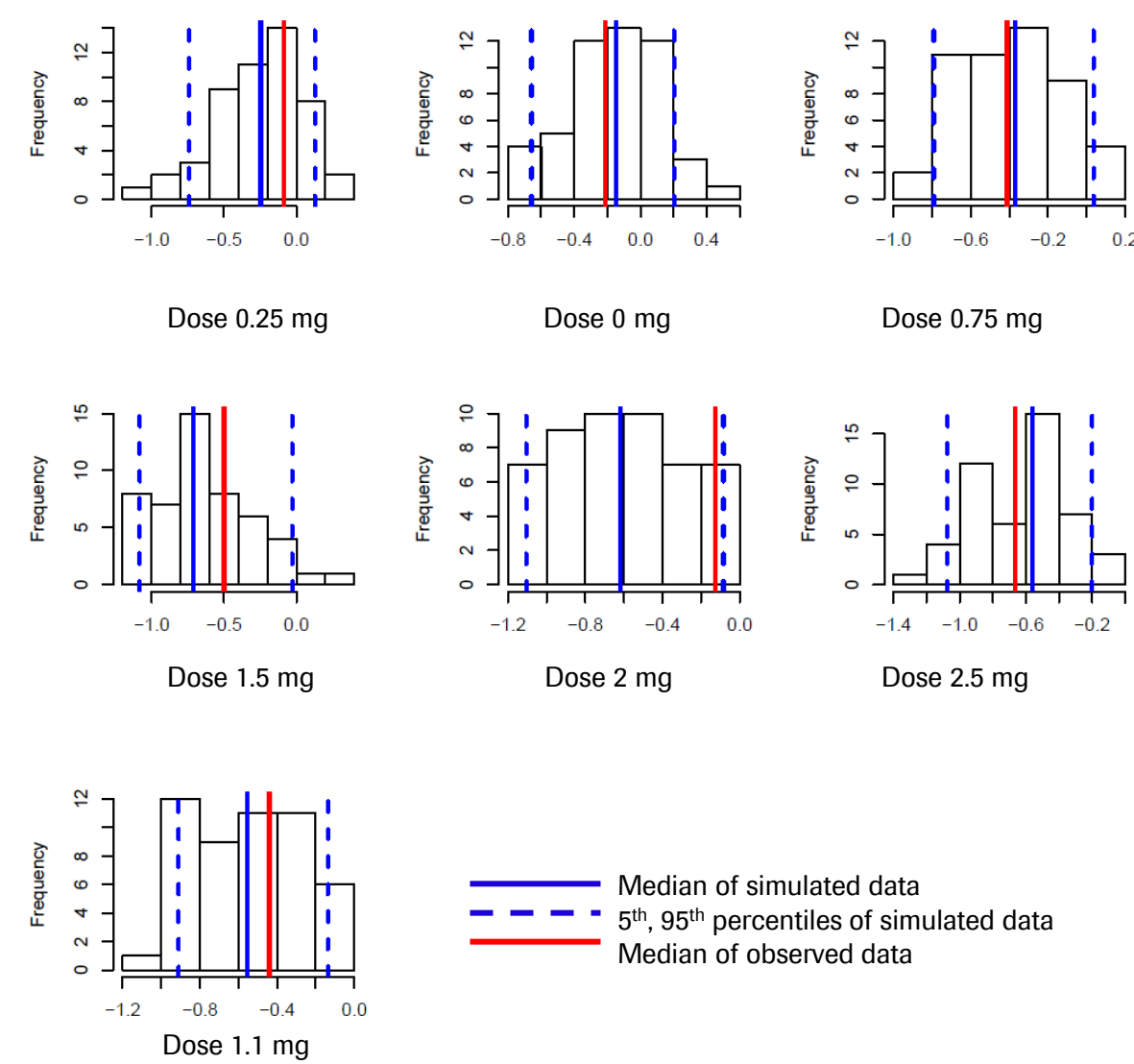


Figure 7. Posterior Predictive check of HbA1c change from baseline following 2 weeks treatment confirmed the performance of the model.

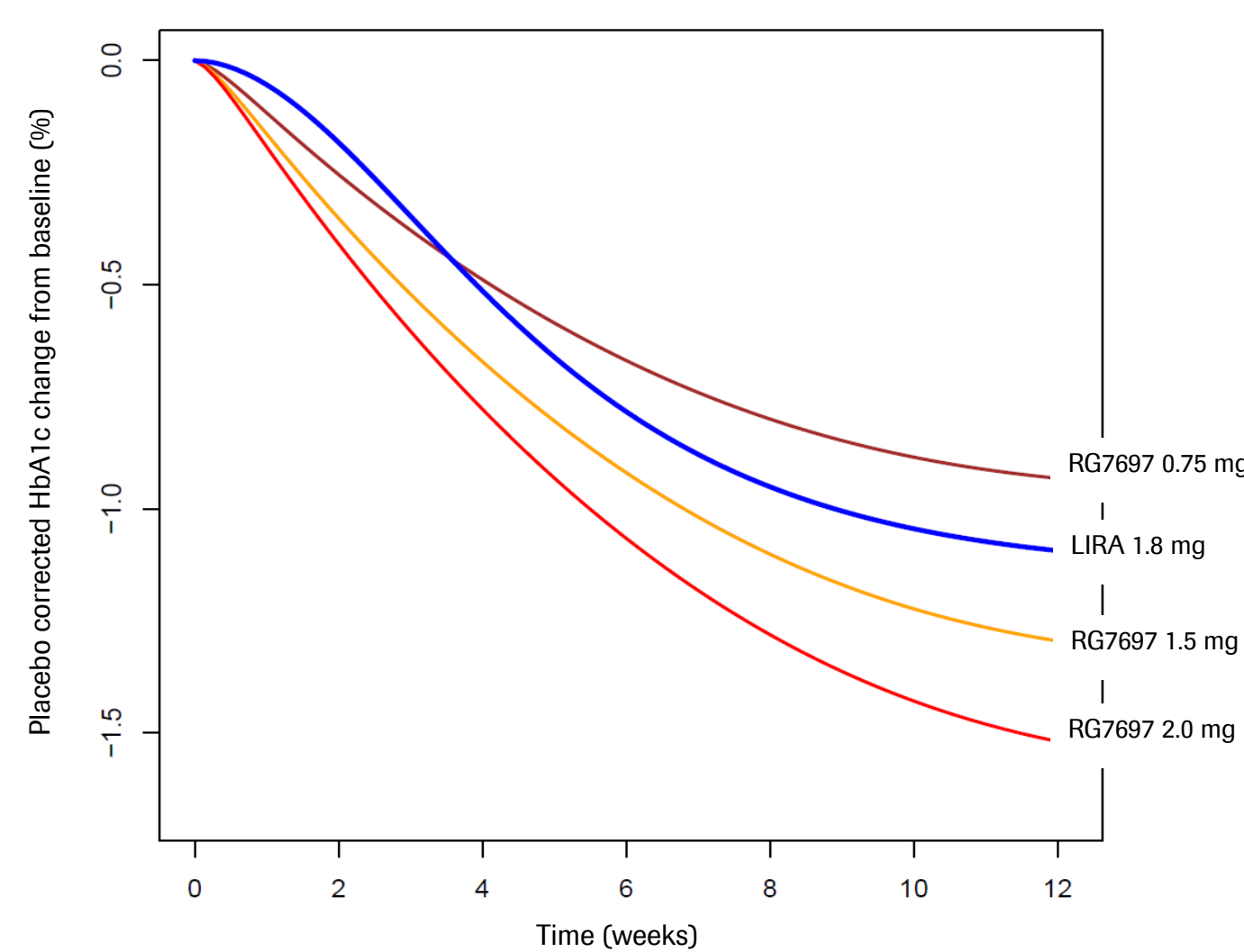


Figure 8. Predicted HbA1c reduction over 12 weeks following different doses of RG7697 compared to the standard dose of Liraglutide

Conclusions

- RG7697 non-linear PK could be adequately accounted for by including functions of dose and time on the absorption phase.
- The reduction in MPG over 2 weeks was adequately described using an IDR model with the stimulating effect on K_{out}.
- The predicted 12-week reduction in HbA1c indicated that well tolerated doses of the dual GIP/GLP-1 agonist RG7697 should compare favorably to liraglutide 1.8 mg in Phase II.

References:

1. Lledo-Garcia R et al, A semi-mechanistic model for the relationship between average glucose and HbA1c in healthy and diabetic subjects., J Pharmacokin Pharmacodyn, 2013