Untangling absorption mechanisms and variability in bioequivalence studies using population analysis

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DEVELOPMENT OF INNOVATIVE PRODUCTS

PK

EFFICACY

SAFETY

DEVELOPMENT OF HYBRID/GENERIC PRODUCTS

DDI

Food effect

Special populations

BA/BE

Clinical Trials
VARIABILITY

BA/BE

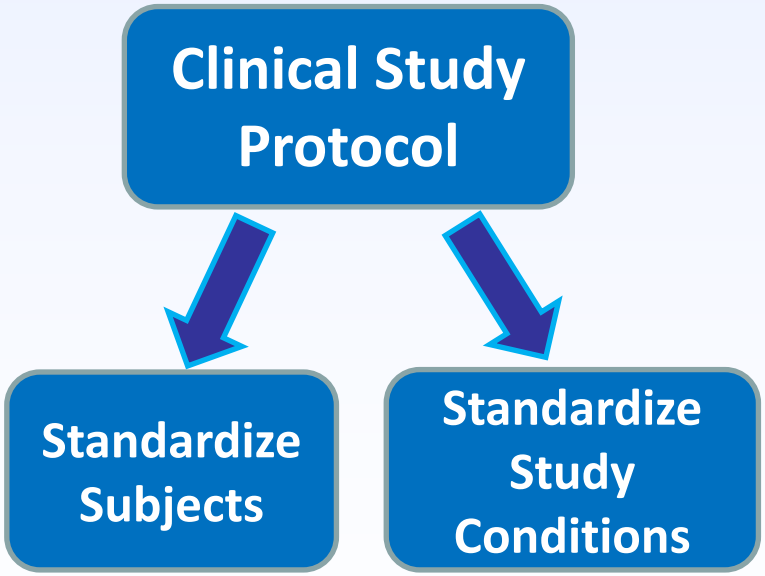
Inter-individual variability (IIV)

Inter-occasion variability (IOV)

Inter-Individual Variability (IIV)

Between Subject Variability / Inter Subject Variability

- **Demographics**
  (age, gender, race, BMI, weight)
- **Environmental factors**
  (diet, smoking, exposure to pollutants)
- **Genetic phenotype**
  (polymorphic enzymes, transporters)
- **Physiological and pathological**
  (pregnancy, hepatic and renal impairment)
- **Other factors**
  (food effect, posture, other drugs)



Inter-Occasion Variability (IOV)

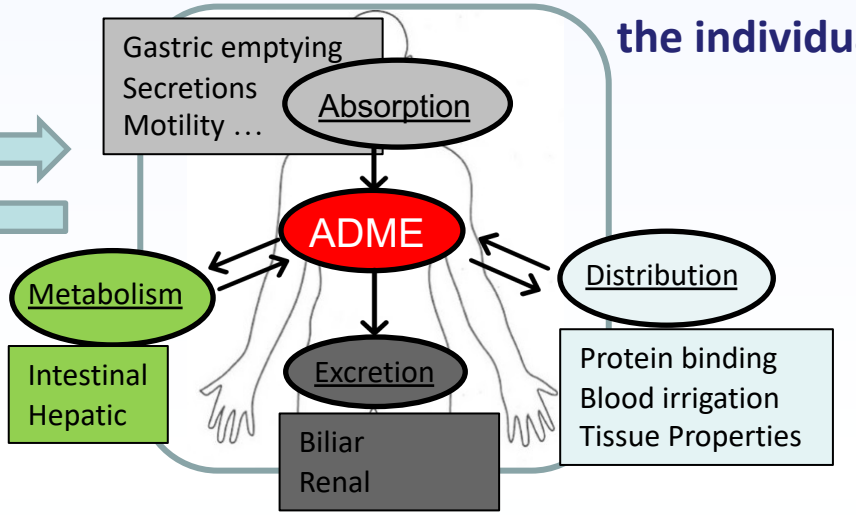
Responsible for many studies fail or lead to inconclusive results → **Need for study design optimization to increase the efficiency of crossover studies**

ORIGINATED BY:

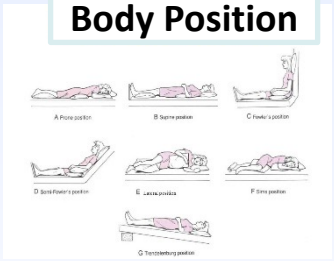
Bio-performance of drug formulation

- ✓ Route of Administration
- ✓ Pharmaceutical Form
- ✓ Physicochemical Properties of Drugs
- ✓ Excipients
- ✓ Manufacturing process

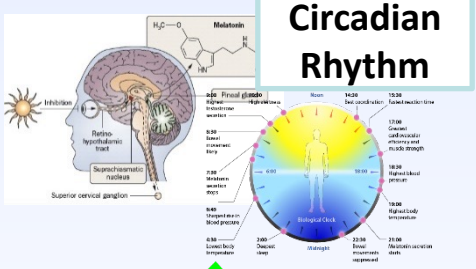
Factors related to the individual



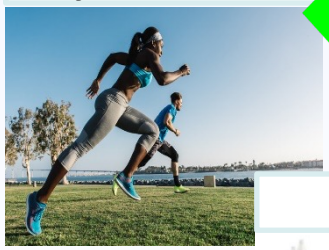
Body Position



Circadian Rhythm



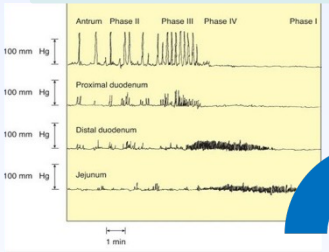
Physical Exercise



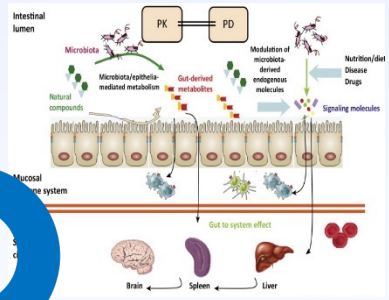
Hormonal Contraception

Meals

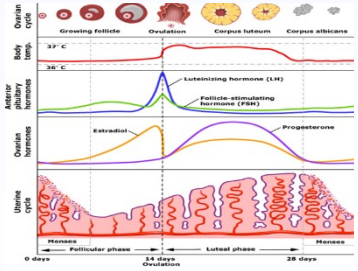
Migrating Motor Complex



Changes in Microbiota



Menstrual Cycle



Emotional State

Use of Population Pharmacokinetics Modelling

- Best tool to quantify variability and identify its causes
- Allows to work with sparse and heterogeneous data
- Very useful in PK studies with special population
- Interesting cost / benefit ratio

MAIN APPLICATIONS POPULATION PK

- **KNOW THE BEHAVIOR OF A CERTAIN POPULATION**
  - Through of the typical values parameters
- **IDENTIFY FACTORS THAT AFFECT THE PK OF A DRUG**
  - Demographic, pathophysiological, environmental
- **EVALUATE VARIABILITY AND RESIDUAL ERROR**
  - Variance of parameters and residual error

Population Pharmacokinetics Modelling

Non-Linear Mixed Effects (NLME)

Fixed Effects

Random Effects

θ
(Theta)
K_a V_d Cl

Interindividual
η
$\eta \in N(0, \omega^2)$

Occasion
κ
$\kappa \in N(0, \gamma^2)$

Residual
ε
$\varepsilon \in N(0, \sigma^2)$

Covariates

Continuous

Weight

Age

Categorical

Sex

Horm. Cont.

Biopharmaceutical Drug Disposition Classification System (BDDCS)

	High Solubility	Low Solubility	
Extensive Metabolism	**Class I** (37%) Transporter effects minimal	**Class II** (31%) Efflux transporter effects predominate	High Permeability
Poor Metabolism	**Class III** (26%) Absortive transporter effects predominate Renal and/or biliary elimination of unchanged drug	**Class IV** (6%) Absorptive and efflux transporter effects can be important Renal and/or biliary elimination of unchanged drug	Low Permeability

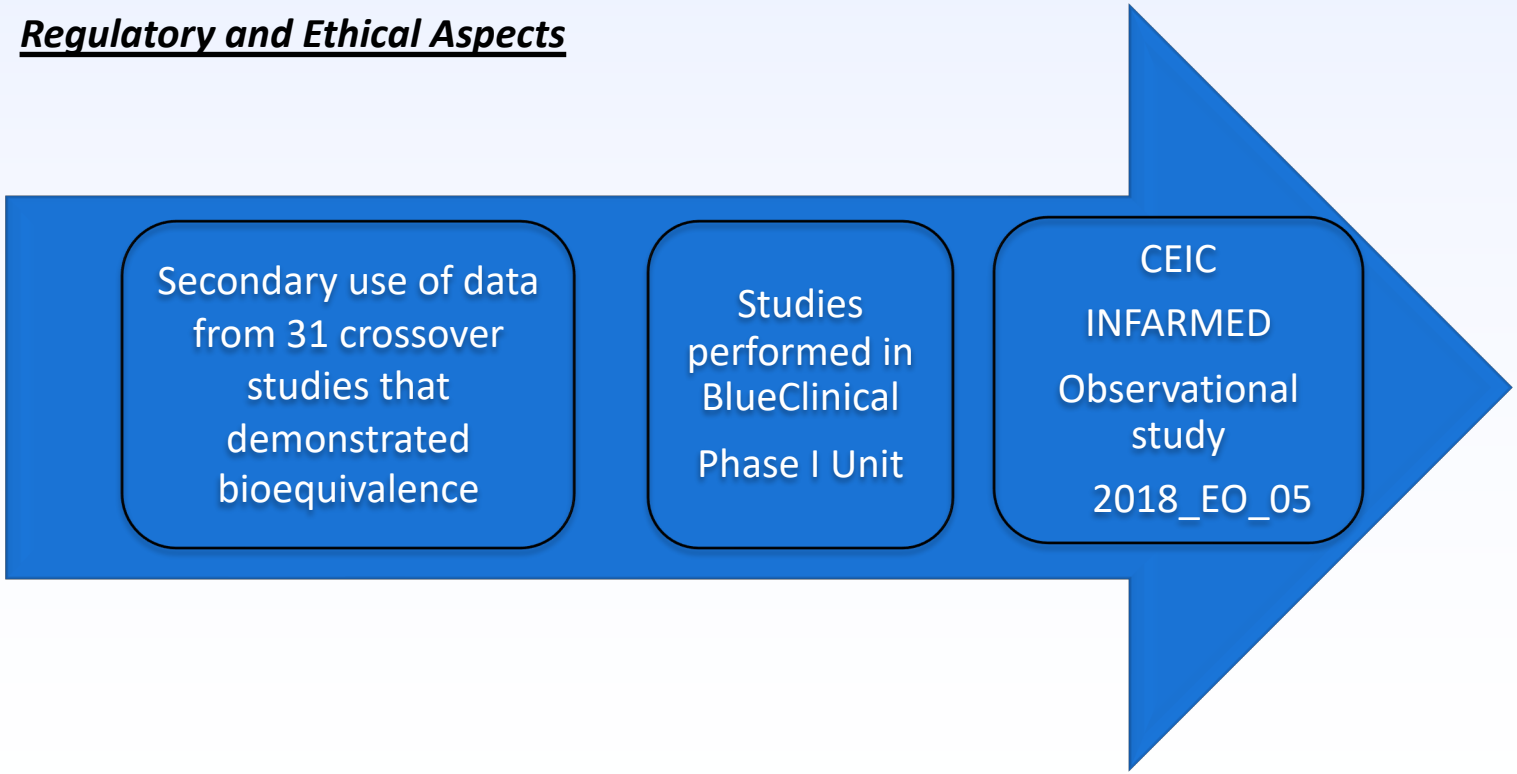
Objectives

To identify subject-related factors affecting Inter Occasion Variability of pharmacokinetic parameters using data from bioequivalence trials

- ✓ To develop population pharmacokinetics models for each drug from bioequivalence trials
- ✓ To identify the most relevant factors (covariates) related to subjects that can affect PK parameters
- ✓ To relate BDDCS class and drug absorption and disposition PK parameters
- ✓ To investigate other means of controlling intra-subject variability by refining the inclusion/exclusion criteria for study participation and optimize study design of crossover studies

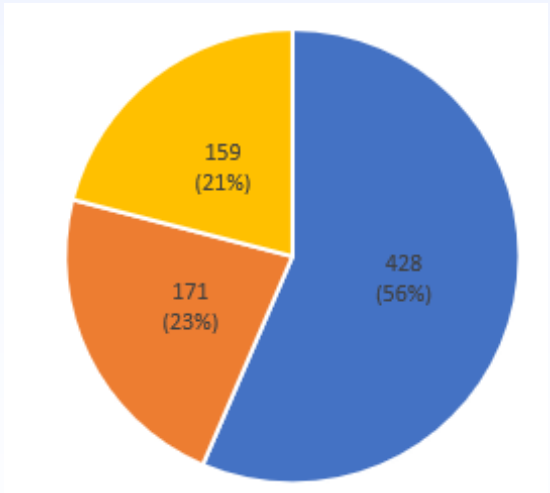
Data Sources

- **Clinical Trial Data**
  - ***Regulatory and Ethical Aspects***



Data Sources

- **Clinical Trial Data**
  - ***Population Subject Characteristics***



Male
Female without hormonal contraceptive
Female with hormonal contraceptive

Inclusion criteria

- Age 18 - 55 years
- Weight ≥48 kg
- BMI 18.0 - 31.0 kg/m2
- Without clinically significant abnormalities
- Negative viral serology
- Non-smokers or ex-smokers
- Accept and comply with study restrictions

Exclusion criteria

- Hypersensitivity/allergy reaction to the study drug, excipients or other drug
- Medical or surgical condition that could affect drug PK or subject safety
- History of regular consumption alcohol, drugs of abuse and methylxanthines
- Use of drugs (except hormonal contraceptive)

Data Sources

- **Drug Substances**

17 Drug substances

Antihypertensive

- Amlodipine (C09DB01)
- Chlorthalidone (C03BA04)
- Clonidine (C02AC01)
- Hydrochlorothiazide (C03AA03)
- Zofenopril (C09AA15)

Antidepressants / Anxiolytics

- Alprazolam (N05BA12)
- Fluoxetine (N06AB03)
- Paroxetine (N06AB05)
- Sertraline (N06AB06)

Anti-inflammatory / Gout suppressants

- Etoricoxib (M01AH05)
- Febuxostat (M04AA03)

Antineoplastic

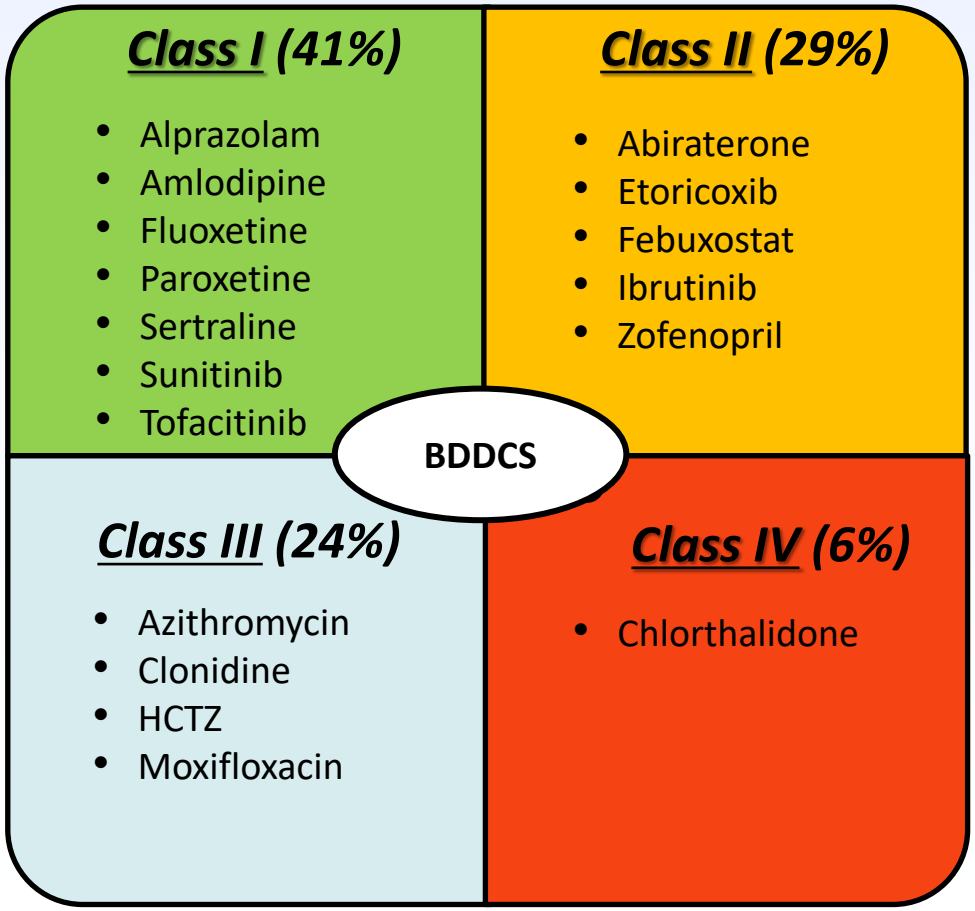
- Abiraterone (L02BX03)
- Ibrutinib (L01EL01)
- Sunitinib (L01EX01)
- Tofacitinib (L04AA29)

Anti-bacterial

- Azithromycin (J01FA10)
- Moxifloxacin (J01MA14)

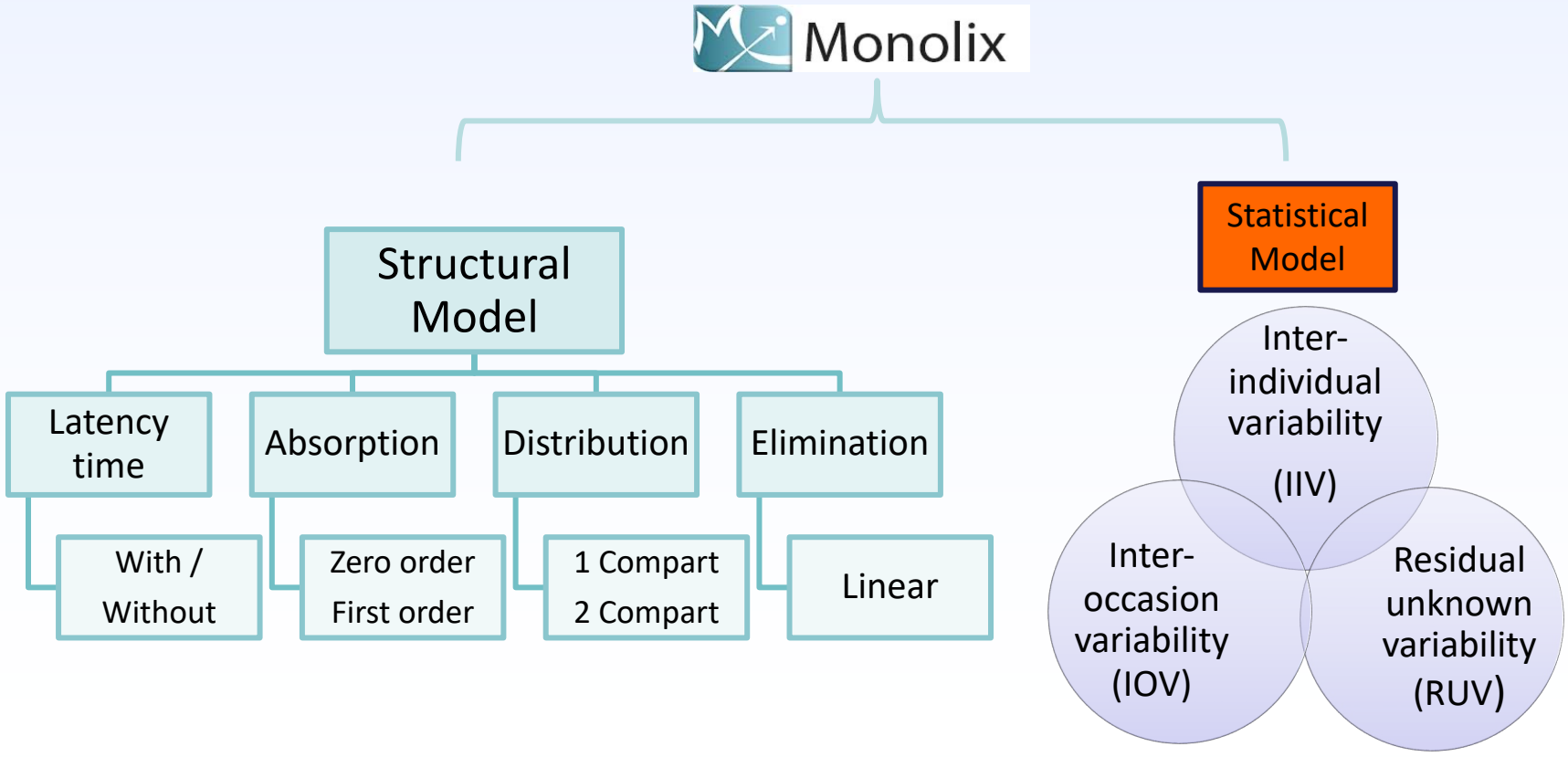
Data Sources

- Drug Substances Clustered by BDDCS Class



Data Analysis

- Population Analysis
  - *Structural and Statistical Model*



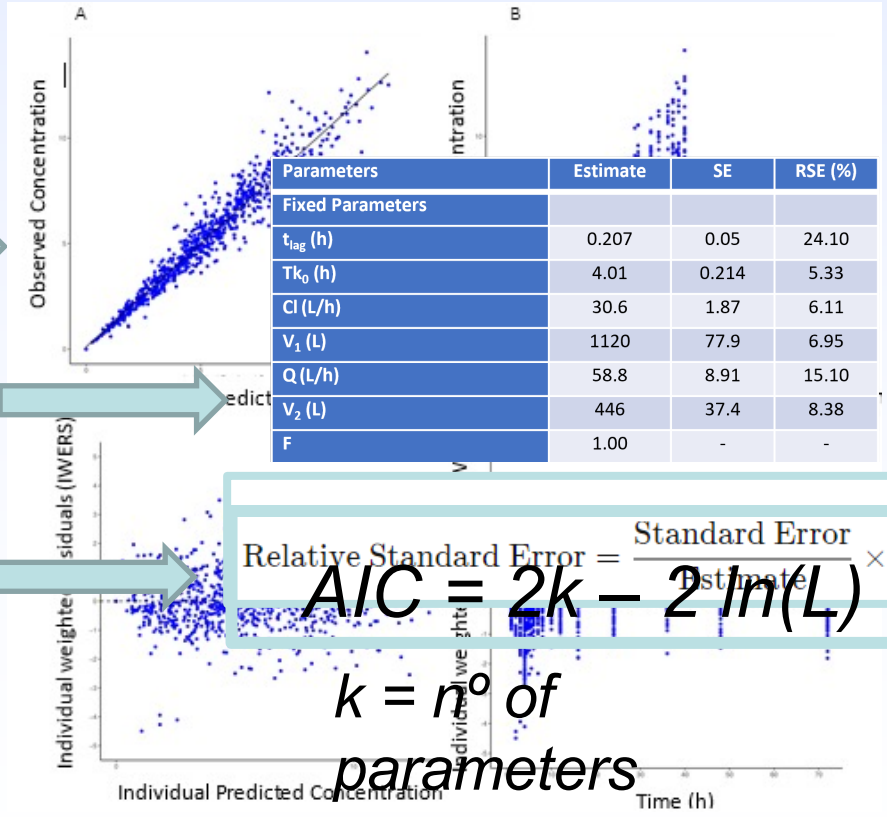
Data Analysis

- Population Analysis
  - *Model Selection*

Goodness of Fit Plots

Relative Standard Error (RSE)< 50%

Akaike Information Criteria (AIC)



Parameters	Estimate	SE	RSE (%)
Fixed Parameters			
t_{lag} (h)	0.207	0.05	24.10
Tk_0 (h)	4.01	0.214	5.33
Cl (L/h)	30.6	1.87	6.11
V_1 (L)	1120	77.9	6.95
Q (L/h)	58.8	8.91	15.10
V_2 (L)	446	37.4	8.38
F	1.00	-	-

$$\text{Relative Standard Error} = \frac{\text{Standard Error}}{\text{Estimate}} \times 100$$

$$AIC = 2k - 2\ln(L)$$

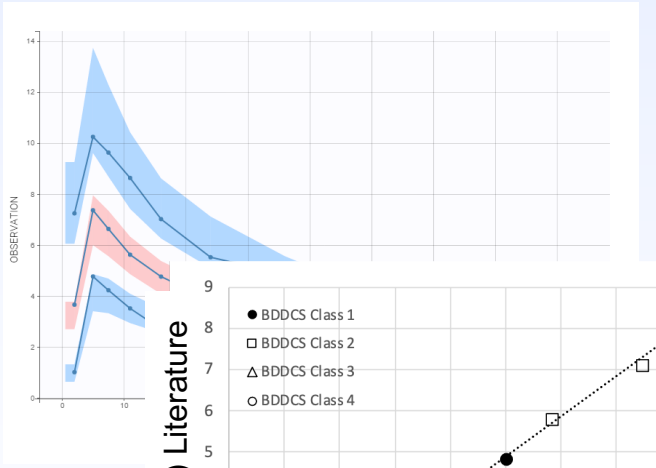
k = nº of parameters

L = Likelihood

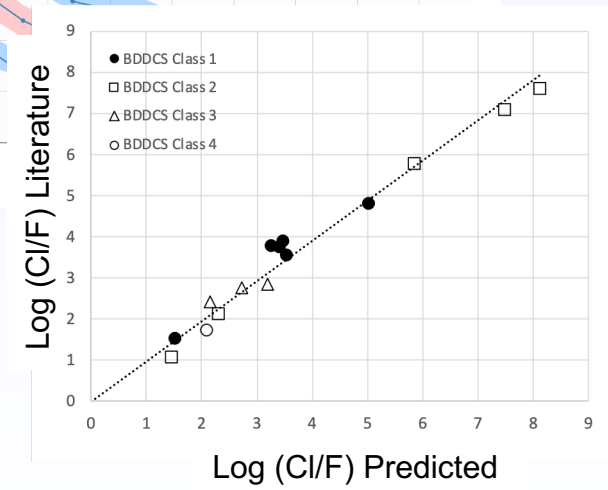
Data Analysis

- Population Analysis
  - *Model Evaluation / Validation*

Visual Predictive Check (VPC)

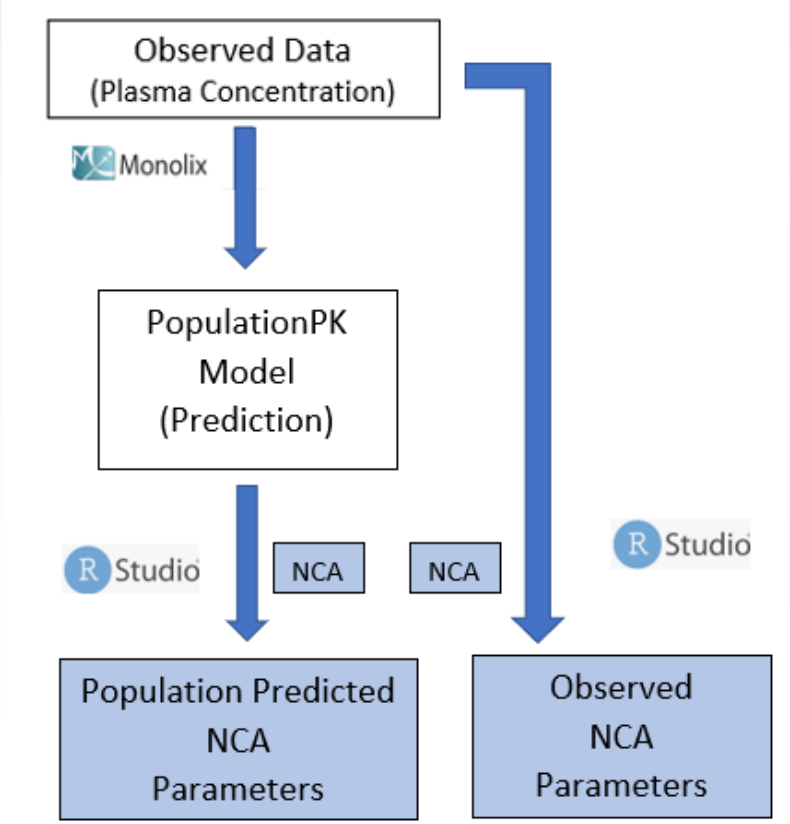


Comparison between parameters predicted by population model with those published in literature

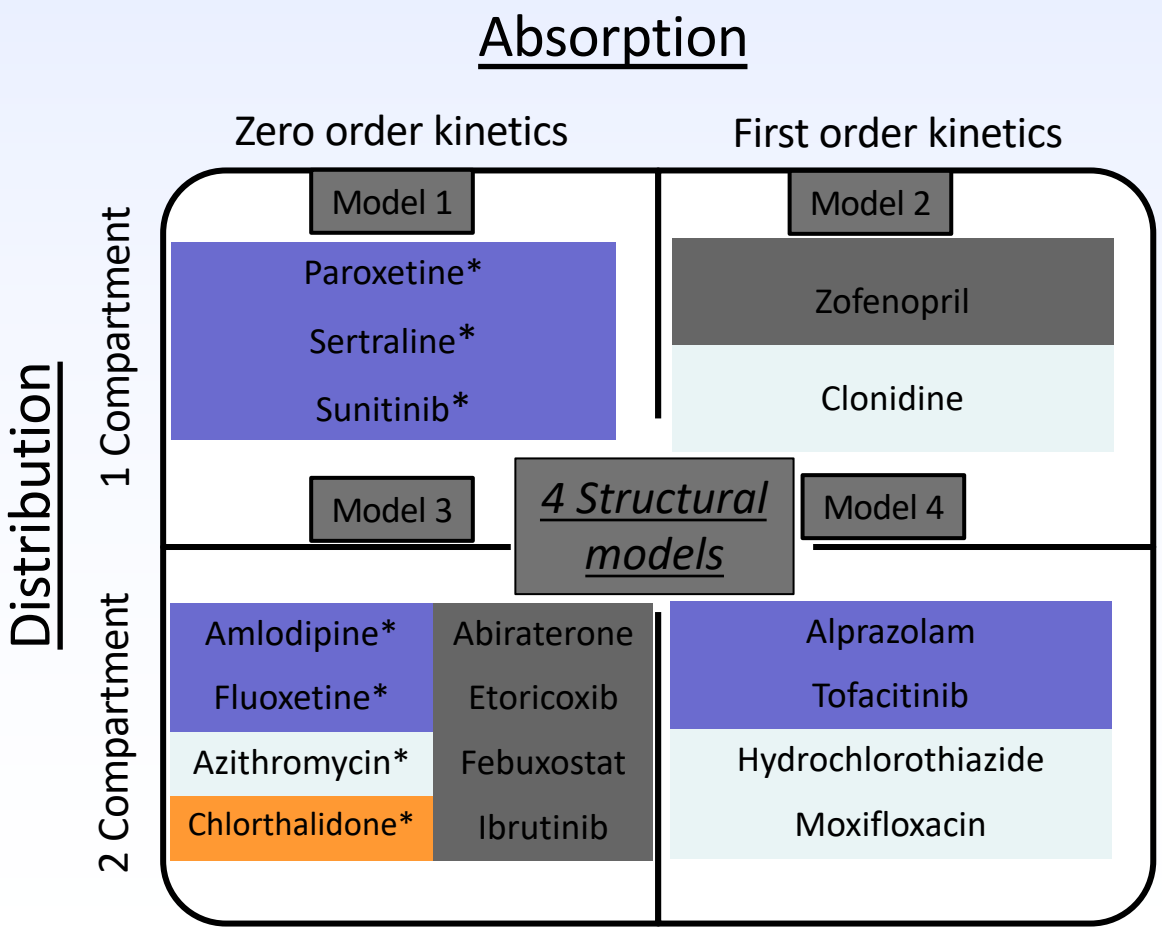


Data Analysis

- Noncompartmental Analysis
  - *Covariate Analysis*



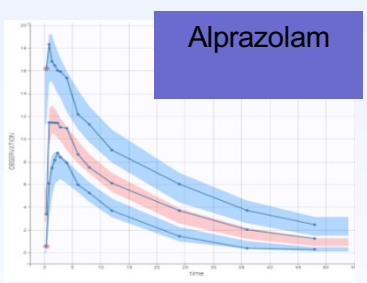
Population Pharmacokinetic Analysis

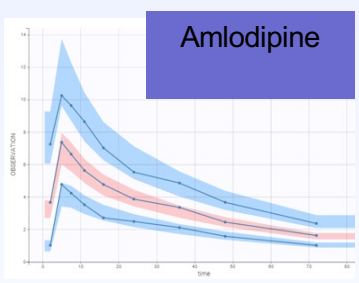


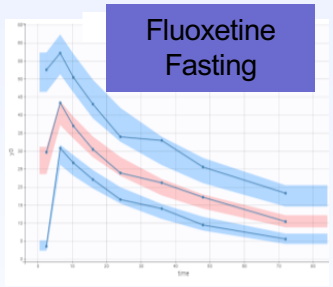
(*) P-Glycoprotein

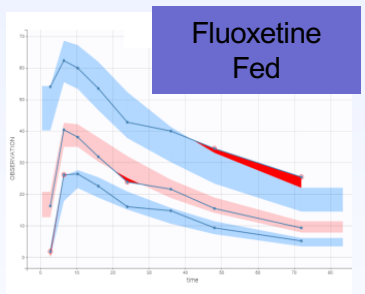
BDDCS	DRUG
I	Alprazolam Amlodipine* Fluoxetine Fasting* Fluoxetine Fed* Paroxetine Fed* Sertraline* Sunitinib* Tofacitinib Fasting Tofacitinib Fed
II	Abiraterone Etoricoxib Febuxostat Ibrutinib Fasting Ibrutinib Fed Zofenopril
III	Azithromycin Fed* Clonidine Fasting Clonidine Fed Hydrochlorothiazide Moxifloxacin
IV	Chlorthalidone Fasting* Chlorthalidone Fed*

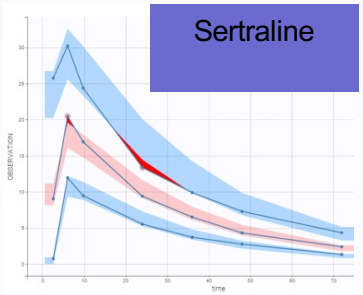
Model Evaluation: Visual Predictive Check (VPC)

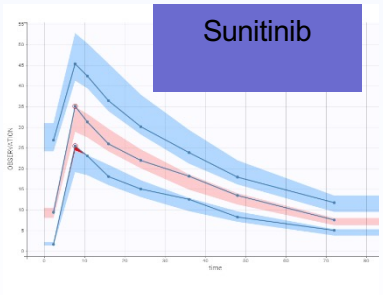


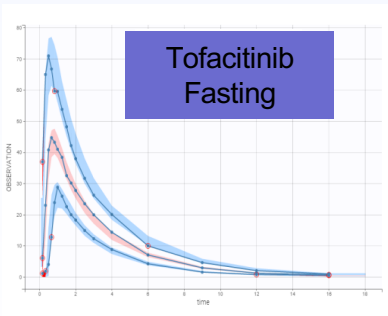


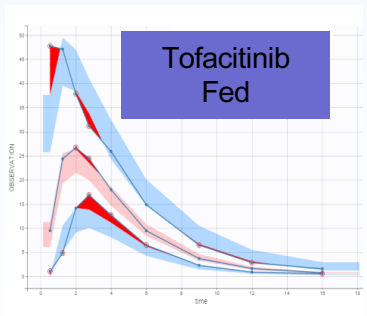






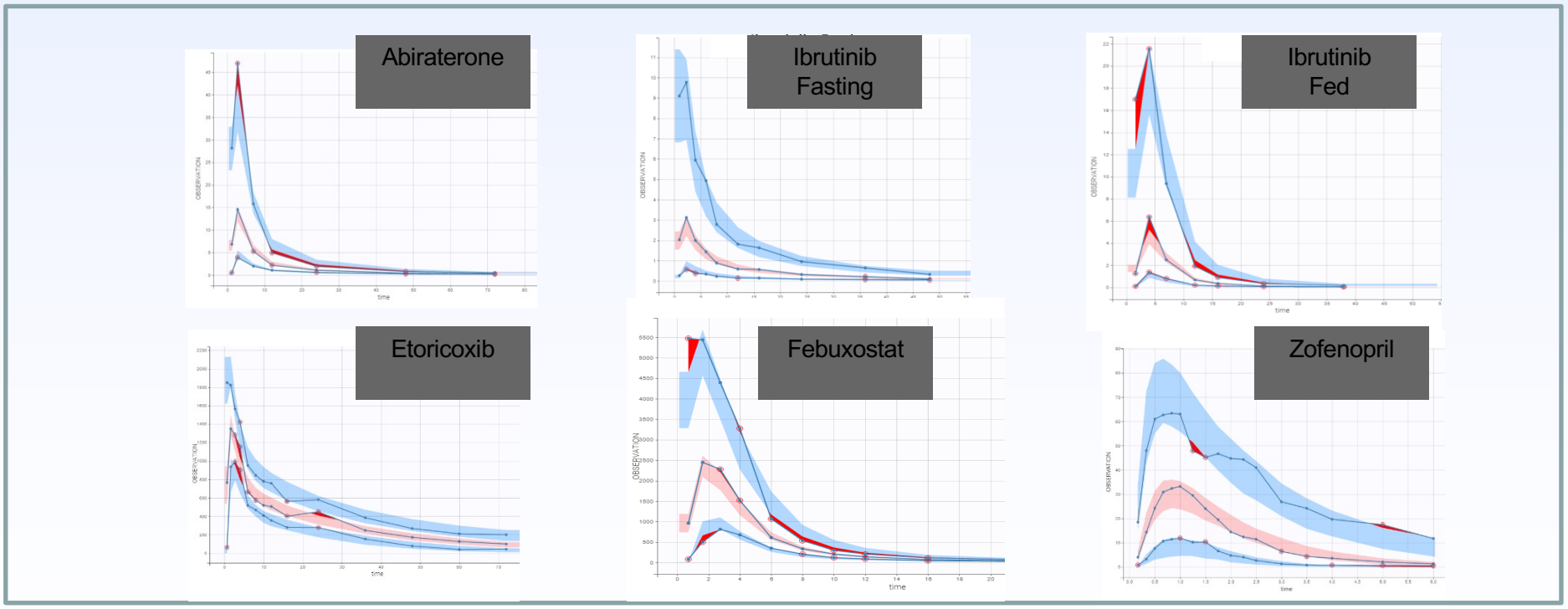






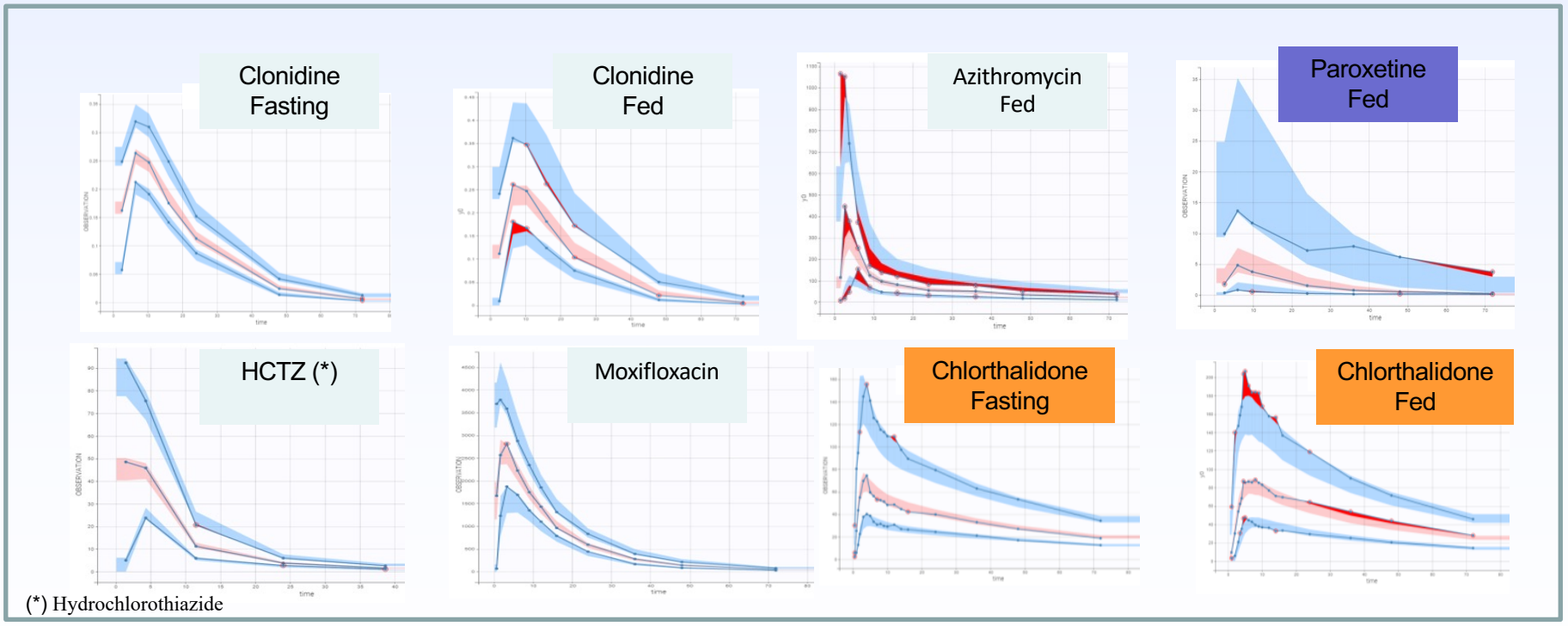
BDDCS	Class I	Class II	Class III	Class IV

Model Evaluation: Visual Predictive Check (VPC)



BDDCS	Class I	Class II	Class III	Class IV

Model Evaluation: Visual Predictive Check (VPC)



(*) Hydrochlorothiazide

BDDCS	Class I	Class II	Class III	Class IV

Fixed Effects

BDDCS	DRUG	T_{lag} (h)	k_a (h^{-1}) / Tk_0 (h) [a]	Cl/F (L/h)	Cl_D/F (L/h)	V_1/F (L)	V_2/F (L)
I	Alprazolam	0.225	3.24	4.55	9.08	63.9	16.8
	Amlodipine [b]	0.207	4.01 [a]	30.6	58.8	1120	446
	Fluoxetine Fasting [b]	0.702	2.62 [a]	26.2	13.5	1250	452
	Fluoxetine Fed [b]	1.150	3.46 [a]	29.6	0.48[*]	1310	0.008[*]
	Paroxetine Fed [b]	0.616	3.13 [a]	161	NA	2650	NA
	Sertraline [b]	0.875	2.97 [a]	157	NA	*4810*	NA
	Sunitinib [b]	0.619	5.20 [a]	32.5	NA	1380	NA
	Tofacitinib Fasting	0.225	4.03	34.2	27.1	67	31.9
	Tofacitinib Fed	0.232	1.01	11.8	24.8	*102*	*6710*
II	Abiraterone	0.526	1.77 [a]	1780	1060	*10000*	*18100*
	Etoricoxib	0.306	0.75 [a]	4.35	13.4	62.5	68.2
	Febuxostat	0.316	1.34 [a]	9.97	1.81	26.1	14.9
	Ibrutinib Fasting	0.320	1.00 [a]	4070	5570	*27300*	*44500*
	Ibrutinib Fed	0.473	3.95 [a]	3690	435	*13400*	*7040*
	Zofenopril	0.100	1.04	346	NA	264.42	NA
III	Azithromycin Fed [b]	0.861	2.54 [a]	102	175	*1080*	*2680*
	Clonidine Fasting	0.270	0.30	15.5	NA	251	NA
	Clonidine Fed	0.845	0.25	15.9	NA	246	NA
	HCTZ	0.436	0.79	24.8	13.4	96.4	121
	Moxifloxacin	0.225	2.16	8.64	1.12	116	24.8
IV	Chlorthalidone Fasting [b]	0.431	1.88 [a]	8.07	39.7	371	179
	Chlorthalidone Fed [b]	0.705	3.11 [a]	6.5	4.73	344	159

All parameters (θ)
RSE < 50 %
[*]Except

RATIFIES ROBUSTNESS MODELS

[a] Parameter corresponding to the duration of the absorption process (Tk_0)

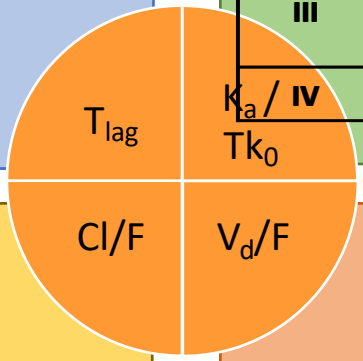
[b] P-Glycoprotein

Results

- No patterns observed by BDDCS class
- Within physiological range of gastric emptying
- Fed > Fasting
  - Fasting: 0.10 to 0.87 h
  - Fed: 0.23 to 1.15 h

BDDCS	Zero order absorption Tk0 (h)	First order absorption k_a (h^{-1})	Time for complete absorption in first order kinetics (h)
I	2.62 - 5.20	3.24 - 4.03 (1.01*)	2.14 - 1.72 (6.86*)
II	0.75 - 1.77 (3.95*)	1.04	6.66
III	2.54	0.30 –2.16 (0.25*)	23.10- 3.21 (27.72*)
IV	1.88 (3.11*)	NA	NA

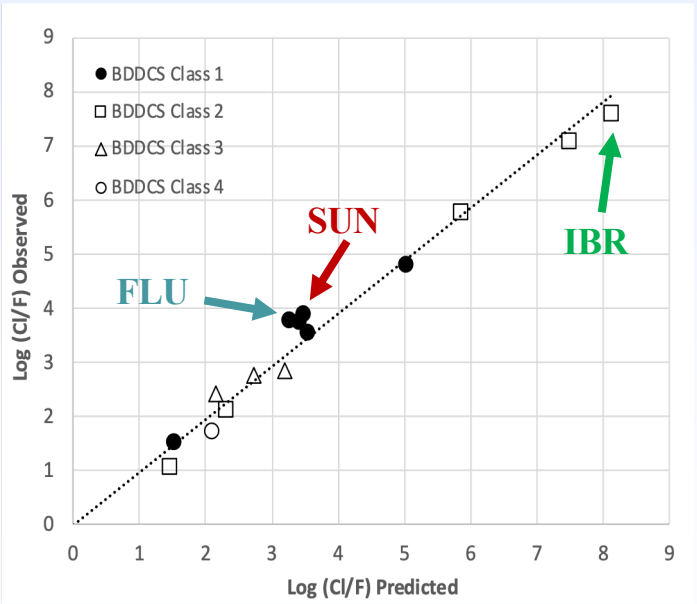
(*) Fed

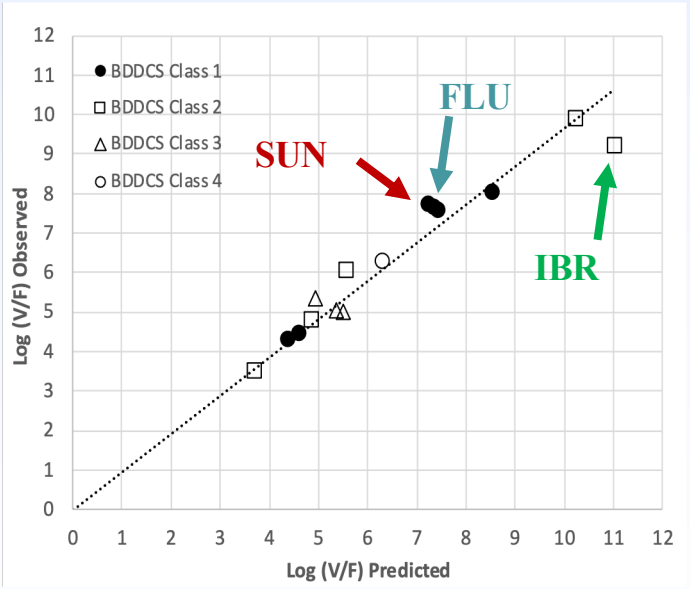


- **Cl/F:** 1.12 - 161 L/h
  - except ABI, IBR, ZOF
- Typical parameter estimates in accordance with literature

- **$V_d > V_{physiologic}$**
  - mainly SER, TOF Fed, ABI, IBR, AZT Fed
  - V_d higher in Class I and II (high perm.)
- Typical parameter estimates in accordance with literature

Results – literature comparison





Drug	F (%)	t½ (h)
IBRUTINIB	2.9	4-6
FLUOXETINE	< 90	24-72
SUNITINIB	High	40-60

→ Very low Bioavailability

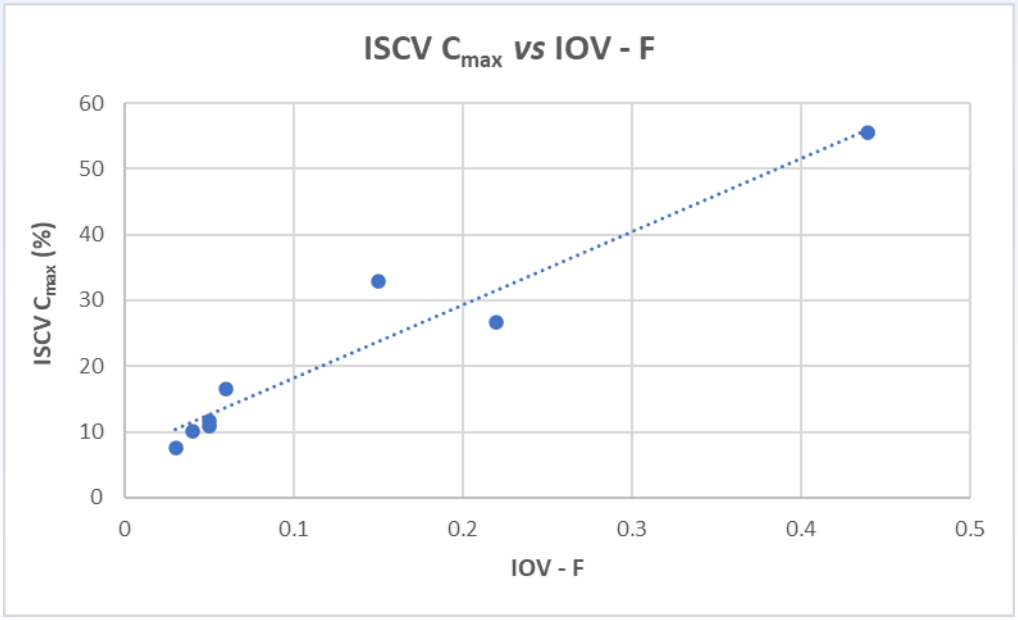
Sampling collection until 72h. Expanding sampling periods could hamper proper characterization of terminal disposition phase

Random Effects

	IIV (η)	IOV (k)
Correlation with **BDDCS**	Not found	
PK parameters that **most often** show variability	$F > k_a/Tk_0 > T_{lag}$	$T_{lag} \sim k_a/Tk_0 > F$
Magnitude of PK parameters IIV *vs* IOV	• **Tlag** and **k_a/Tk_0**: IIV < IOV • **F**: IIV > IOV	

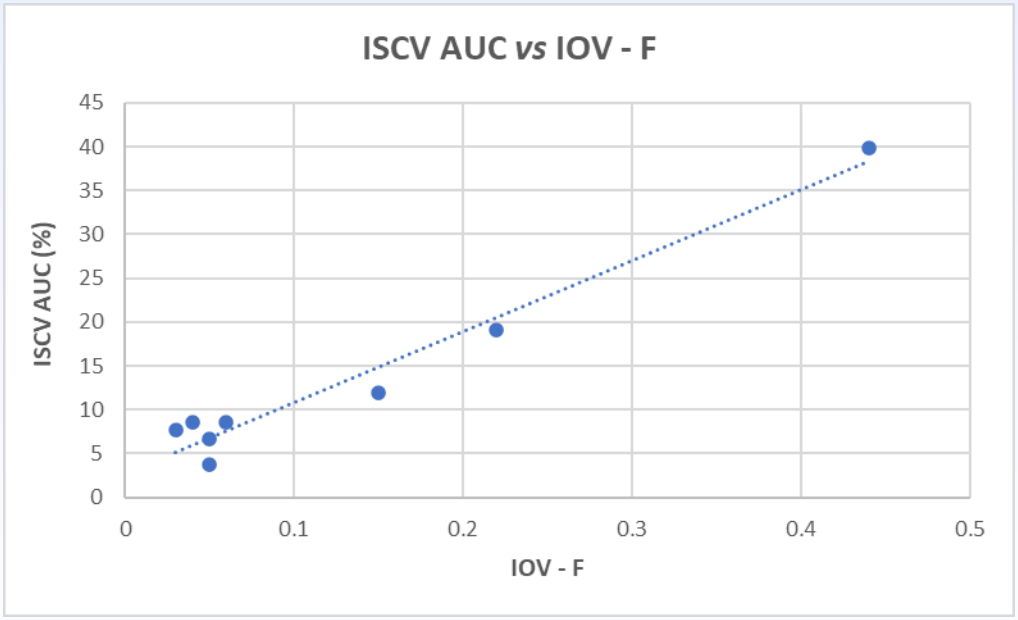
RUV (ε)
Class 1 / 3 < Class 2
RUV Fasting < RUV Fed (+2x)

ISCV (ANOVA) *vs* IOV (PopPK modelling)



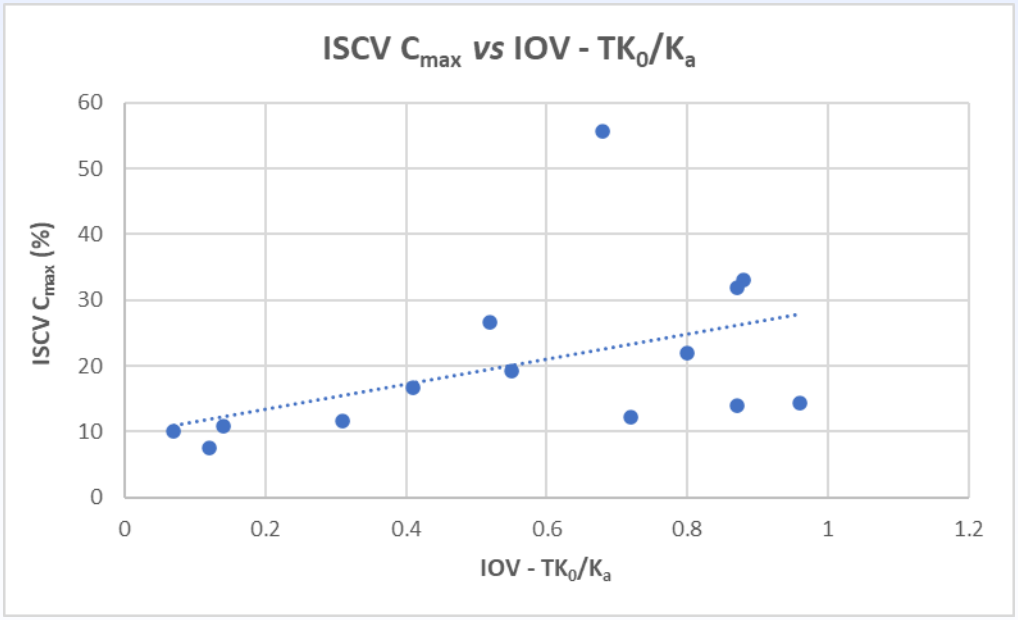
Correlation between ISCV (%) derived for C_{max} and IOV for Bioavailability (F)

ISCV (ANOVA) *vs* IOV (PopPK modelling)



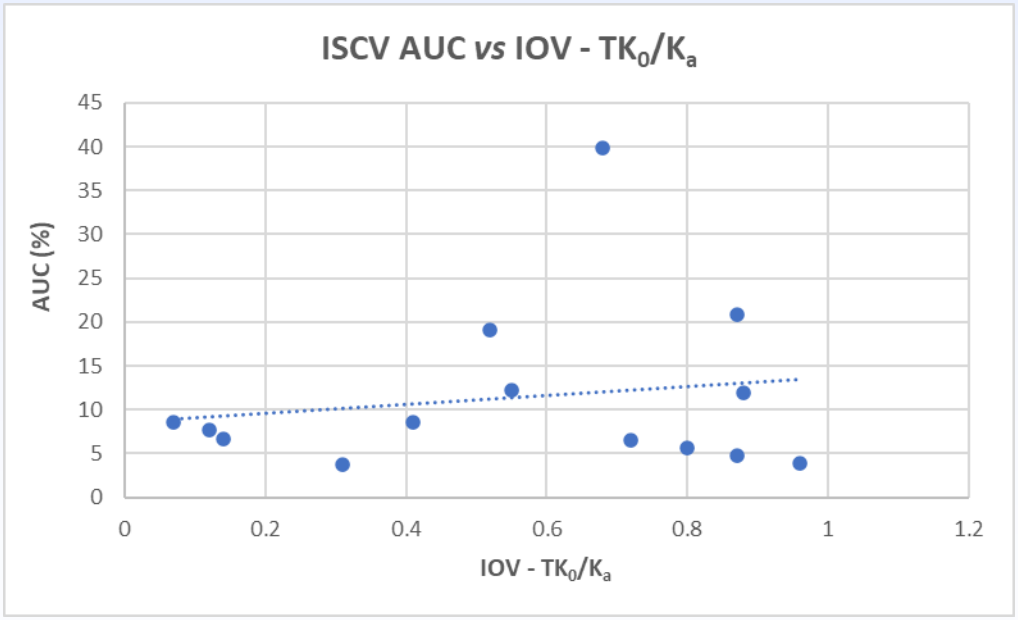
Correlation between ISCV (%) derived for AUC and IOV for Bioavailability (F)

ISCV (ANOVA) *vs* IOV (PopPK modelling)



Very slight correlation between ISCV (%) derived for C_{max} and IOV for TK_0/K_a

ISCV (ANOVA) *vs* IOV (PopPK modelling)



No correlation between ISCV (%) derived for AUC and IOV for TK_0/K_a

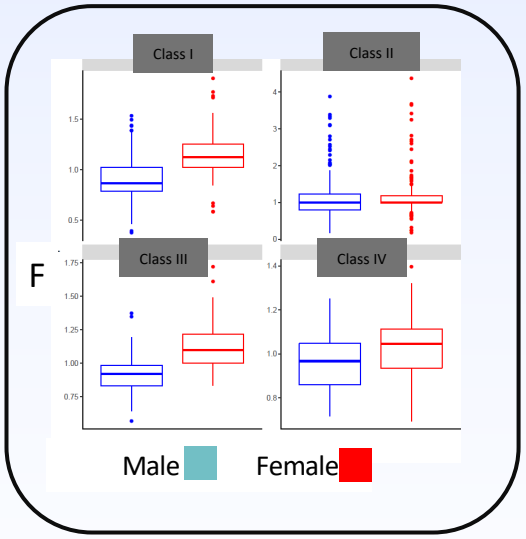
Non-Compartmental Analysis

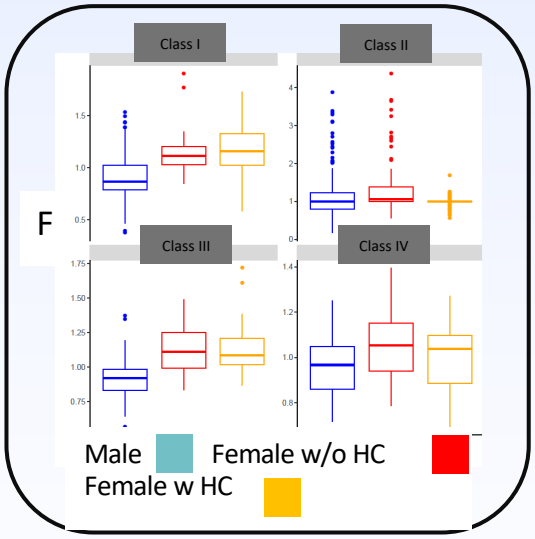
Impact of BDDCS class and demographics on PK parameters

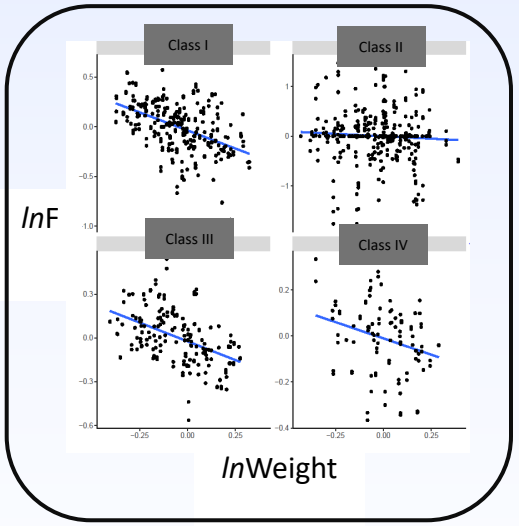
BDDCS	C_{max}		AUC		V/F		Cl/F	
	Sex	**HC**	**Sex**	**HC**	**Sex**	**HC**	**Sex**	**HC**
I	Male < Female		Male < Female (Except ALP, PAR)		Male > Female (Except PAR)		Male > Female (Except ALP, PAR)	
II	**No Diff**		**No Diff**		**No Diff**		**No Diff**	
III	Male < Female	**No Diff**	Male < Female		Male > Female		Male > Female	
IV	Male < Female		**No Diff**		Male > Female	**No Diff**	**No Diff**	

HC Hormonal Contraceptive

Impact of demographics on Bioavailability (F) Parameter







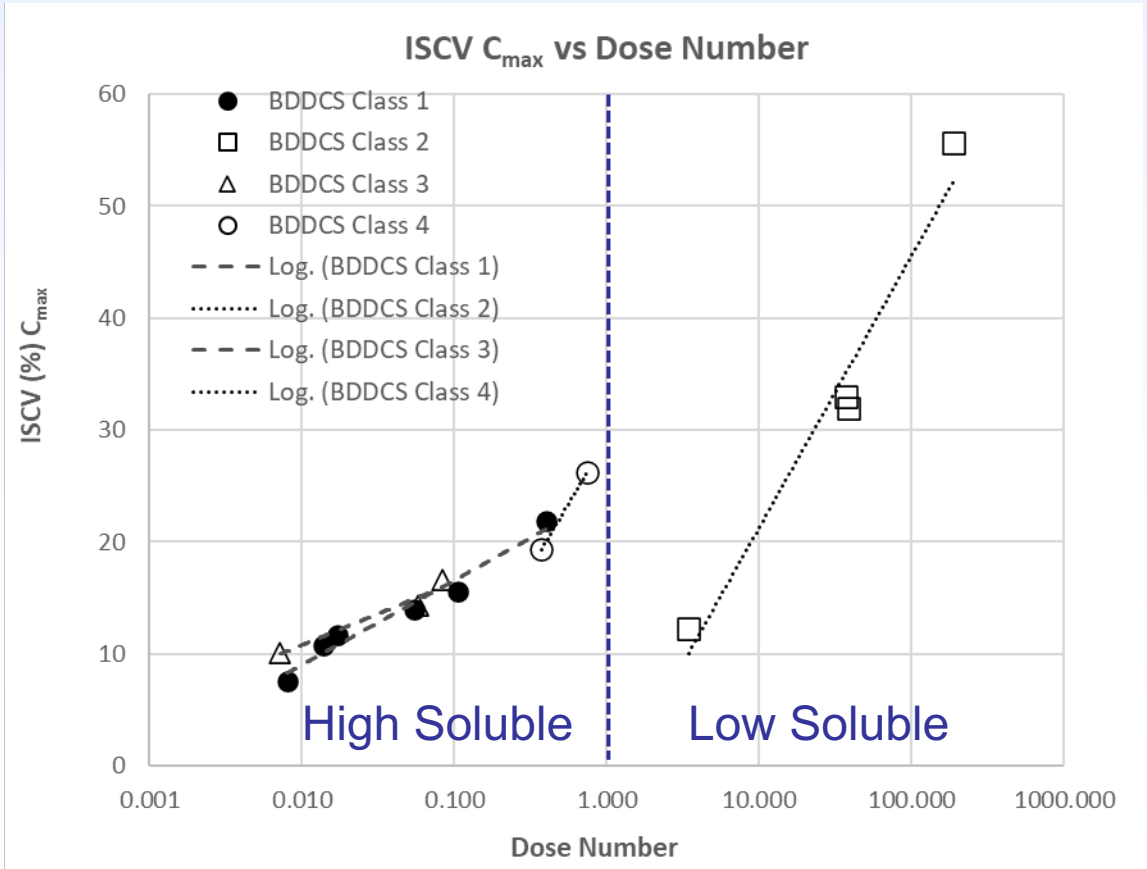

```
lm(formula = log(F) ~ SEX + CONTRACEPTIVE + lnWeight70, data = PKParam_Class1)

Residuals:
     Min       1Q   Median       3Q      Max
-0.78843 -0.11415  0.00825  0.11016  0.54534

Coefficients: (1 not defined because of singularities)
              Estimate Std. Error t value Pr(>|t|)
(Intercept)    -0.09780    0.01681  -5.816 1.42e-08 ***
SEXF            0.16927    0.03510   4.823 2.16e-06 ***
CONTRACEPTIVEN -0.02905    0.03366  -0.863    0.389
CONTRACEPTIVEY       NA         NA      NA       NA
lnWeight70     -0.41450    0.09513  -4.357 1.76e-05 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.2115 on 330 degrees of freedom
Multiple R-squared:  0.2794,    Adjusted R-squared:  0.2728
F-statistic: 42.64 on 3 and 330 DF,  p-value: < 2.2e-16
```

F
Class 1

```
lm(formula = log(F) ~ SEX + CONTRACEPTIVE + lnWeight70, data = PKParam_Class3)

Residuals:
     Min       1Q   Median       3Q      Max
-0.48419 -0.10745 -0.00563  0.08915  0.45435

Coefficients: (1 not defined because of singularities)
              Estimate Std. Error t value Pr(>|t|)
(Intercept)    -0.08002    0.01591  -5.030 1.12e-06 ***
SEXF            0.14344    0.03403   4.215 3.84e-05 ***
CONTRACEPTIVEN  0.01089    0.03108   0.350   0.7265
CONTRACEPTIVEY       NA         NA      NA       NA
lnWeight70     -0.21127    0.08961  -2.358   0.0194 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.1484 on 192 degrees of freedom
Multiple R-squared:  0.3249,    Adjusted R-squared:  0.3144
F-statistic:  30.8 on 3 and 192 DF,  p-value: 2.654e-16
```

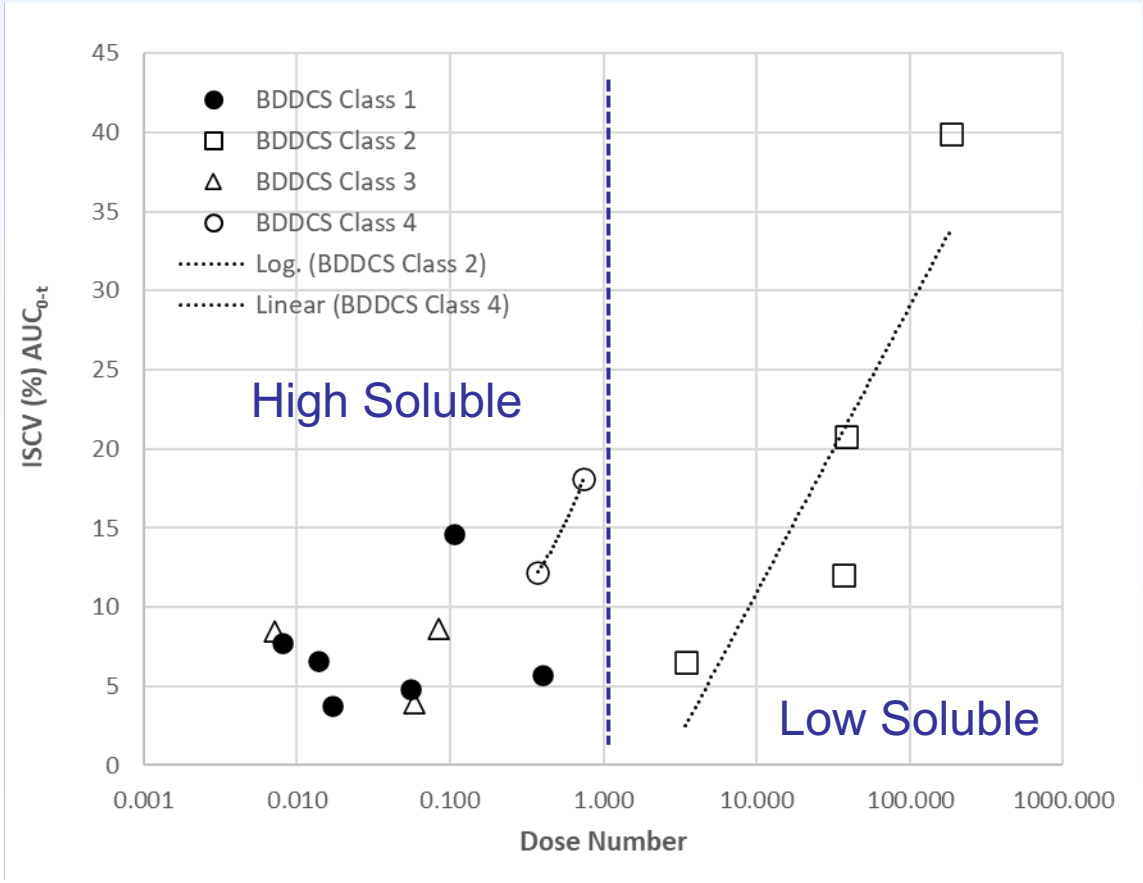
F
Class 3

Correlation analysis between ISCV and Dose Number by BDDCS class

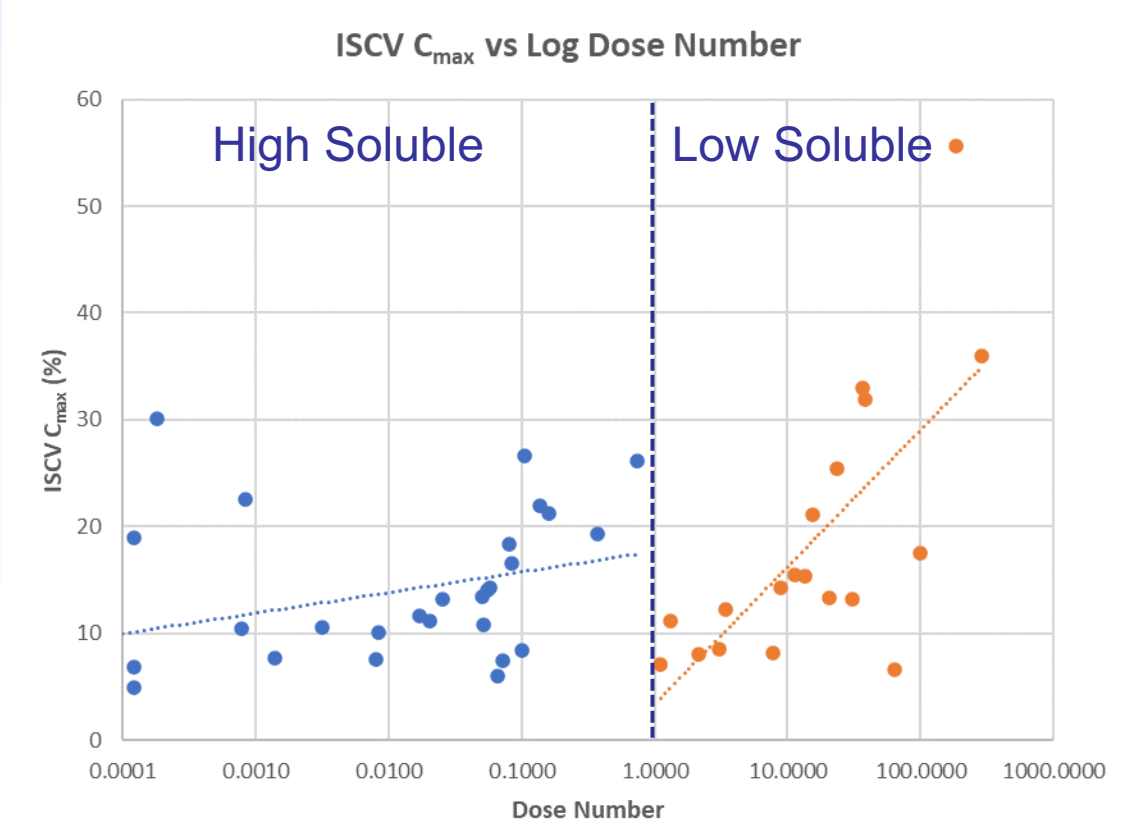


$$D_0 = \frac{\frac{Dose\ (mg)}{250\ mL}}{Solubility\ (m\,g/L)}$$

Correlation analysis between ISCV and Dose Number by BDDCS class



Correlation analysis between ISCV and Dose Number complemented with literature data



Literature data included from Mol Pharm. 2009 Jan-Feb;6(1):48-59. doi: 10.1021/mp800140m

Conclusions

- The PopPK models successfully described the PK profiles for all the drugs explored in this work, providing meaningful and precise pharmacokinetic parameters estimates

- The majority of BDDCS class 1 and 2 drugs followed a zero order absorption kinetics. In class 1, this tendency is observed for drugs characterized to be P-gp substrates

- The majority of BDDCS class 3 drugs followed a first order absorption kinetics. The exception is azithromycin, the only drug in this class that is a P-gp substrate

- The parameters that showed the most variability were those related to the absorption process
  - For IIV, the parameters that most showed variability were $F_{relative}$ and k_a/Tk_0
  - For IOV, the parameters that most showed variability were relative T_{lag} and k_a/Tk_0
  - No pattern was found between BDDCS class and IOV
  - A correlation was found between ISCV derived from ANOVA for C_{max} / AUC and IOV derived for $F_{relative}$

Conclusions

- RUV estimates was found to be higher for BDDCS class 2 and more than double in fed studies compared to fasting
- T_{lag} was within the physiological range of gastric emptying and no pattern was found related to BDDCS class. Variability in IIV lower than in IOV
- Gender seems to have an influence on the $F_{relative}$ for class 1 and 3 drugs, with higher estimates for women in comparison to men
- ISCV for C_{max} seems to be correlated with the Dose Number for Low Soluble Drugs
  - Is Ad Libitum water after 1 hour a source of inter and intra-subject variability for low soluble drugs?
  - Should all subjects be administered with same water volumes in the morning, after product administration?

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RESEARCH PAPER

Untangling Absorption Mechanisms and Variability in Bioequivalence Studies Using Population Analysis

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Questions?