Population Analysis of Maraviroc Phase 1 Noncompartmental Pharmacokinetic Data

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Introduction

Maraviroc, an antagonist of the human CCR5 receptor, is being developed for the treatment of HIV. Noncompartmental analysis (NCA) of Phase 1 studies showed the PK of maraviroc after single and multiple oral doses are not dose proportional. Food caused a reduction in the rate and extent of absorption with a greater effect at 100 mg than at 600 mg. In monotherapy patient studies, food had a much smaller effect upon viral load response than on the rate and extent of absorption[1].

Objectives

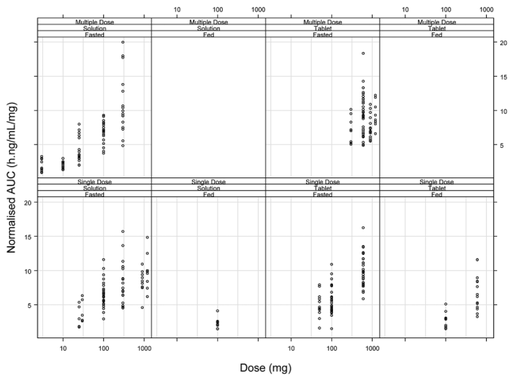
- To combine the NCA AUC and C_{max} values from single and multiple dose Phase 1 studies to derive parametric models describing the effects of dose, food, formulation (solution and immediate release tablet) and steady state on the PK of maraviroc.
- To predict AUC and C_{max} for food and formulation combinations not included in the model data set.

Data

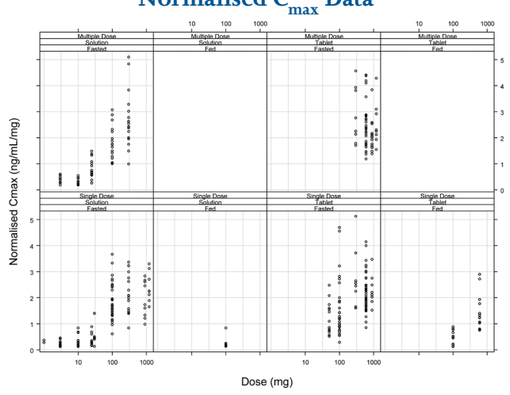
330 AUC and 395 C_{max} values from 134 healthy subjects in 5 Phase 1 studies were used. Single and multiple QD and BID solution and IR tablet doses ranged from 1 to 1200 mg. $AUC_{0-\infty}$ single dose and AUC_{τ} multiple dosing, and C_{max} were dose normalised.

Single Dose, Multiple Dose, Solution, Tablet Fasted and Fed Data by Covariates

Normalised AUC Data



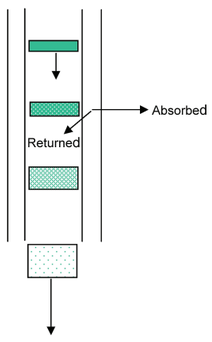
Normalised C_{max} Data



Methods

Sigmoid E_{max} models with intercept (E_0) were applied to dose-normalised AUC (NAUC) or C_{max} (NCMX). Additive and proportional residual error models with log-transformed data were used. Constraints were placed on changes in E_0, E_{max}, Hill coefficient and ED_{50} arising from the dose, food, formulation and steady state covariates. Parameter estimation utilised non-linear mixed effect regression (NONMEM V). Evaluation included 1000 nonparametric bootstrap runs with data stratified by study

Semi-Mechanistic View of the Absorption Process



- Absorption represented by a bolus of maraviroc travelling down an absorbing tube with walls containing saturable transporters (Pgp) returning part of the drug back into the lumen
- Passage down the tube is spreading and diluting the bolus
- Effect of formulation and/or food is to delay dissolution and/or spread and dilute the bolus
- The more dilute bolus reduces relative saturation of the transporters and returns relatively more to the lumen
- Multiple doses superimpose upon any residual maraviroc unabsorbed from previous doses and increase concentrations

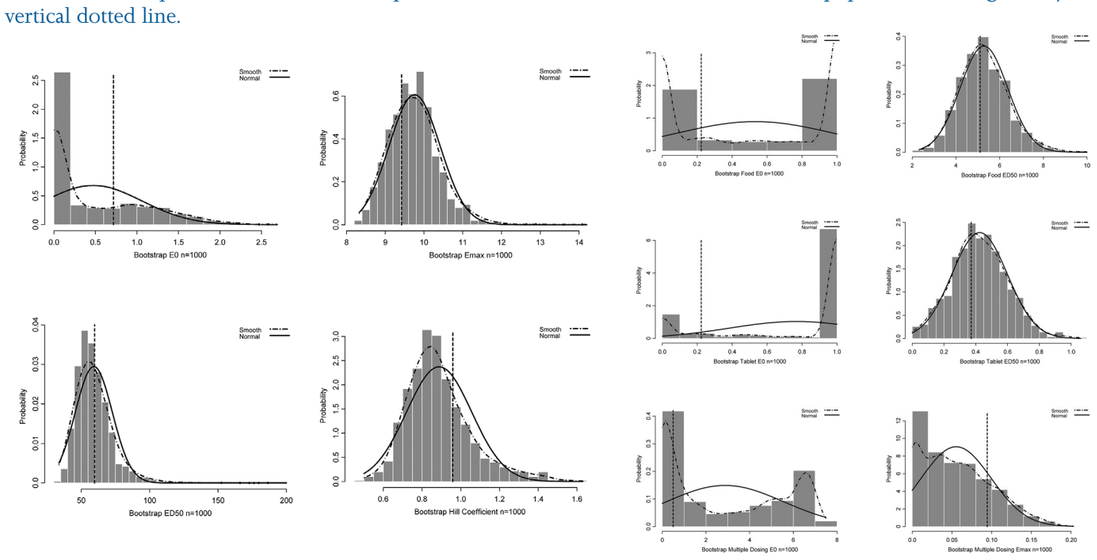
Assumptions and Limits on Absorption Model

$$E = E_0 + (E_{max} - E_0)\frac{Dose^{\gamma}}{ED^{\gamma}_{50} + Dose^{\gamma}}$$

- ♦ No dose or covariate changes in disposition pharmacokinetics (including first pass metabolism)
- ♦ Fasted solution dose would give the highest single dose overall absorption and quickest single dose absorption.
- ♦ Hence fasted solution would have the highest NAUC and NCMX.
- ♦ QD dosing would give higher or equal NAUC/NCMX to same single dose
- ♦ BID dosing would give higher or equal NAUC/NCMX to same QD dose
- ♦ Reference model is single dose, solution, fasted
- ♦ High enough doses would eventually overcome any effects of absorption transporters

Results

Selected bootstrap distributions of NAUC parameters are illustrated with the NONMEM population value given by the vertical dotted line.



The bootstrap distributions show E_{max}, ED_{50} and Hill coefficient γ are well defined but the data are insufficient to support the model and covariate effects on E_0.

The final NONMEM parameters are shown below including the bootstrap confidence intervals.

Normalised AUC

Parameter	Model Theta/Omega	Value	%SE	Bootstrap Median (95% CI)	Comment
Solution Single Dose					
E_0 (h.ng/mL/mg)	θ_1	0.716	97	0.135 (0.001,1.82)	
E_{max} (h.ng/mL/mg)	θ_2	9.42	7.5	9.72 (8.64,11.2)	
ED_{50} (mg)	θ_3	59.7	17	56.8 (40.7,90.2)	
Hill Coefficient	θ_4	0.959	24	0.863 (0.625,1.31)	
Food Covariates					
E_0	θ_7	0.223	400	0.606 (0,1)	22.3% reduction vs fasted
ED_{50}	θ_8	5.11	34	5.22 (3.33,7.61)	511% increase vs fasted
Tablet Covariates					
E_0	θ_9	0.223	400	1 (0,1)	22.3% reduction vs solution
ED_{50}	θ_{10}	0.371	58	0.414 (0.093,0.769)	37.1% increase vs solution
Tablet x Food Covariates					
E_0	θ_{11}	1 FIXED			Limit. E_0 is equal to lower of food and tablet covariates. Tablet fed = solution fed: 22.3% lower than solution fasted
ED_{50}	θ_{12}	1 FIXED			Limit. ED_{50} is equal to food covariate. Tablet fed = solution fed : 511% higher than solution fasted.
Multiple Dose BID Covariates					
E_0	θ_{13}	0.498	140	1.91 (0,6.96)	65% increase vs single dose
E_{max}	θ_{14}	0.0944	48	0.0492 (0,0.153)	9.9% increase vs single dose
ED_{50}	θ_{15}	0 FIX			Limit. ED_{50} BID is equal to single dose.
Multiple Dose QD Covariates					
E_0	θ_{17}	0 FIX			Limit. ED_0 QD is equal to BID.
E_{max}	θ_{18}	0 FIX			Limit. ED_{max} QD is equal to BID.
ED_{50}	θ_{19}	0 FIX			Limit. ED_{50} QD is equal to BID.
Inter-Subject Variability					
E_{max} (%)	ω_1	25	19	24.3 (20.5,28.5)	
Residual Variability					
Proportional (%)	θ_5	15.3	24	12.5 (2.2,18.2)	

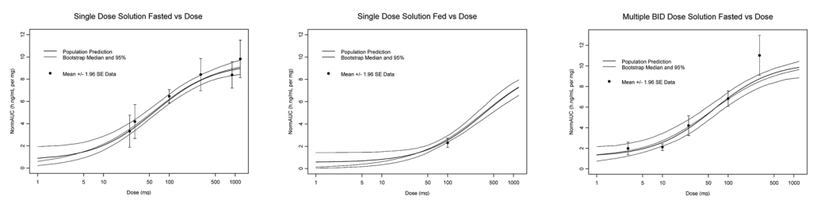
Normalised C_{max}

Parameter	Model Theta/Omega	Value	%SE	Bootstrap Median (95% CI)	Comment
Solution Single Dose					
E_0 (ng/mL/mg)	θ_1	0.232	9.8	0.249 (0.195,0.332)	
E_{max} (ng/mL/mg)	θ_2	2.06	4.8	2.04 (1.83,2.23)	
ED_{50} (mg)	θ_3	62.6	12	60.9 (47.0,74.9)	
Hill Coefficient	θ_4	2.23	19	2.08 (1.51,4.25)	
Food Covariates					
E_0	θ_7	0.072	200	0.0348 (0,0.373)	7.2% reduction vs fasted
ED_{50}	θ_8	7.32	16	7.48 (5.65,10.2)	732% increase vs fasted
Tablet Covariates					
E_0	θ_9	0 FIX			Limit. Fasted tablet E_0 is equal to solution E_0.
ED_{50}	θ_{10}	0.0172	910	0.0606 (0,0.414)	1.7% increase vs solution
Tablet x Food Covariates					
E_0	θ_{11}	1 FIXED			Limit. E_0 is equal to lower of food and tablet covariates. Tablet fed = solution fed: 7.2% lower than solution fasted
ED_{50}	θ_{12}	1 FIXED			Limit. ED_{50} is equal to food covariate. Tablet fed = solution fed : 732% higher than solution fasted.
Multiple Dose BID Covariates					
E_0	θ_{13}	0.347	41	0.281 (0,0.618)	42% increase vs single dose
E_{max}	θ_{14}	0.116	58	0.142 (0.0342,0.258)	12.3% increase vs single dose
ED_{50}	θ_{15}	-0.191	150	-0.0370 (-0.541,0)	17.4% decrease vs single dose
Multiple Dose QD Covariates					
E_0	θ_{17}	0 FIX			Limit. E_0 QD is equal to BID.
E_{max}	θ_{18}	0.291	290	0.238 (0,10)	QD is between BID and single dose at 9.1% higher than single dose
ED_{50}	θ_{19}	14 FIX			High Limit. ED_{50} QD is equal to single dose.
Inter-Subject Variability					
E_{max} (%)	ω_1	24	28	24.6 (18.3,30.9)	
Residual Variability					
Proportional (%)	θ_5	33.1	7.5	33.1 (25.9,38.5)	
Additive (ng/mL/mg)	θ_6	0.144	21	0.170 (0.116,0.315)	

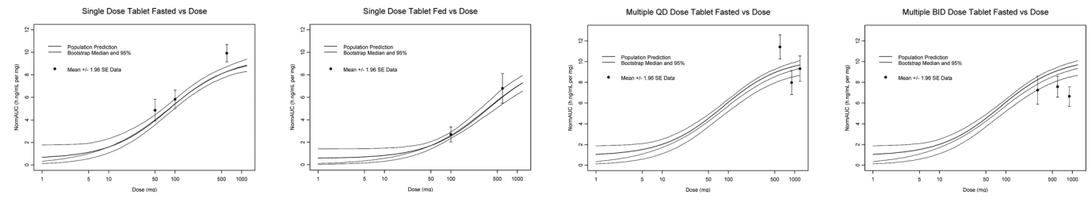
The ill-defined NONMEM parameters with large standard errors are those with the poor bootstrap distributions.

NONMEM population predictions with the model bootstrap 95% intervals (not inter-subject or residual variability) with mean data (±1.96 SE) are shown to illustrate the dose nonlinearity and reliability of prediction at different doses and covariate situations.

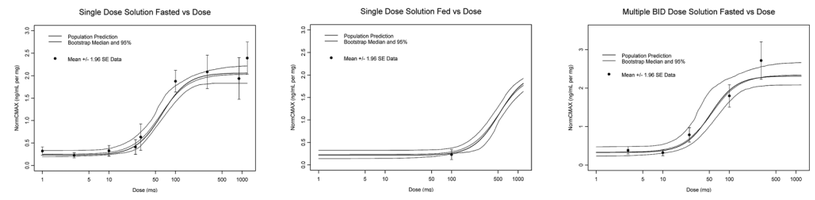
Normalised AUC Solution Model Predictions and Mean Data



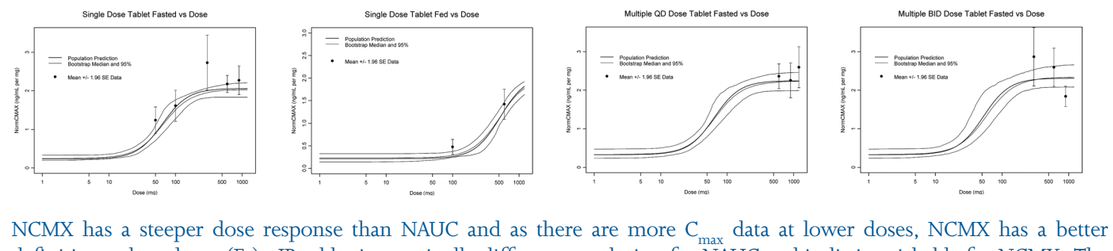
Normalised AUC Tablet Model Predictions and Mean Data



Normalised C_{max} Solution Model Predictions and Mean Data

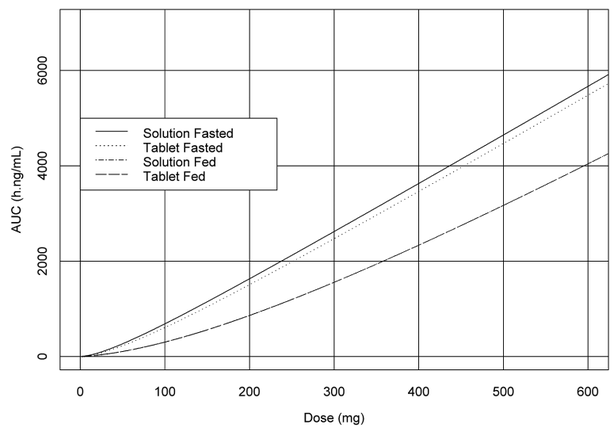


Normalised C_{max} Tablet Model Predictions and Mean Data



NCMX has a steeper dose response than NAUC and as there are more C_{max} data at lower doses, NCMX has a better definition at low doses (E_0). IR tablet is marginally different to solution for NAUC and indistinguishable for NCMX. The effect of food is better defined for NAUC than for NCMX so prediction of food effects on C_{max} is therefore less certain.

Model Prediction Of Multiple Dosing AUC



Conclusion

The parametric models allow prediction of maraviroc AUC and C_{max} under different dose size and frequency, food, solution and IR tablet conditions not studied.

References

1. Fatkenheuer G *et al. Nat Med* 2005; **11:**1170-2

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