

A Novel Application of Population Pharmacokinetic Analysis: Simulating Nevirapine Dose Adjustment According to *CYP2B6* 516G>T Polymorphism

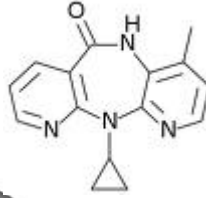
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Polymorphic *CYP2B6*



516G>T
(Gln172His)

- Caucasian 22-32%
- Asian 14-21%
- West African, Tanzanian 49%
- African-American 28%
- Hispanic 37%

983T>C
(Ile328Thr)

- West African 1.6-7.6%
- African American 4.4-7.5%
- Hispanic 1.1%
- Caucasian 0%

Aim of the study

- The aim of this study was to quantify the impact of *CYP2B6* 516G>T and 983T>C SNPs on NVP clearance (CL) estimated from a population PK analysis.
- Examine the impact of 516G>T on simulated trough concentrations (C_{trough}) obtained from once daily and twice daily NVP regimens.

Population Pharmacokinetics modelling

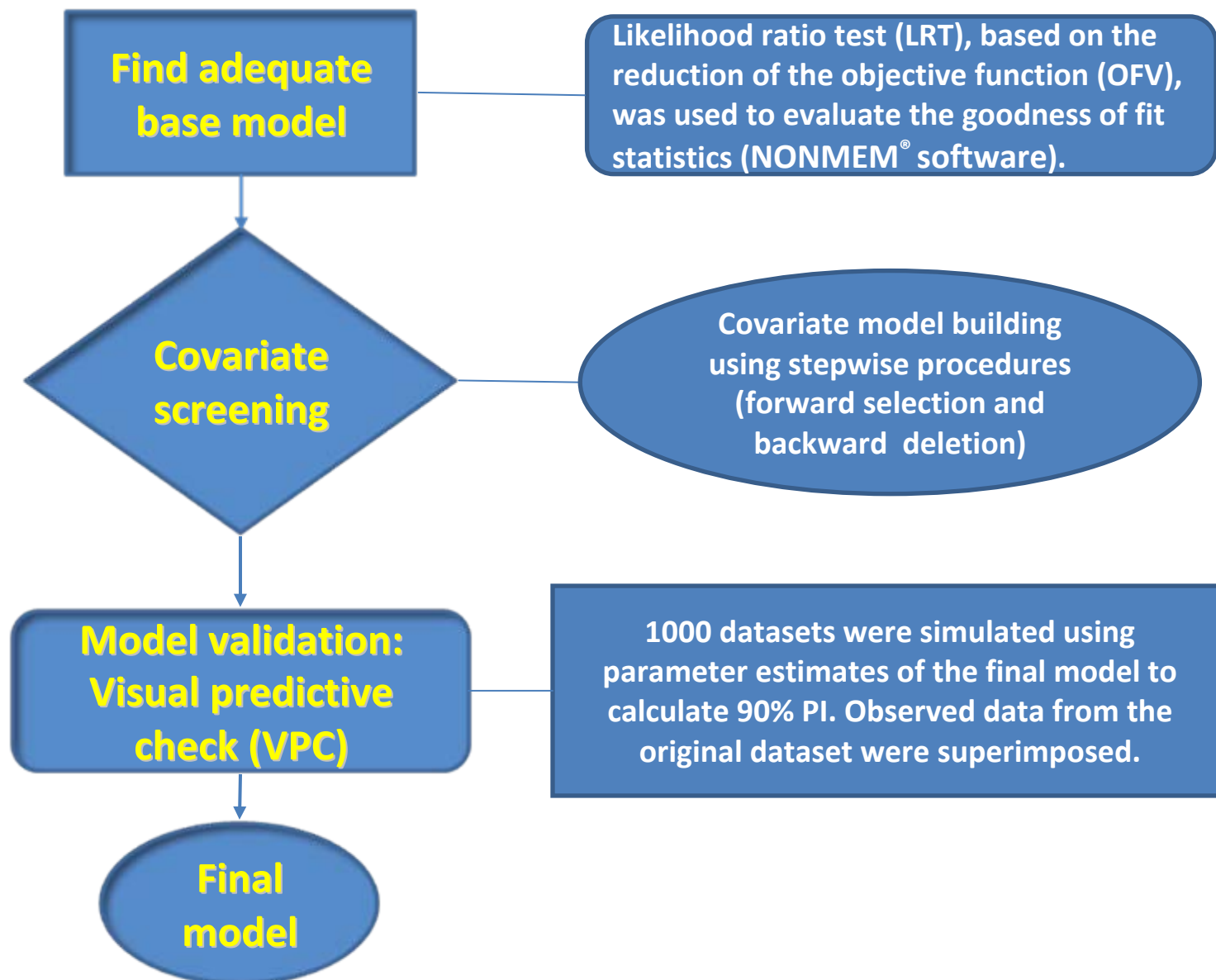
- The population PK approach offers the possibility of gaining integrated information on pharmacokinetics.
- This can be conducted from relatively sparse data obtained from study subjects, from rich data or a combination of sparse and rich data.

PK data

Demographic and physical characteristics	
Number of patients	275
N. Patients 200mg <i>bid</i>	237
N. Patients 400mg <i>od</i>	38
Males (%)	58.3%
Age, median years (IQR)	42 (22-82)
Weight, median kg (IQR)	72.5 (47-110)
Ethnicity (%)	66.7% Caucasian
	33.3% Black

- Patients recruited in UK 120, patients recruited in Germany 156
- Rich data 11 (recruited in UK)
- 983 TC = 3%
- 516 GT = 46%
- 516 TT = 7%

Population PK analysis

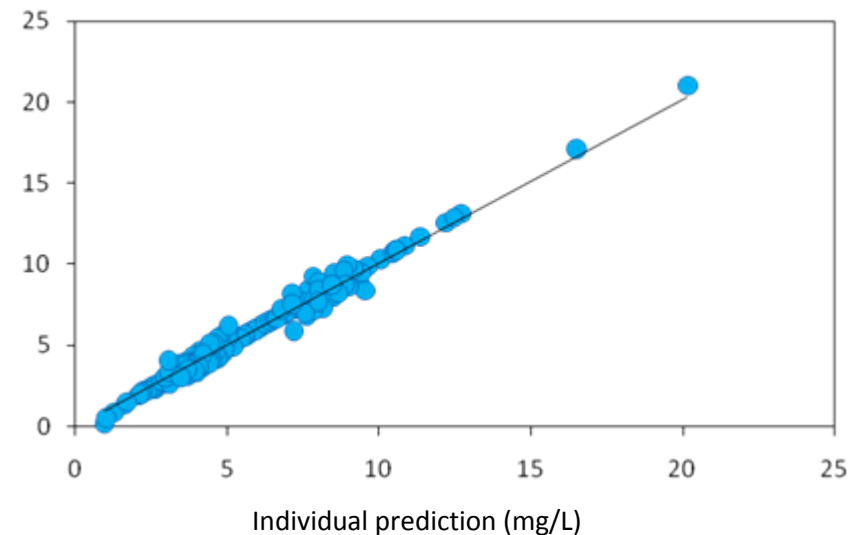
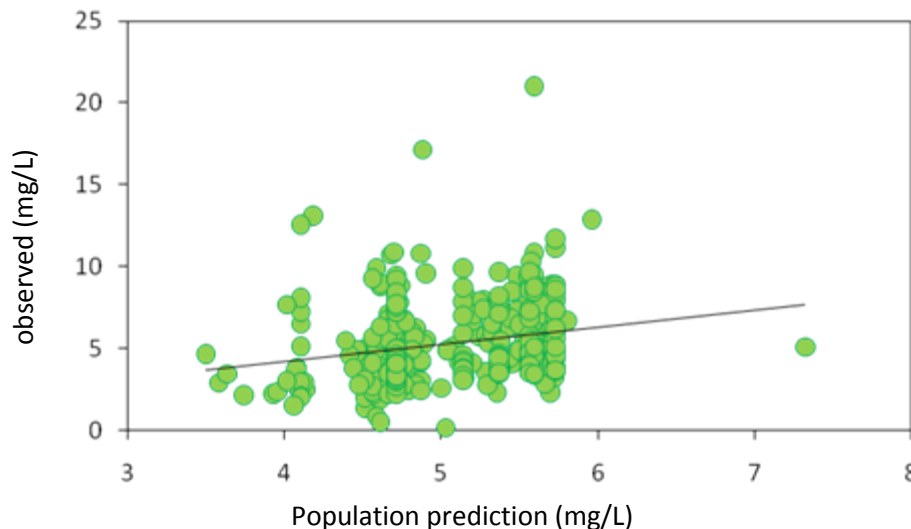


PK analysis NVP base model

Parameter	estimate	RSE%
CL/F	3.15	2.4
V/F	146	9.1
ka	1.21	17.3
IOV CL/F(%)	11	23.1
IIV CL/F(%)	38	12.4
<i>Residual error</i>		
proportional (%)	6.7	28.4
Additional (%)	31.9	41.6

Parameter	400 mg once-daily	200 mg twice-daily	P-value
CL/F (L/h)	3.93 (2.76–4.32)	3.67 (2.80–4.21)	0.63
V/F (L)	116.5 (88.5–161.8)	82.5 (70.5–103.9)	0.73

CL Cooper and RPG van Heeswijk 2007 (Review)



Covariate model building

Demographic model

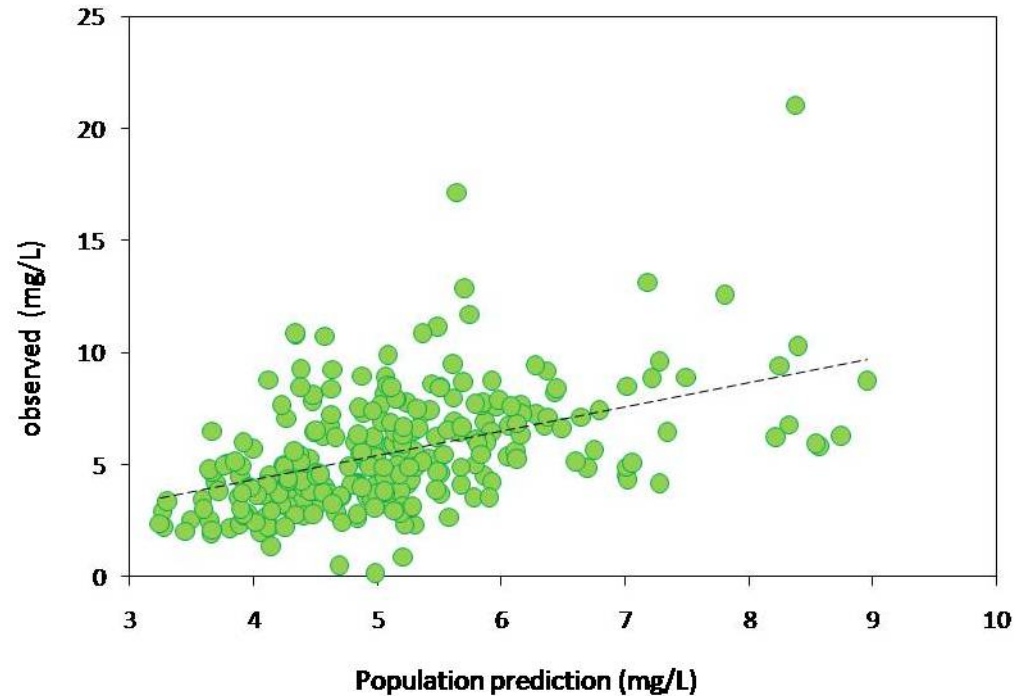
Covariate	Model	Δ OFV	p value
Influence of sex on CL/F	$CL = \theta_0 * (1 + \theta_1 \cdot SEX)$	2.44	NS
<u>Influence of weight on CL/F</u>	$CL = \theta_0 + (WT - 72.5) * \theta_1$	6.671	<0.01
Influence of age on CL/F	$CL = \theta_0 + \theta_1 * (AGE - 44)$	1.52	NS
Influence of ethnicity on CL/F	$CL = \theta_0 * (1 + \theta_1 \cdot RACE)$	2.31	NS

Pharmacogenetic model

<i>Genotype-variant analysis</i>	Model	Δ OFV	p value
Model <u>516G>T</u> Influence of <i>Het</i> and <i>Mut</i> on CL/F	$CL = \theta_0 + \theta_1 \cdot Het + \theta_2 \cdot Mut$	26.4	<0.001
Model <u>983T>C</u> Influence of <i>Het</i> on CL/F	$CL = \theta_0 + \theta_1 \cdot Het$	7.335	< 0.01
Model <u>516G>T, 983T>C</u> Influence on CL/F	$CL = \theta_0 + \theta_1 \cdot Het_{516G>T} + \theta_2 \cdot Mut_{516G>T} + \theta_3 \cdot Het_{983T>C}$	32.2	<0.001

Final population pharmacokinetic parameter estimates of NVP

Parameter	estimate	RSE(%)
CL/F	3.47	3.0
V/F	142	9.3
ka	1.16	21.2
IIV CL/F(%)	34	12.7
θ_1 WT	0.35	35.5
θ_2 Het _{516GT}	-0.4	38
θ_3 Mut _{516GT}	-1.27	17
θ_4 Het _{983TC}	-1	20
<i>Residual error</i>		
Proportional (%)	6.5	30
Additional (%)	34	42.4



$$CL = CL_0 + \text{Body Weight} + \theta_2 * \text{Het}_{516GT} + \theta_3 * \text{Mut}_{516TT} + \theta_4 * \text{Het}_{983TC}$$

5%

-11%

-37%

-28%

Change in CL
every 10Kg

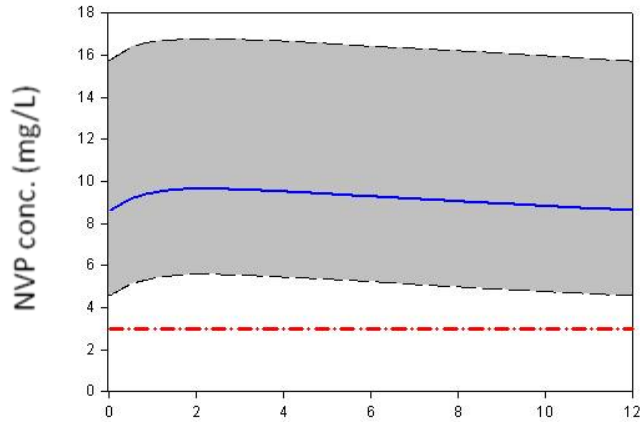
516 GT

516 TT

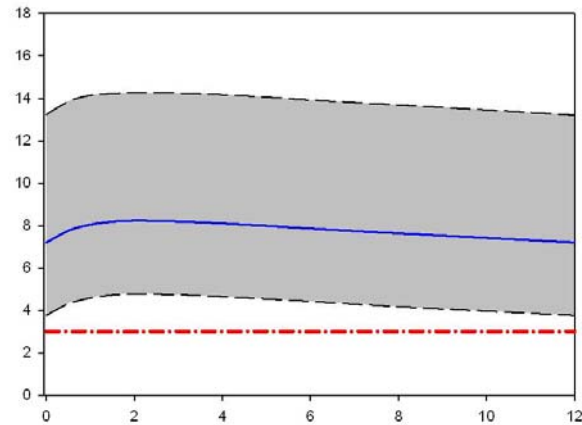
983 TC

Steady-state NVP concentrations predicted at 200mg bid (90% prediction interval)

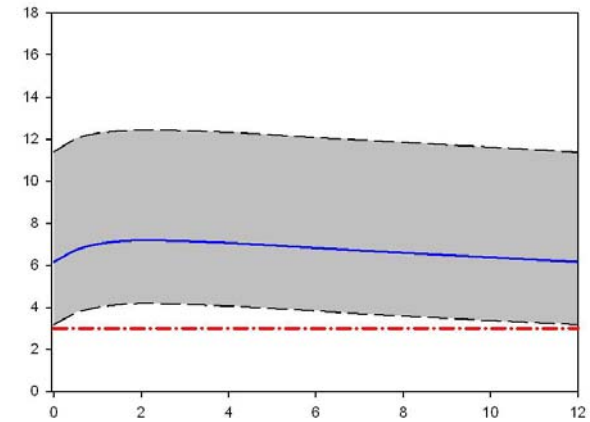
516 TT 50Kg



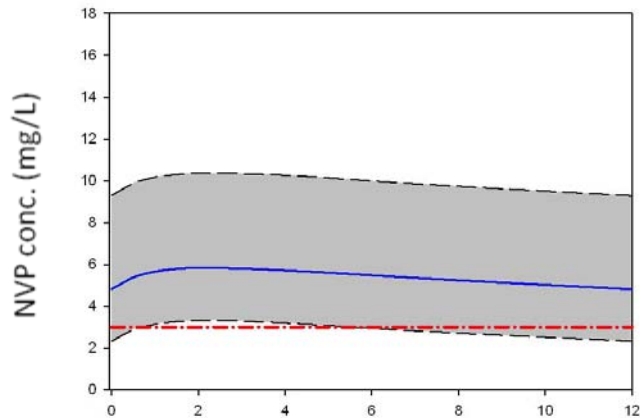
516 TT 70Kg



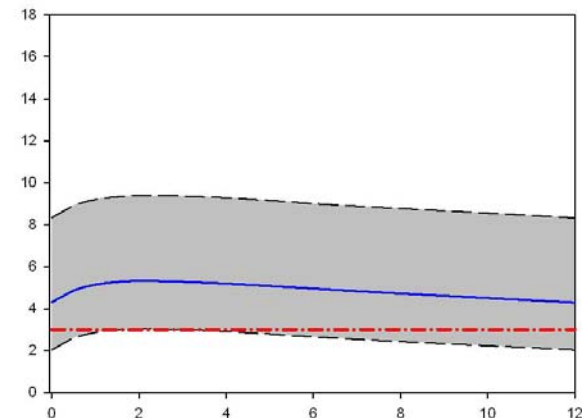
516 TT 90Kg



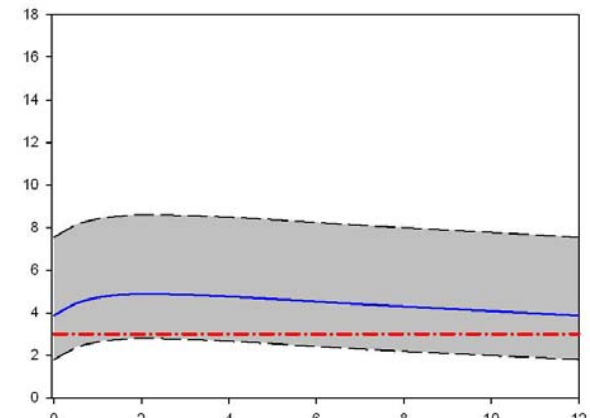
516 GG 50Kg



516 GG 70Kg



516 GG 90Kg



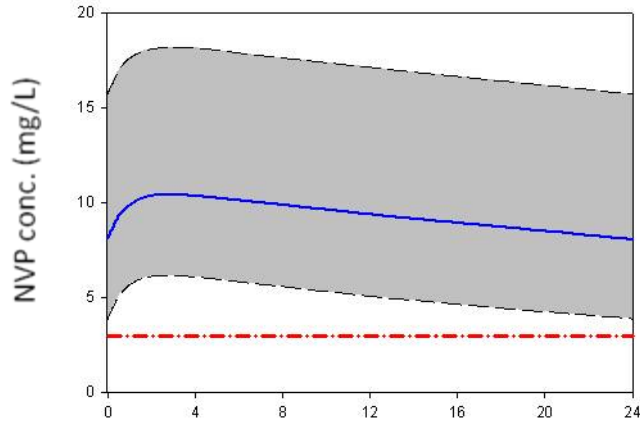
Time (h)

Time (h)

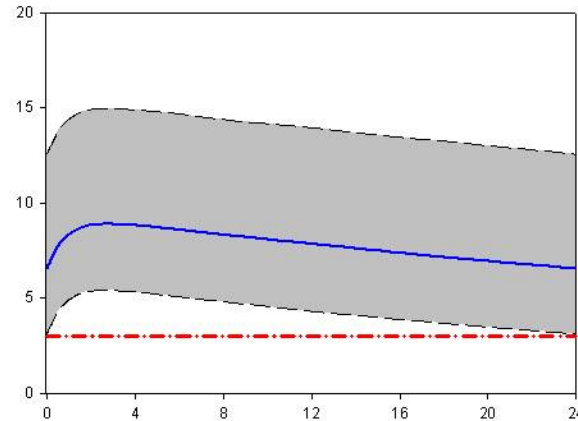
Time (h)

Steady-state NVP concentrations predicted at 400mg od (90% prediction interval)

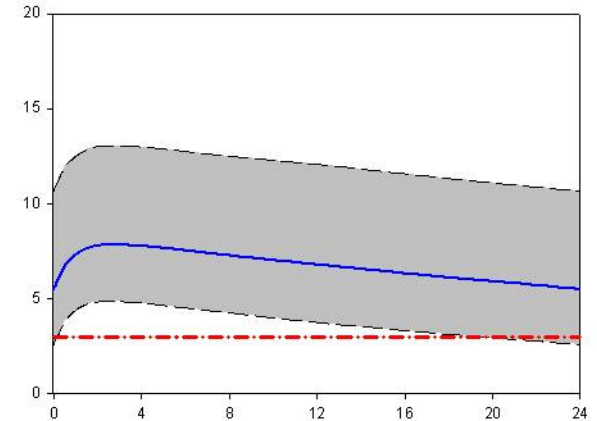
516 TT 50Kg



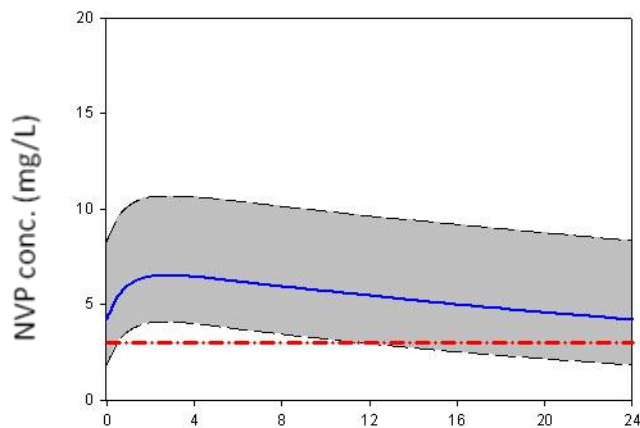
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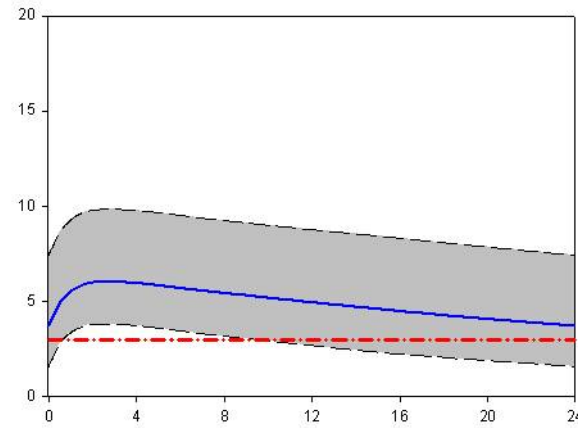
516 TT 90Kg



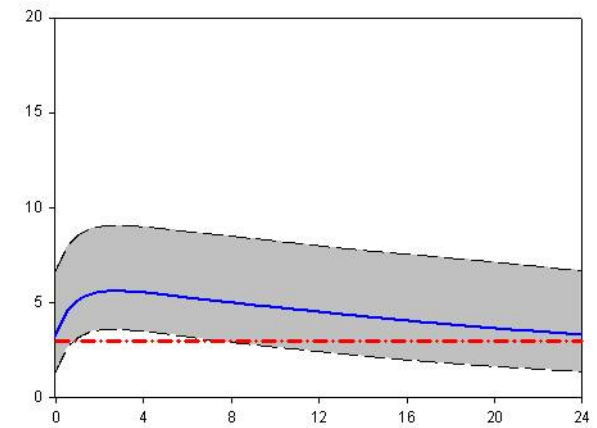
516 GG 50Kg



516 GG 70Kg



516 GG 90Kg



Time (h)

Time (h)

Time (h)

Conclusions

- This approach of integrating population PK analysis, simulated dosing regimens and pharmacogenetics may have wider application.
- For individuals with higher body weight, a once daily NVP regimen was associated with greater risk of sub-therapeutic drug exposure than a twice daily regimen.
- This risk may be offset in individuals who are 516T homozygous in which drug exposure was optimal for >95% of patients with body weight of 70kg and below.
- For those with body weight of 90kg (especially for 516GG), twice daily dosing is likely to be more robust.

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