

PKPD modelling of PGE2 inhibition and dose rationale for a COX-2 inhibitor in humans

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Introduction

The assessment of the analgesic effect of NCEs is primarily based on qualitative behavioural measures of pain. This however, does not reflect the mechanisms underlying the anti-inflammatory response in chronic inflammatory pain conditions. In contrast, prostaglandins are known to be important mediators of inflammation, resulting from the activation of cyclo-oxygenase (COX) after tissue damage. Here we investigate the role of PGE₂ inhibition as a biomarker of the analgesic effect and as basis for the dose selection in humans. Using a model-based approach, the concept is illustrated for GW406381, an investigational selective COX-2 inhibitor.

Methods

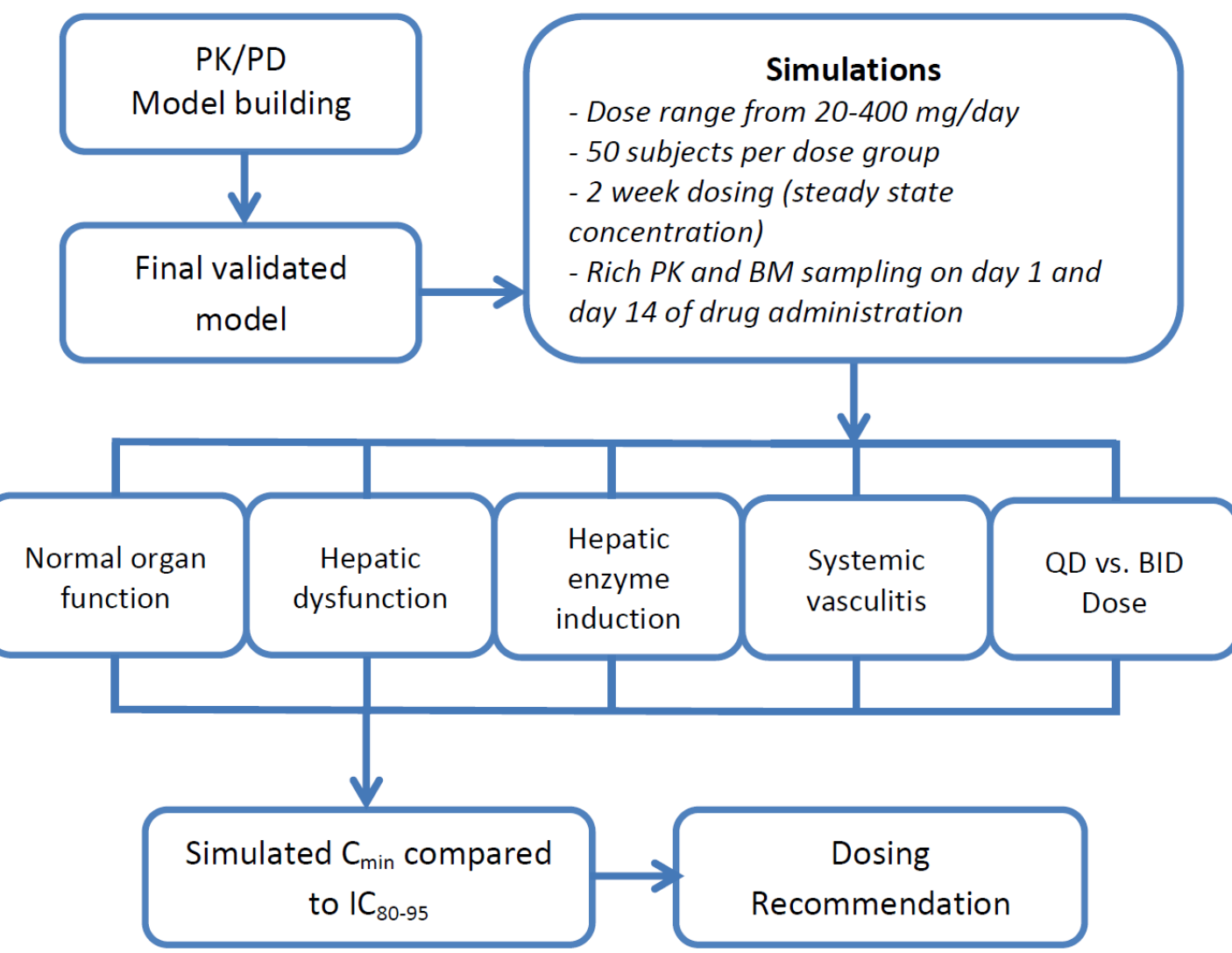


Figure 1: Diagram depicting the simulation protocol. Five different clinical scenarios were simulated; each having the characteristics shown in table 1.

PKPD analysis: Using nonlinear mixed effects modelling, a pharmacokinetic model was developed first and predicted drug concentrations were used subsequently to assess the exposure-response relationship. A two-compartment model with first-order absorption was used to describe the time course of GW406381 in plasma. The model was parameterised in terms of absorption rate constant, clearance, central and peripheral, volumes of distribution, inter-compartmental clearance and lag time. Inter-individual variability was assumed to be log-normally distributed. PGE₂ was assayed as a measure of drug response. The exposure-drug response relationships were described by an I_{max} equation (*equation 1*). Data analysis was performed in NONMEM[®], version 7.2.

Table 1: Characteristics of each of the simulation scenarios		
Scenario	Range of variation	Reference
Liver impairment	CL: -25% CL: -50% CL: -75%	Schmitt-Hoffmann et al. 2009
Systemic vasculitis; general inflammation	I ₀ : +30% I ₀ : +50%	Ambrus JL, et al. 1997
CYP3A4 induction	CL: +25% CL: +50%	Maronpot et al. 2009 Hewitt et al. 2007
Combination of liver dysfunction and general inflammation	CL: -25% - I ₀ : +30% CL: -50% - I ₀ : +50%	Vet, N et al. 2011
Once vs. twice daily dosing	NA	NA

Clinical Study: Data from a randomised, placebo controlled, double-blind, dose escalation parallel group study in healthy subjects was used for the purposes of this analysis. GW406381 was administered as a single dose followed by a 10-day multiple dosing phase. Subjects (n=12) were sampled throughout the study duration for pharmacokinetics and pharmacodynamics (PGE₂ and TXB₂). The subjects received placebo, 35 or 70 mg in the single dose phase. Only data from the 35 mg dose was available for the multiple dose phase.

$$Eff = I_0 - (I_0 - I_{max}) * \frac{C^\gamma}{C^\gamma + IC_{50}^\gamma}$$

Equation 1: I_{max} equation used to describe the prostaglandin inhibition

Simulations: Different simulation scenarios were evaluated to assess dosing requirements across different populations and treatment conditions. For each dose, the C_{min} (trough) concentrations at the steady state were simulated and compared to the predicted IC₈₀, IC₉₀ and IC₉₅ estimates. A ratio (C_{min}/IC₈₀) between 1 - 2.5 was considered to represent the therapeutic window, above which toxicity could be expected. This range was based on the level of enzyme inhibition required to block the inducible fraction of COX-2, whilst ensuring basal activity for the housekeeping effects. Exposure levels ≥ IC₉₅ were considered a risk for toxicity. Effective but non toxic doses were those at which the C_{min} concentrations were between the IC₈₀ and the IC₉₅.

Results

PK analysis: The PK parameters from the final model as well as the results of a non parametric bootstrap are presented in *table 2*. The medians of the predicted and observed data are very similar, however, wide prediction intervals were obtained for the 95th percentile, especially in the multiple-dose-phase for the 35 mg dose group.

PKPD analysis: The PGE₂ data on an I_{max} model was fitted using an I_{max} model. The PKPD model was able to describe the data adequately, as assessed by the basic goodness of fit plots (*figure 2*). High variability was seen in the baseline (I₀) PGE₂, which is most conspicuous in the placebo group. PD parameter estimates and nonparametric bootstrap results are shown in *table 2*. The visual predictive checks showed wide prediction intervals at the 95th percentile boundary.

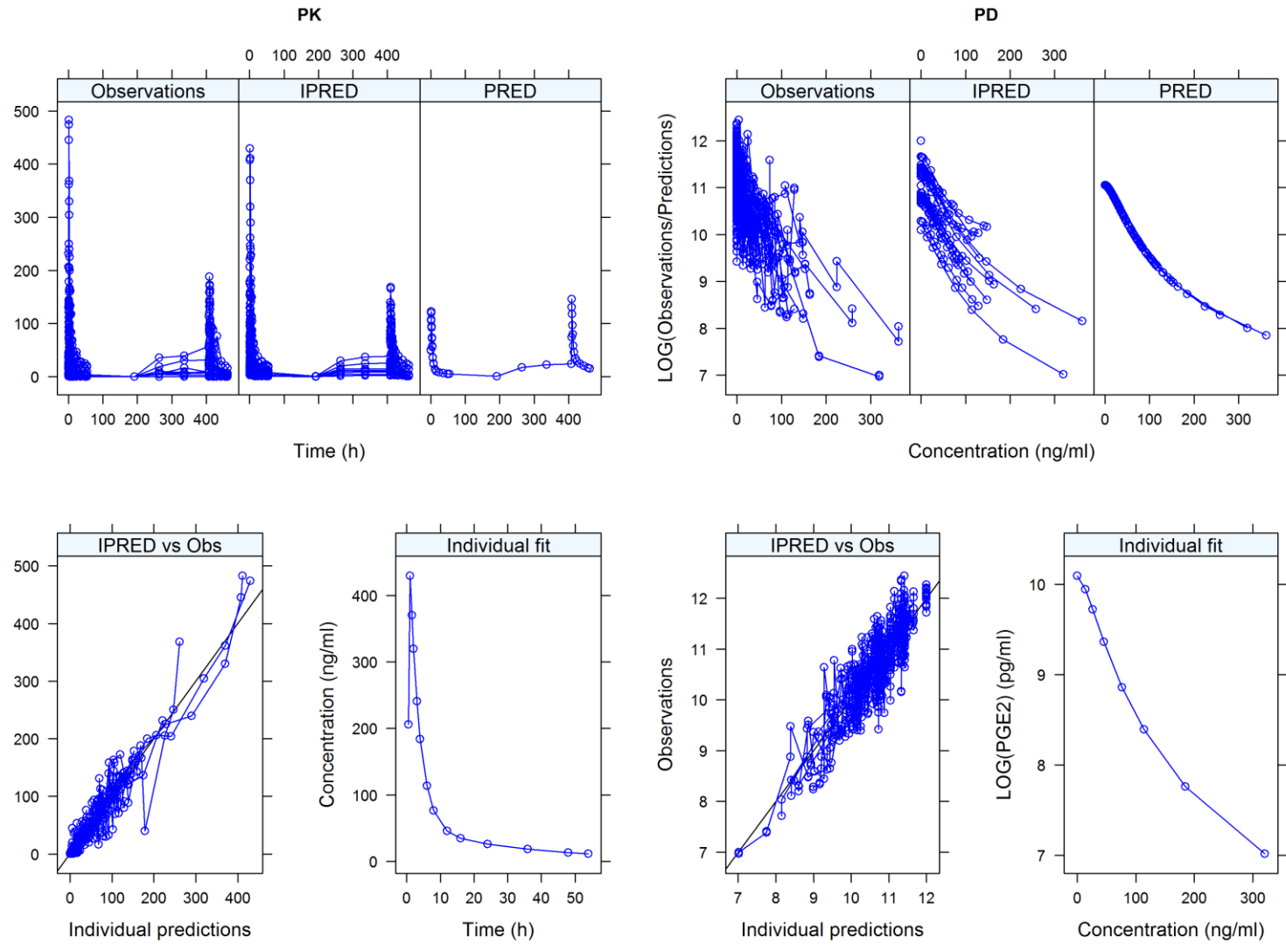


Figure 2: PK (left panels) and PD (right panels) model diagnostics. The upper panels are the observations, individual predictions and population predictions *versus* time (PK panel) or *versus* concentration (PD panel). The lower left figure on either side are the individual predictions *versus* the observations, whilst the lower right panel depicts an individual predicted profile.

Table 2: Final PK and PD model parameter estimates, including the results of a non-parametric bootstrap (n=2000).

	Final Model Results		Bootstrap Results		
	Parameter	Final Model estimates	CV%	Median	%5 CI 95% CI
PK parameters	V ₂ (L)	252.38	35.06	242.93	160.39 416.84
	V ₃ (L)	959.78	60.54	954.25	476.81 2115.03
	CL (L/h)	30.21	43.97	29.89	17.86 58.61
	k _a (h ⁻¹)	15.24	78.7	10.83	3.92 35.81
	Q (h ⁻¹)	37.28	35.82	35.6	23.83 62.44
	Lag time (h)	0.47	6.05	0.47	0.41 0.49
	F1 (35mg)	1.00	FIXED	FIXED	FIXED FIXED
	F1 (70mg)	0.49	44.2	0.48	0.25 0.93
	IIV V ₃	93%	73.05	98%	30% 145%
	IIV CL	56%	76.4	53%	32% 84%
	IIV k _a	198%	48.84	166%	98% 258%
	IIV F	95%	50.58	91%	53% 133%
	Residual error	0.11	58.99	0.1	0.05 0.23
	I ₀ (pg/ml)	63196	9.74	63077	53861 73871
	I _{max} (pg/ml)	479.00	FIXED	FIXED	FIXED FIXED
PD parameters	IC ₅₀ (ng/ml)	43.25	12.22	43.69	36.04 53.21
	Hill factor	1.59	10.37	1.61	1.42 1.94
	IIV I ₀	44%	28.63	42%	33% 54%
	IIV I _{max}	272%	107.38	241%	0% 343%
	Residual error	0.002	10.91	0.002	0.001 0.002

Simulations: Based on the predicted potency estimates, a range of doses from 20-400 mg/day were investigated. CL and I₀ were considered to fluctuate in the target population, depending on intrinsic or extrinsic factors, such as differences in metabolism and disease conditions. *Patients with normal organ function* (*figure 3A*) are used as reference to other scenarios. The median effective therapeutic dose for this group appears to lie between 100 mg and <250mg/day. The doses of GW406381 to be used in *patients with mild hepatic impairment* (*figure 3B*) should be between 100 - 150mg, whilst for moderate and severe impairment further reductions should be considered. IC₈₀ values were reached at trough levels for doses between 250 and 400 mg when clearance increased by 25%, whilst a 50% increase in clearance results in median plasma concentrations below IC₈₀ estimates (*figure 3C*).

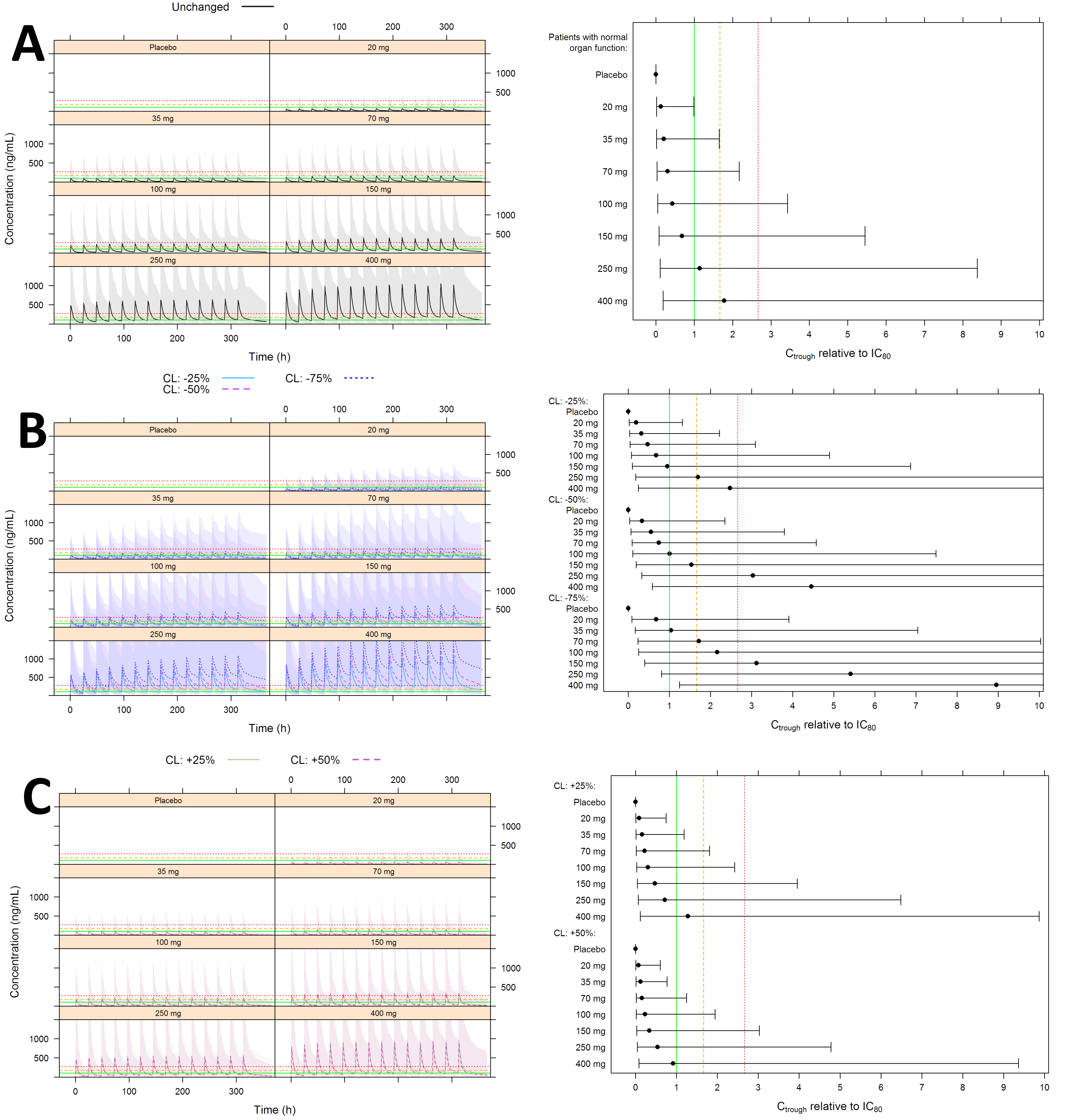


Figure 3: Concentration vs. time plots (left) and forest plots (right) for some of the simulated scenarios. A) Patients with normal organ function B) patients with liver impairment C) CYP3A4 induction. Green, orange and red lines are the IC₈₀, IC₉₀ and IC₉₅ respectively.

Finally, simulations show that a **b.i.d. regimen** allows peak concentrations to remain above the IC₉₅ for a shorter time and at much higher dosages, without significant effect on trough concentrations (*figure 4*).

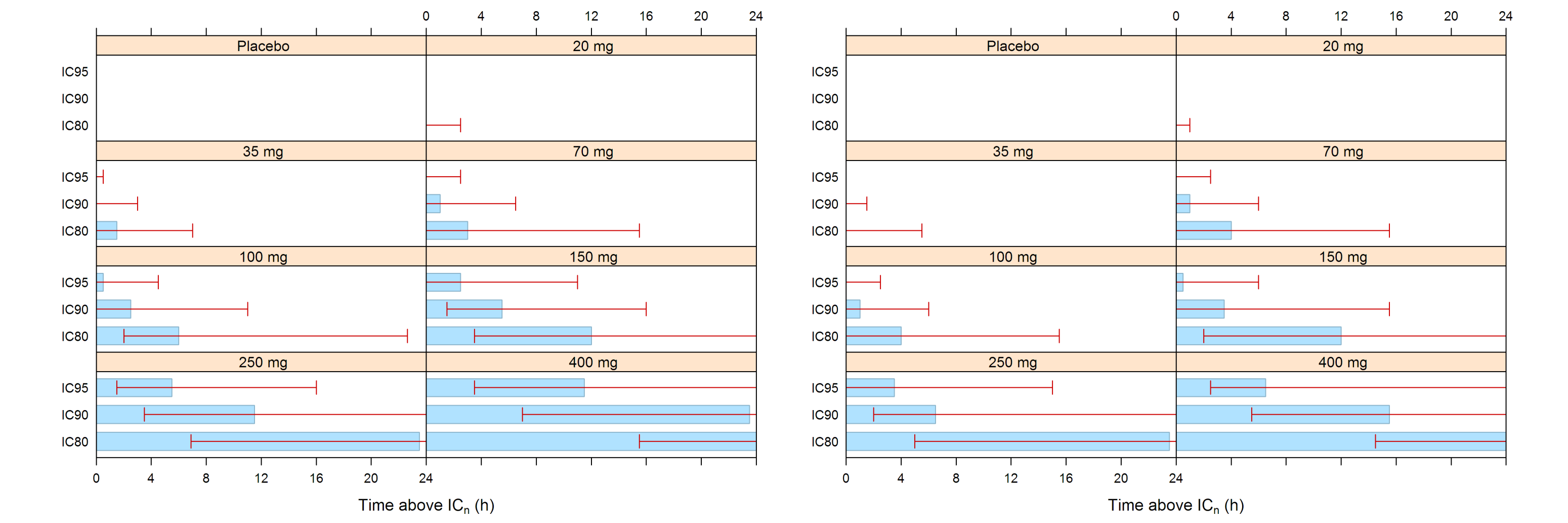


Figure 4: Time above the IC₈₀, IC₉₀, and IC₉₅ respectively for once daily (q.d., left panel) and twice daily (b.i.d., right panel) stratified by dose group, in patients with normal organ function. Red bars depict the 25 and 75%-confidence intervals respectively.

Discussion and Conclusion

The rationale for the therapeutic dose range is a critical milestone in drug development. Recommended doses and dosing regimens are often defined without accurate understanding of the underlying pharmacological effects. The possibility of generating data on a compound's pharmacology represents an opportunity to optimise and personalise treatment taking into account different patient population and conditions.

The use of a biomarker-driven approach provided insight into the underlying pharmacological effects of GW406381 and consequently into the putative therapeutic window for this compound.

Biomarkers offer a mechanistic basis for the characterisation of PKPD relationships and as such provide valuable guidance for the dose selection as well as for the design of subsequent studies during clinical development. Moreover, this approach contributes to further dismantling of an entrenched belief that still pervades the field of clinical pharmacology, i.e., that the maximum tolerated dose should be evaluated in subsequent efficacy trials, irrespective of any evidence of underlying target engagement.