

POPULATION PHARMACOKINETIC ANALYSIS ON DATA FROM A BIOEQUIVALENCE STUDY – EFFECTS OF HORMONAL CONTRACEPTIVES ON DRUG EXPOSURE

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Introduction

The application of population pharmacokinetics (PopPK) modelling to data from bioequivalence studies can provide valuable insight on the pharmacokinetics (PK) and identify covariates that might explain the variability in exposure of drugs, as population used on these trials usually includes healthy subjects that are highly standardized.

Objectives

To assess the PK and to identify covariates that might explain variability in exposure following oral administration of Sunitinib.

Methods

Data: Authorised secondary use of data from a 2x2x2 crossover study in 20 healthy volunteers under fasting conditions that demonstrated bioequivalence between 50 mg Sunitinib Test and Reference formulations.

Noncompartmental Analysis (NCA): NCA was performed to the observed plasma concentration-time profiles (R 4.0.3).

Population Analysis: Plasma concentration-time data (759 samples) were analysed using nonlinear mixed-effects modelling (Monolix 2019R2).

Table 1. Population Information

Characteristic	Value
N	20
Sex (Male/Female)	9/11
Female under contraceptive use	5
Age (years)	31 (20 – 48)
Height (cm)	169 (157 – 185)
Weight (kg)	72.9 (53.5 – 96.6)
Body Mass Index (kg/m ²)	25.4 (19.7 – 29.2)

Conclusions

- The developed model adequately described plasma concentration-time profiles of sunitinib on healthy subjects.
- The model showed good performance as suggested by the simulation-based diagnostic.
- Model covariates and model estimates for sunitinib PK parameters are similar to the described in literature [1]. However, V/F population estimates were below the ones reported in the literature (2230 L) [1].
- Hormonal contraception use was correlated with an increase of sunitinib bioavailability (F), following oral administration. Such an investigation is of interest and warrants further analysis, considering the increase in sunitinib exposure at this population.

Results

Table 2. Sunitinib geometric mean (CV%) NCA PK parameters following administration on Female subjects not under and under stable hormonal contraceptive use.

Parameter (Unit)	Male (n = 18)	Female w/o contraceptive (n = 12)	Female w/ contraceptive (n = 10)
C _{max} (µg/L)	28.94 (27.1%)	40.64 (6.0%)	52.03 (15.2%)
t _{max} (h)	8.00 (6.00 – 11.50)	8.50 (6.00 – 10.00)	7.51 (6.00 – 11.00)
AUC _{0-t} (µg.h/L)	947.33 (37.6%)	1379.92 (7.8%)	1688.35 (20.2%)
AUC _{0-∞} (µg.h/L)	1182.79 (41.7%)	1720.27 (10.2%)	2256.27 (27.5%)
%AUC _{extrap} (%)	18.93 (30.8%)	19.32 (20.9%)	23.97 (29.7%)
λ _z (h ⁻¹)	0.024 (18.9%)	0.025 (14.1%)	0.020 (23.6%)
t _{1/2} (h)	28.56 (18.9%)	28.17 (14.1%)	34.38 (23.6%)
V/F (L)	1742.05 (33.9%)	1181.21 (11.1%)	1099.19 (16.4%)
Cl/F (L/h)	42.27 (41.7%)	29.07 (10.2%)	22.16 (27.5%)

n = number of observations (twice in each study participant); %AUC_{extrap}: Residual area, AUC_{0-t}: Area under the plasma concentration-time curve (AUC) from time zero until the last quantifiable timepoint, AUC_{0-∞}: AUC from time zero until infinity, Cl/F: Apparent oral clearance, C_{max}: Maximum plasma concentration, λ_z: Apparent elimination rate constant, t_{max}: Time of occurrence of C_{max}, t_{1/2}: Apparent terminal elimination half-life, V/F: Apparent volume of distribution. t_{max} values are median with range between parenthesis

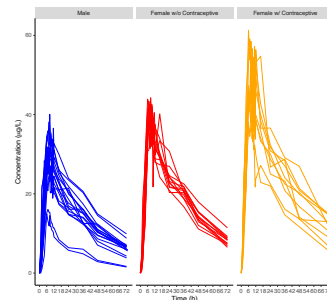


Figure 1. Sunitinib plasma concentrations versus time profiles, following administration to Male (blue), Female not under (red) and under stable (i.e. continuous) hormonal contraception (yellow) subjects

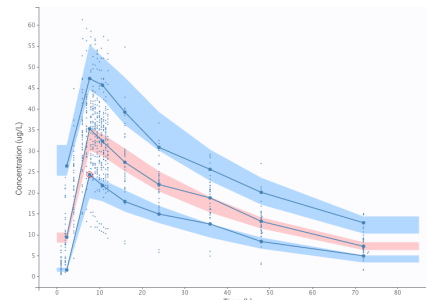


Figure 2. Sunitinib simulation-based diagnostic plots for plasma concentration (µg/mL) versus time (h). Prediction intervals for each percentile estimated across all simulated data, computed with a level of 90% confidence interval (CI), are displayed as coloured areas (red for the 50th percentile, blue for the 10th and 90th percentiles). Outliers are highlighted with red circles.

References

- [1] U.S. Food and Drug Administration (FDA) Sutent (Sunitinib Malate) Capsules Clinical Pharmacology and Biopharmaceutics Review. Application No.: NDA 21-938 (GIST) & NDA 21-968 (MRCC). Approval Date: 26 Jan 2006.

Table 3. Sunitinib Population Pharmacokinetic Parameters Estimates and Corresponding Standard Errors (SE), Relative Standard Errors (RSE) and 90% Confidence Interval (90% CI)

Parameters	Estimate	SE	RSE (%)	90% CI
Fixed Parameters				
t _{lag} (h)	0.63	0.03	5.3	0.57 – 0.68
Tk ₀ (h)	5.37	0.25	4.7	4.97 – 5.8
V/F (L)	1542.43	98.21	6.4	1389.06 – 1712.73
β _{V/F} , Weight	0.812	0.197	24.3	0.488 – 1.136
Cl/F (L/h)	41.30	3.01	7.3	36.63 – 46.57
β _{Cl/F} , Female	-0.223	0.073	32.6	-0.342 – -0.103
F	1.00 ¹			
β _F , Female w/o Contraceptive	0.163	0.103	62.7	-0.005 – 0.332
β _F , Female w/ Contraceptive	0.341	0.108	31.7	0.163 – 0.518
Standard Deviation of the Random Effects				
ω _{Tk0} ²	0.170	0.042	24.9	0.113 – 0.257
ω _{Cl/F} ²	0.109	0.027	25.3	0.072 – 0.164
ω _F ²	0.303	0.049	16.1	0.133 – 0.229
γ _{t_{lag}} ²	0.310	0.039	12.6	0.245 – 0.374
γ _{Tk0} ²	0.142	0.031	22.1	0.091 – 0.195
γ _{Cl/F} ²	0.084	0.021	25.2	0.047 – 0.116
γ _F ²	0.038	0.011	29.4	0.021 – 0.058
Error Model Parameter				
σ ²	0.122	0.004	3.0	0.116 – 0.127

Cl/F: Apparent oral clearance, F: Bioavailability, t_{lag}: Latency time, Tk₀: Apparent absorption rate time (zero order), V/F: Apparent volume of distribution.

β: Exponent that quantifies the effect of the covariate on the average PK parameter estimate, γ²: Inter-occasion variance, ω²: Inter-subject variance, σ²: Residual variance (additive error model)

¹ Parameter was fixed

- Female subjects presented a higher exposure (C_{max} and AUC) in general, in comparison to male subjects.
- Female subjects under continuous hormonal contraception presented a higher exposure and a higher variability in comparison to female subjects without hormonal contraception.
- Following oral absorption, sunitinib disposition was described by a one-compartment model with zero-order absorption and latency time (t_{lag}).
- The model included individual random effects for absorption (Tk₀), clearance (Cl/F), and bioavailability (F), and occasion random effects for t_{lag}, Tk₀, Cl/F, and F.
- Body weight explained the variability observed for V/F, and sex the variability in Cl/F.
- The use of continuous hormonal contraception was correlated with an increase in F