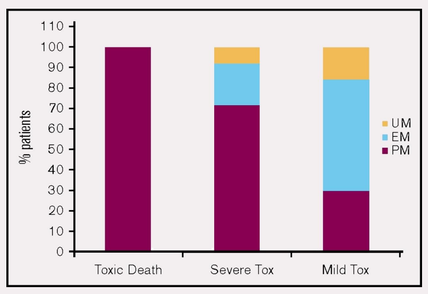
Cytidine deaminase deficiency results in higher exposure to cytarabine in patients with acute myeloid leukemia, which put poor metabolizers at risk of experiencing severe toxicities

ABSTRACT

BACKGROUND

Why did we conduct this study?

- Cytarabine (Ara-C) remains the backbone therapy of acute myeloid leukemia (AML).
- Severe non-hematological toxicities are regularly reported (i.e., 23% to 61%) with Ara-C, and leads to lethal toxicities in up to 16% of patients.
- Patients with Cytidine deaminase (CDA) deficiency, the enzyme responsible for the conversion of Ara-C to inactive uracil arabinoside (Ara-U), are more likely to experience severe toxicities



(Fanciullino et al., Blood Adv. 2018)

What was our objective?

We aimed to establish a link between CDA activity and exposure to Ara-C, by developing a parent-metabolite joint population pharmacokinetic (PK) model.

METHODS

Design: Prospective Population PK study (EUDRACT 2017-A0007053).

Participants: Adults (≥18 years) with AML.

Treatment: 7-day continuous infusion of Ara-C at 200 mg/m² per day on days 1 to 7 and daunorubicin/idarubicin on days 1 to 3 (induction cycle).

Collected data: semi-dense PK sampling (6 samples per patient) on Day 7 of the induction cycle for both Ara-C and Ara-U.

Model development : Candidate population PK models were fitted to the PK data using SAEM algorithm within the Monolix® software. The influence of factors, including CDA activity, on PK of Ara-C , was investigated using a stepwise multivariate procedure.

CONCLUSIONS

Key findings

CDA activity significantly impacts exposure to Ara-C

Patients with CDA deficiency may receive inadequate treatment doses, inducing over-exposure to Ara-C.

Population pharmacokinetics of cytarabine and its metabolite in patients with acute myeloid leukemia: effect of cytidine deaminase activity.

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MODEL DEVELOPMENT

Study population

37 patients
Median age, 62 years (22, 78)

30% women

Median **CDA** at baseline
2.1 UA/mg (0.4, 17.4)

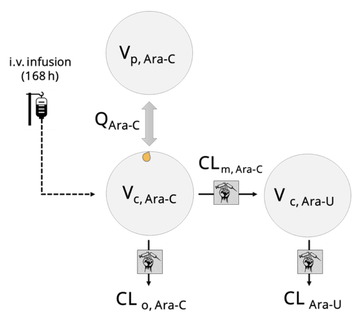
Renal clearance at baseline (No.)
12 eGFR 60–89 mL/min /1.73m²
04 eGFR 45–59 mL/min /1.73m²
01 eGFR <45 mL/min /1.73m²

Flowchart of key steps in the model development process

Ara-C base model

- Two-compartment structure
- Residual error : Log-additive
- Handling of BLQ data (14.5%): M4 method from Stuart L. Beal., 2001

(see ESM, online version)



Parent-metabolite PK Model

- To solve the structural identifiability issue:

Scenario N°	Assumption on (Reference)
1	Ara-C non-metabolic clearance : $CL_{o, Ara-C}$ = 6.5 L/h (DeAngelis et al., 1991)
2	Ara-U volume of distribution: $V_{c, Ara-U}$ = 88 L/m² (Schleyer et al., 1989) = 41 L (Kern et al., 1996) = 118 L (Radeski et al., 2011)
3	Ara-U clearance: CL_{Ara-U} = 4.02 L/h/m² (Schleyer et al., 1989) = 7.86 L (Kern et al., 1996)
4	Ara-C clearance: $CL_{o, Ara-C}$ = 0 L/h (fully biotransformed)
5	$V_{c, Ara-U}$ = 41 L and $CL_{o, Ara-C}$ = 0 L/h

Final PK model (Table 1)

- Covariate sub-models building and identification of major determinants of PK variability (see ESM, online version)
- Clinical relevance of significant covariates was tested by simulating Ara-C exposure metrics ($C_{avg,ss}$ and AUC_{0-inf}), at many covariate values (Figure 2)

MAIN FINDINGS

A 2-compartment model best described Ara-C data, whereas 1-compartment model best described Ara-U observations.

Table 1. Population PK parameter estimates of cytarabine and its metabolite.

PK parameter	Unit	Final model: Population estimate	Precision (RSE, %) Shrinkage [η-sh, %]	Nonparametric Bootstrap Median (5th and 95th Percentiles)
Structural model				
$V_{c, Ara-C}$	L	12.11	17.9	15.5 (7.55 – 30.0)
Q_{Ara-C}	L/h	3.43	26.9	4.24 (1.94 – 9.99)
$V_{p, Ara-C}$	L	9.48	25.4	12.2 (4.98 – 28.3)
$CL_{o, Ara-C}$	L/h	0.00	FIXED	NA
$CL_{m, Ara-C}$	L/h	130	13.2	147 (94 – 241)
β_{CDA}		0.36	18.5	0.38 (0.23 – 0.49)
$V_{c, Ara-U}$	L	41.0	FIXED	NA
CL_{Ara-U}	L/h	5.20	4.78	5.20 (4.78 – 5.58)
β_{eGFR}		0.84	20.0	0.84 (0.62 – 1.11)
Statistical model				
Inter-individual variability				
$\omega_{Vc, Ara-C}$	CV%	47.9	19.8 [48]	43.2 (24.0 – 89.4)
$\omega_{Vc, Ara-U}$	CV%	63.2	14.9 [28]	60.7 (42.8 – 81.1)
$\omega_{CLm, Ara-C}$	CV%	52.1	14.0 [23]	52.1 (35.0 – 71.1)
$\omega_{CL Ara-U}$	CV%	29.6	11.9 [1]	28.6 (21.2 – 36.1)
Residual unidentified variability				
$\sigma_{a, Ara-C}$	SD (µg/L)	0.65	6.39	0.64 (0.53 – 0.74)
$\sigma_{b, Ara-U}$	CV%	7.30	6.56	7.30 (6.00 – 8.00)

Abbreviations: $\beta_{covariate}$, effect estimate for the covariate of interest; **CDA**, Cytidine deaminase activity; **eGFR**, estimated glomerular filtration rate (calculated by CKD-EPI equation); **RSE:** relative standard error; **CV:** coefficient of variation, calculated as follows: CV% = 100%×$\sqrt{exp(\omega) - 1}$; **η-sh**, variance-based η-shrinkage; **NA,** not applicable.

$CL_{m, Ara-C}$ = 130 * (CDA/2.4)$^{0.36}$ * $e^{\eta CLm, Ara-C}$ (L/h)
CL_{Ara-U} = 5.2 * (eGFR/165)$^{0.84}$ * $e^{\eta CL Ara-U}$ (L/h)

Model diagnosis showed good performances

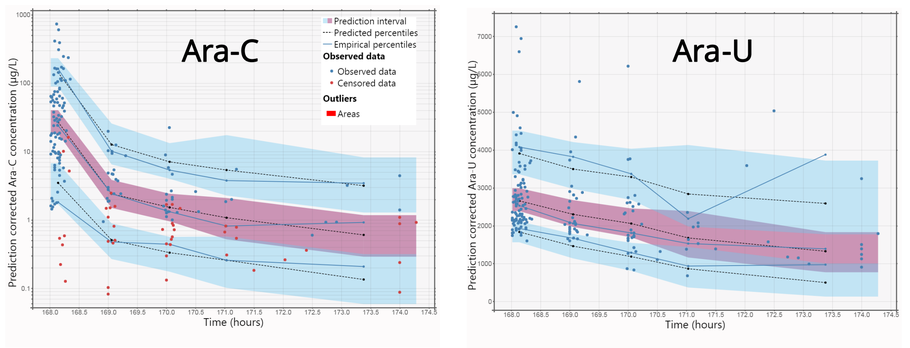


Figure 1 . prediction-corrected Visual predictive check

Low CDA activity was associated with higher AUC and increased incidence of severe toxicities

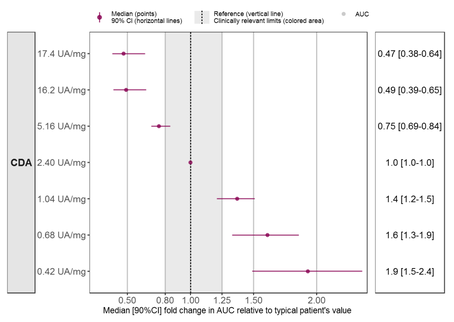


Fig 2. Forest plot of CDA effect on Ara-C PK

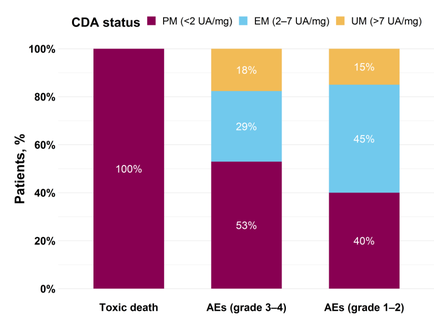


Fig 3. CDA phenotypes vs TRAEs

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Supplementary material to

Population pharmacokinetics of cytarabine and its metabolite in patients with acute myeloid leukemia: effect of cytidine deaminase activity.

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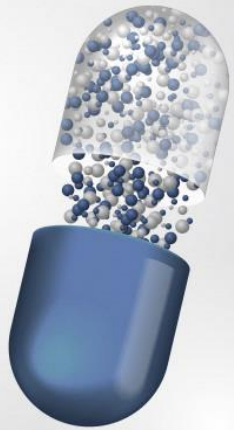


Patients' characteristics

Table 1. Characteristics of the included patients at the initiation of treatment.

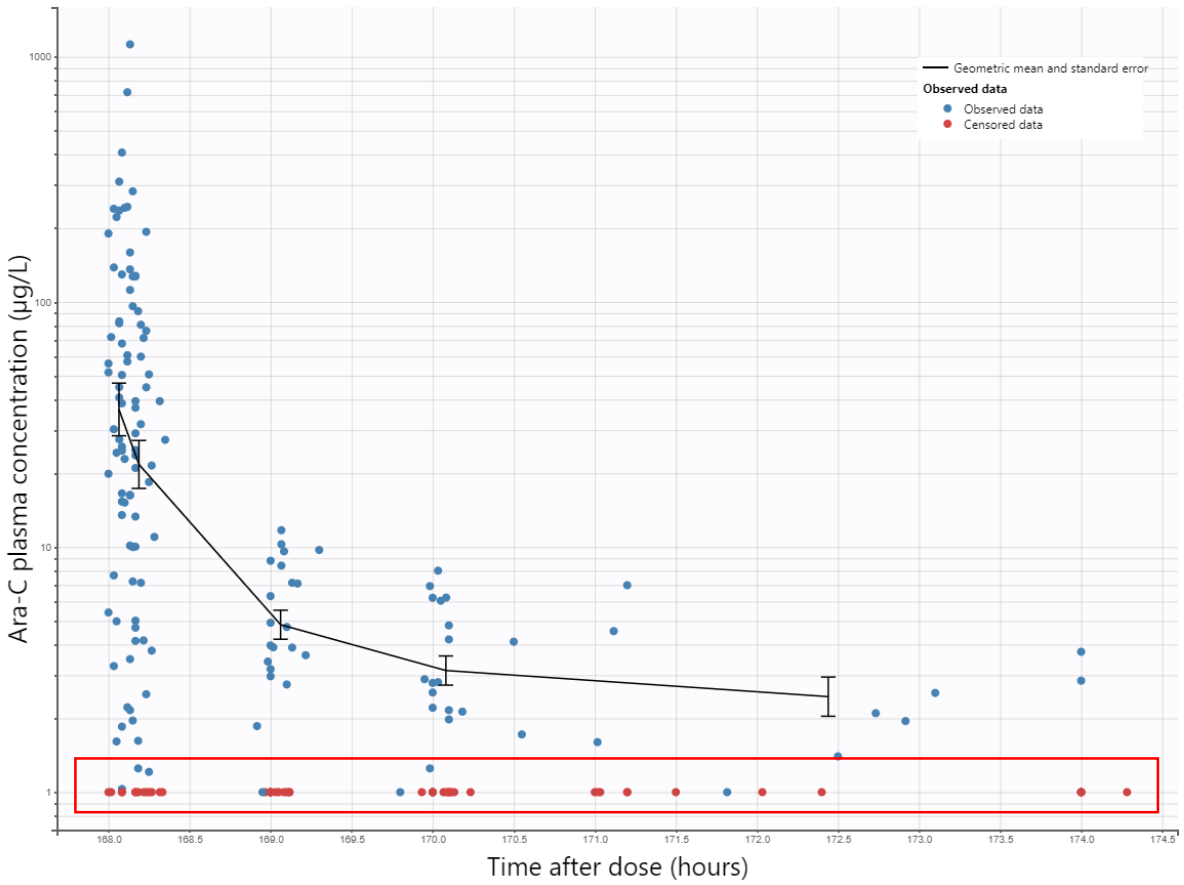
Characteristic	Overall, N = 37[1]	AML Type		p-value[2]
		Primary, N = 24[1]	Secondary, N = 13[1]	
Age (years)	62 (22, 78)	54 (22, 78)	65 (34, 70)	0.26
Sex				>0.99
M	26 (70%)	17 (71%)	9 (69%)	
F	11 (30%)	7 (29%)	4 (31%)	
Body surface area (m²)	1.86 (1.45, 2.29)	1.88 (1.52, 2.29)	1.86 (1.45, 2.09)	0.33
ELN				0.063
Favorable	12 (34%)	9 (39%)	3 (25%)	
Intermediate	12 (34%)	10 (43%)	2 (17%)	
Adverse	11 (31%)	4 (17%)	7 (58%)	
Cytidine deaminase activity (UA/mg)	2.1 (0.6, 17.4)	2.0 (0.6, 8.3)	2.4 (0.9, 17.4)	0.24
CDA status				0.24
PM	17 (46%)	12 (50%)	5 (38%)	
EM	14 (38%)	10 (42%)	4 (31%)	
UM	6 (16%)	2 (8.3%)	4 (31%)	
Lactate dehydrogenase (IU/L)	391 (68, 3,561)	391 (68, 1,596)	391 (107, 3,561)	0.60
C-Reactive Protein (mg/L)	42 (0, 320)	43 (0, 320)	18 (2, 130)	0.39
White blood cells (Giga/L)	7 (1, 138)	9 (1, 89)	3 (1, 138)	0.26
Absolute neutrophil count (Giga/L)	1 (0, 38)	1 (0, 17)	1 (0, 38)	0.86
Peripheral blood blasts	26 (0, 97)	30 (0, 97)	14 (0, 68)	0.13
Bone marrow blasts	66 (1, 100)	73 (1, 96)	36 (16, 100)	0.072
Serum creatinine (µmol/L)	79 (14, 144)	81 (44, 128)	67 (14, 144)	0.40
Creatinine Clearance (mL/min)	104 (44, 342)	112 (44, 240)	80 (52, 342)	0.44
Albumin (g/L)	36 (23, 49)	36 (23, 49)	35 (24, 46)	>0.9
Total bilirubin (µmol/L)	7.0 (2.0, 183.0)	6.3 (3.0, 22.0)	7.0 (2.0, 183.0)	0.95
Aspartate amino transferase (IU/L)	21 (9, 208)	19 (9, 208)	22 (10, 77)	0.41
Alanine amino transferase (IU/L)	22 (6, 291)	20 (9, 291)	24 (6, 228)	0.79

[1] Statistics presented: Median (Range) or Frequency (%)

[2] Wilcoxon rank sum test; Fisher's exact test; Wilcoxon rank sum exact test

Drug exposure

- Ara-C levels ranged between (1 and ~1000 µg/L)
- High variability on the distribution phase.
- Below LLoQ samples : 66/456 =14.5% ➔ should be handled



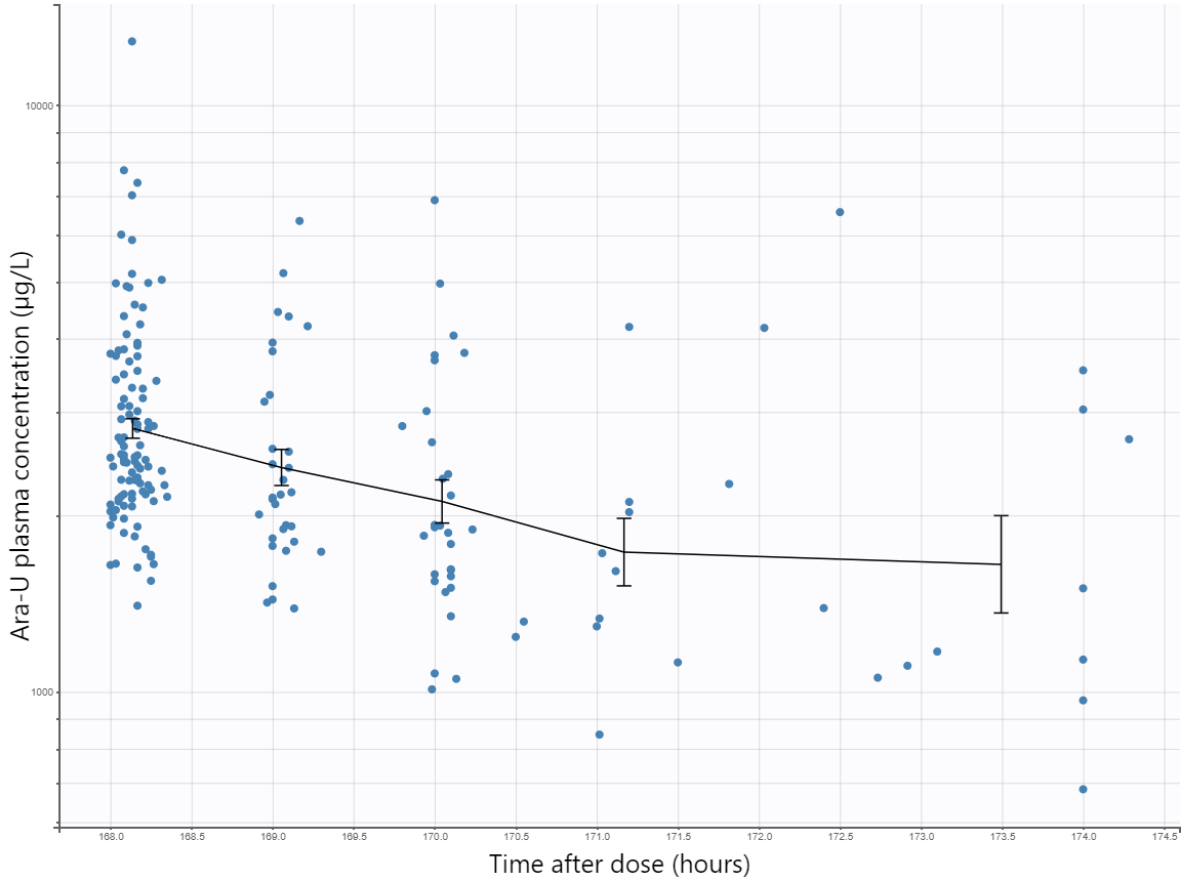


Figure 1. plasma concentration-time profiles of Ara-C and Ara-U

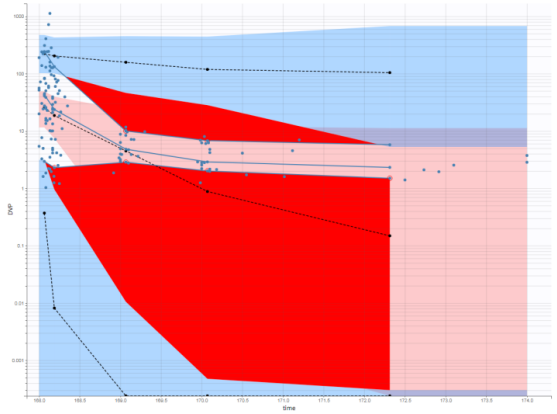
Ara-C Model Structure

… deleting LLoQ data

1-CMPT

Bayesian Information Criteria (BIC)

1345

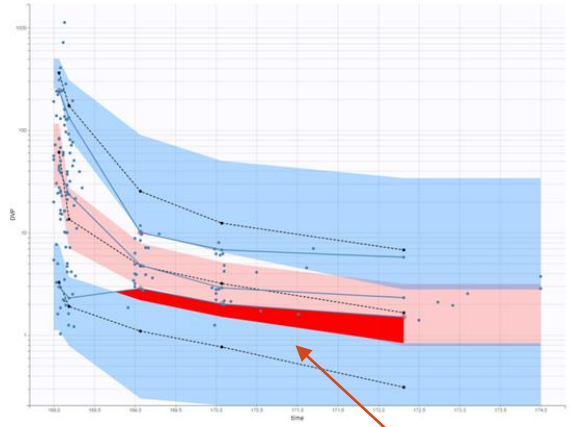


$\Delta_{BIC} = 131$

2-CMPT

Bayesian Information Criteria (BIC)

1214

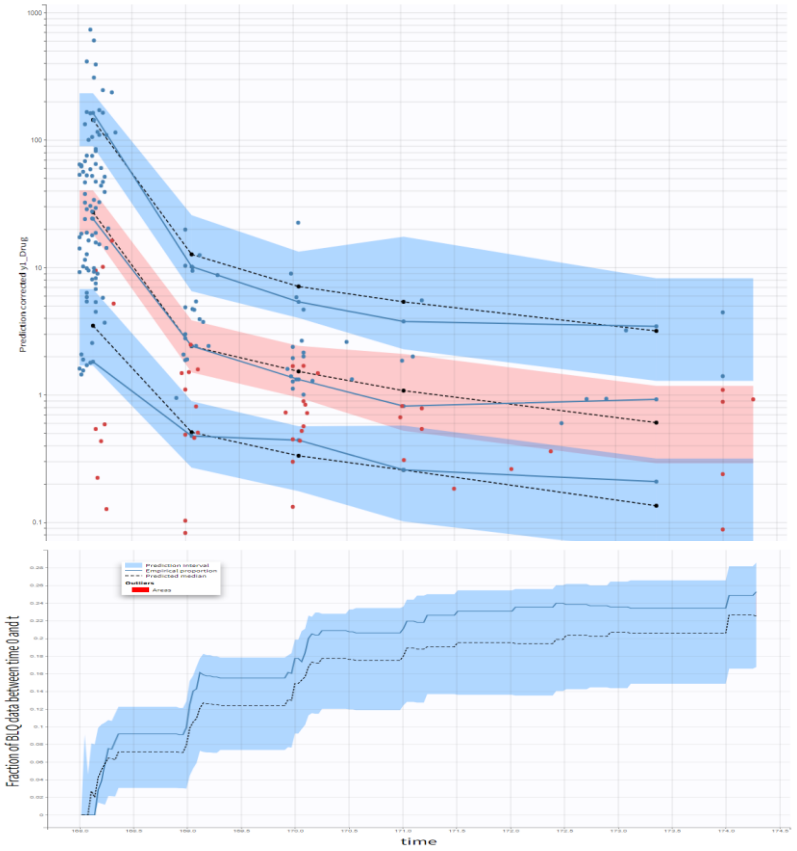


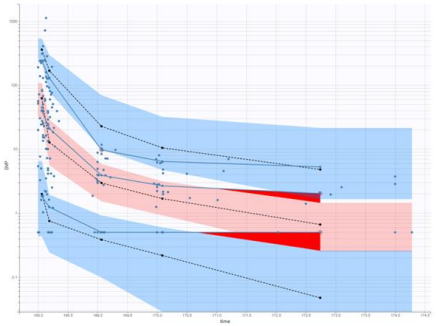
LLoQ data effect

Handling LLoQ data

... methods from Stuart L. Beal., 2001

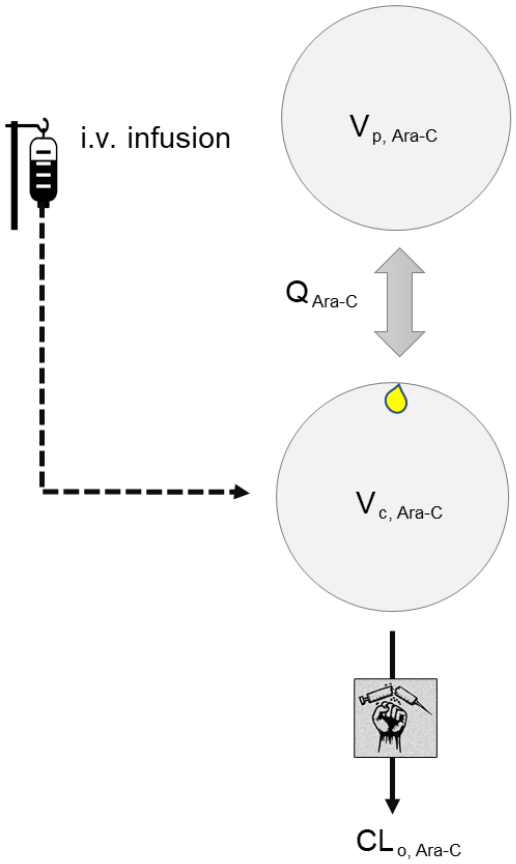
		BIC	
		Prop.	Expo.
M1	Discard	1214	1191
M3	[-∞, LLoQ]	1286	NA
M4	[0, LLoQ]	1295	1284
M5	LLoQ/2	1302	1297
M6	M5 & M1	1265	1262

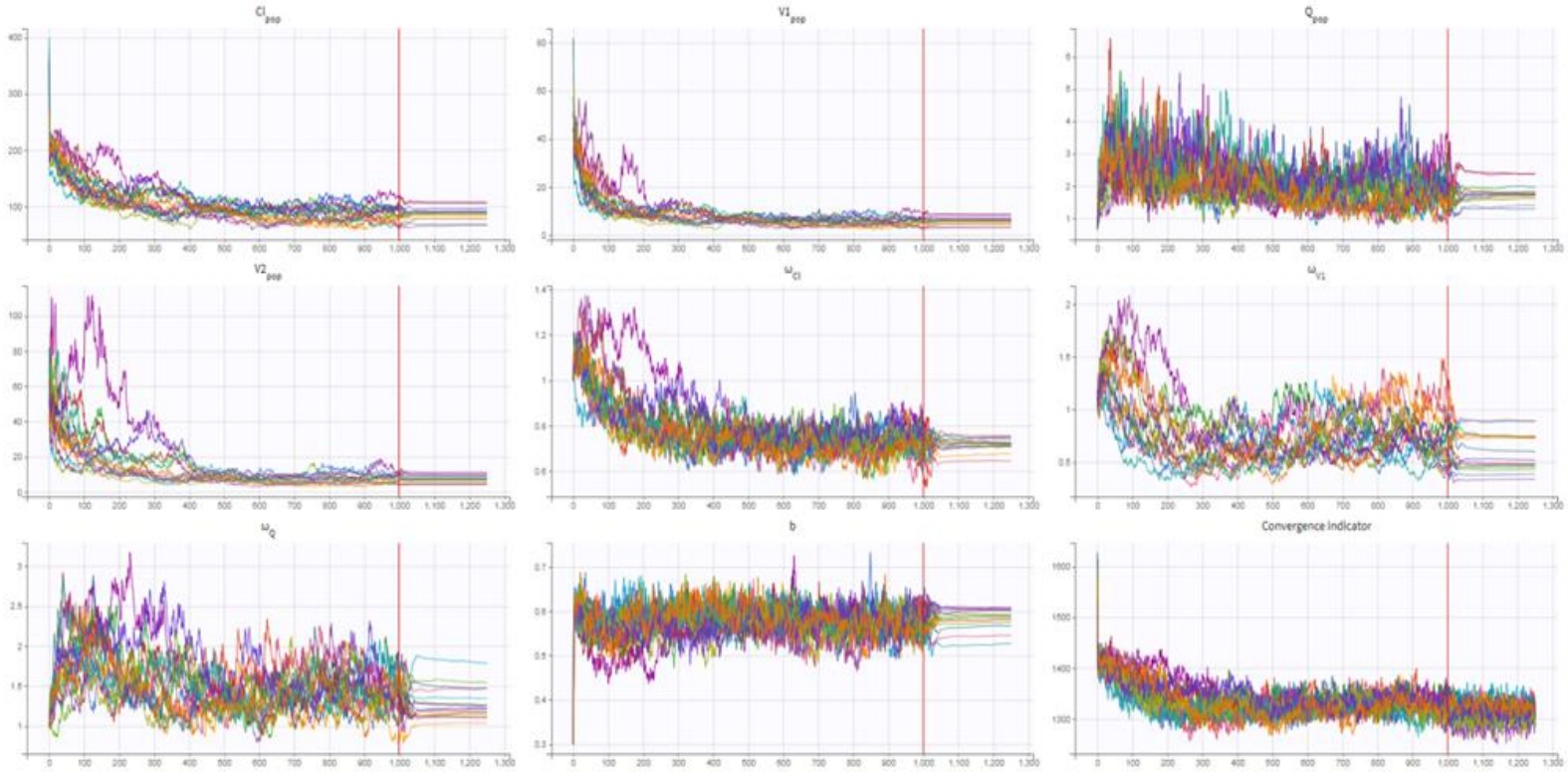




Ara-C Model

… convergence assessment





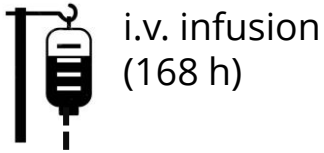
Joint Pharmacokinetic Model

	Assumption on	References	BICc
Scenario 1.	Ara-C non-metabolic clearance: $CL_{o,\ Ara\text{-}C}$	(6.5 L/h; DeAngelis et al 1991)	4130
Scenario 2.	Ara-U volume of distribution : $V_{c,\ Ara\text{-}U}$	(88 L/m² ; Schleyer et al., 1989)	4175
		(41 L; Kern et al., 1996)	4130
		(118 L; Radeski et al., 2011)*	4161
Scenario 3.	Ara-U clearance: $CL_{Ara\text{-}U}$	(4.02 L/h/m² ; Schleyer et al., 1989)	4150
		(7.86 L; Kern et al., 1996)	4158
Scenario 4.	Full biotransformation: Ara-C clearance = 100% metabolic		4129
Scenario 5.	Ara-U volume of distribution : $V_{c,\ Ara\text{-}U}$ = 41 L (Kern et al., 1996) Full biotransformation: $CL_{o,\ Ara\text{-}C}$ = 0 L/h		4124

Fixed Effects	
CLp1_pop	0.0068
V1_pop	15.7
Q_pop	4.60
V2_pop	13.3
V3_pop	41.0
CLp2_pop	162
CLm_pop	5.0
Random Effects	
omega_V1	0.66
omega_V3	0.71
omega_CLp2	0.63
omega_CLm	0.41
Error Model Parameters	
a1_Drug	0.81
b2_Metabolite	0.11

Ara-c & Ara-U PopPK

The base model



i.v. infusion (168 h)

$V_{p,\ Ara\text{-}C} = 12.2\ (L)$

$Q_{Ara\text{-}C} = 4.13\ (L/h)$

$V_{c,\ Ara\text{-}C} = 15.1 + \eta_{Vc,\ Ara\text{-}U}\ (L)$

BSV = 7.08

$\eta_{\text{-}SHR} = 58\%$

$CL_{m,\ Ara\text{-}C} = 147.5 * e^{\eta_{CLm,\ Ara\text{-}C}}\ (L/h)$

BSV = 0.62

$\eta_{\text{-}SHR} = 14\%$

$V_{c,\ Ara\text{-}U} = 41 * e^{\eta_{Vc,\ Ara\text{-}U}}\ (L)$ †

BSV = 0.58

$\eta_{\text{-}SHR} = 29\%$

$CL_{Ara\text{-}U} = 5.16 * e^{\eta_{CL,\ Ara\text{-}U}}$

BSV = 0.37

$\eta_{\text{-}SHR} = 0\%$

$CL_{o,\ Ara\text{-}C} = 0\ (L/h)$ †

† Fixed parameter

BSV models (SD)

Base model diagnosis

… parameters were estimated with good precision

	VALUE	LINEARIZATION S.E.	LINEARIZATION R.S.E.(%)
Fixed Effects			
CLp1_pop	0		
V1_pop	15.1	2.83	18.7
Q_pop	4.13	1.14	27.6
V2_pop	12.2	3.25	26.6
V3_pop	41		
CLp2_pop	147.5	20.51	13.9
CLm_pop	5.16	0.32	6.17
Standard Deviation of the Random Effects			
omega_V1	7.08	1.32	18.6
omega_V3	0.58	0.086	14.9
omega_CLp2	0.62	0.076	12.3
omega_CLm	0.37	0.044	11.8
Error Model Parameters			
a1_Drug	0.65	0.042	6.40
b2_Metabolite	0.073	0.0048	6.56

1 → Parameters were estimated with **good precision**

3
- Condition number = 15 (Eigen values: min=0.2; max= 3.08)
- Correlation matrix: N (| r | > 0.70) = 0

→ Model is **not overparametrized**

2 4 error models were tested (additive, proportional, combined and exponential model) ➔ the **additive model on log-scale** was retained with an SD = 0.65 µg/L

Base model diagnosis

… the selected model **fits the data reasonably well**

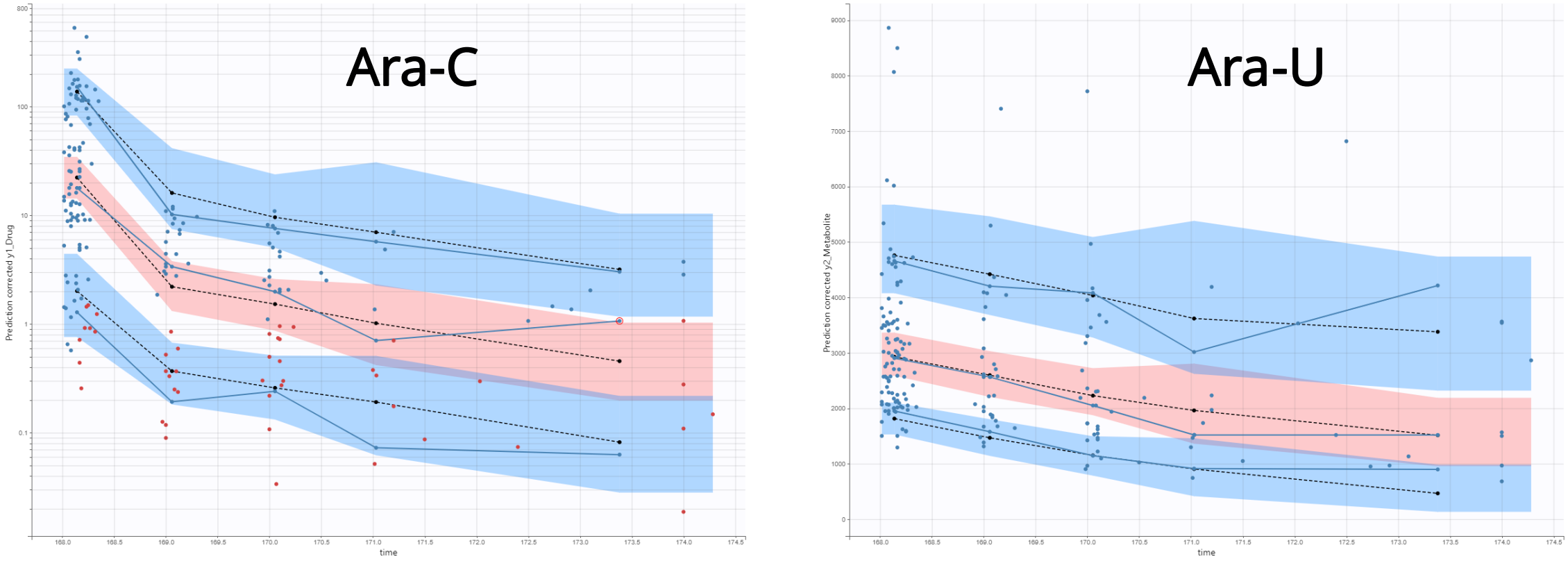


Figure. prediction-corrected Visual predictive check

Base model diagnosis

… the selected model **fits the data reasonably well**

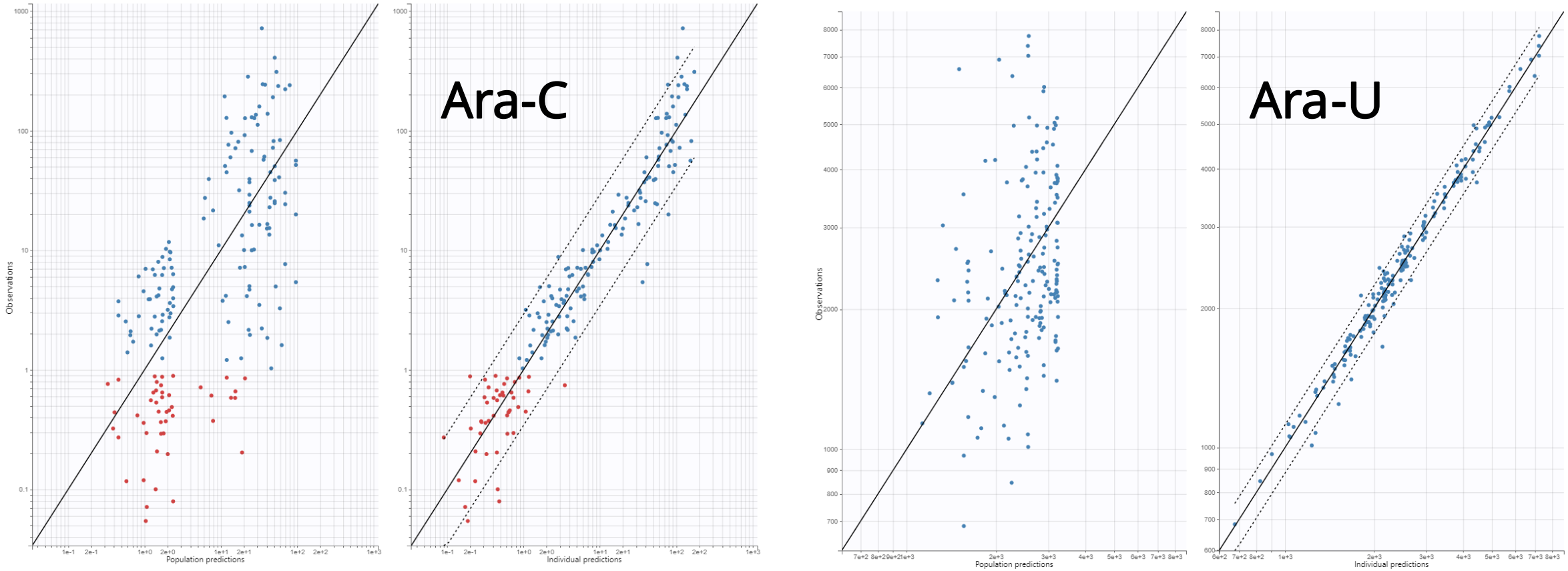


Figure. Predictions vs Observations plots

Covariate sub-models building: analysis plan

1 Selecting "candidate covariates"

❑ Classical tests

- ✓ **Pearson's** correlation coefficient
- ✓ Spearman's rank correlation coefficient
- ✓ Kendall's tau coefficient
- ✓ Kruskal-Wallis and ANOVA tests

CL_{META}	COEFF	P-VALUE
CDA_S		8.76e-1
SEX		8.57e-1
tCDA_S		8.74e-1
AGE	-0.51	1.1e-3
ALAT	0.06	7.19e-1
ASAT	-0.099	5.56e-1
Albumin	0.17	3.01e-1
BSA	0.23	1.61e-1
Blasts	-0.31	5.7e-2
CDA	-0.089	5.95e-1
CRP	-0.1	5.47e-1
Creatinine	-0.23	1.57e-1
Height	0.19	2.53e-1
Hemoblasts	-0.2	2.37e-1
LDH	-0.12	4.77e-1
PNN	-0.17	3.06e-1
Total_bilirubin	-0.0073	9.65e-1
Weight	0.22	1.78e-1
bBWC	-0.13	4.26e-1
eGFR	0.4	1.4e-2
logtAGE	-0.48	2.22e-3
logtBBWC	-0.13	4.29e-1
logtBSA	0.22	1.79e-1
logtBlasts	-0.29	7.35e-2
logtCDA	0.0057	9.73e-1
logtWeight	0.22	1.85e-1

$V_{PARENT1}$	COEFF	P-VALUE
CDA_S		4.79e-1
SEX		2.16e-1
tCDA_S		3.98e-1
AGE	-0.031	8.53e-1
ALAT	0.079	6.37e-1
ASAT	0.089	5.96e-1
Albumin	0.12	4.72e-1
BSA	0.36	2.7e-2
Blasts	0.17	3.21e-1
CDA	-0.078	6.4e-1
CRP	-0.078	6.41e-1
Creatinine	0.24	1.53e-1
Height	0.24	1.42e-1
Hemoblasts	0.2	2.41e-1
LDH	0.043	7.96e-1
PNN	-0.048	7.77e-1
Total_bilirubin	-0.081	6.29e-1
Weight	0.34	3.46e-2
bBWC	-0.048	7.75e-1
eGFR	-0.15	3.76e-1
logtAGE	-0.095	5.69e-1
logtBBWC	-0.2	2.4e-1
logtBSA	0.36	2.44e-2
logtBlasts	0.29	7.51e-2
logtCDA	-0.16	3.39e-1
logtWeight	0.37	2.2e-2

CL_{PM}	COEFF	P-VALUE
CDA_S		2.21e-2
SEX		5.78e-1
tCDA_S		6.74e-3
AGE	-0.084	6.14e-1
ALAT	-0.074	6.57e-1
ASAT	-0.15	3.61e-1
Albumin	-0.12	4.59e-1
BSA	-0.011	9.48e-1
Blasts	-0.38	1.79e-2
CDA	0.42	8.76e-3
CRP	0.17	3.07e-1
Creatinine	-0.22	1.82e-1
Height	-0.096	5.67e-1
Hemoblasts	-0.24	1.51e-1
LDH	0.0033	9.84e-1
PNN	0.35	2.91e-2
Total_bilirubin	0.25	1.26e-1
Weight	-0.01	9.51e-1
bBWC	0.32	5.4e-2
eGFR	0.26	1.21e-1
logtAGE	-0.019	9.08e-1
logtBBWC	0.37	2.1e-2
logtBSA	-0.027	8.74e-1
logtBlasts	-0.44	5.16e-3
logtCDA	0.43	6.39e-3
logtWeight	-0.014	9.34e-1

Covariate sub-models building: analysis plan

2 Handling missing covariates data

- ✓ Covariates with more than 25% of missing values were excluded.
- ✓ Missing data in PGx covariates > 40% ➔ we can not impute them !

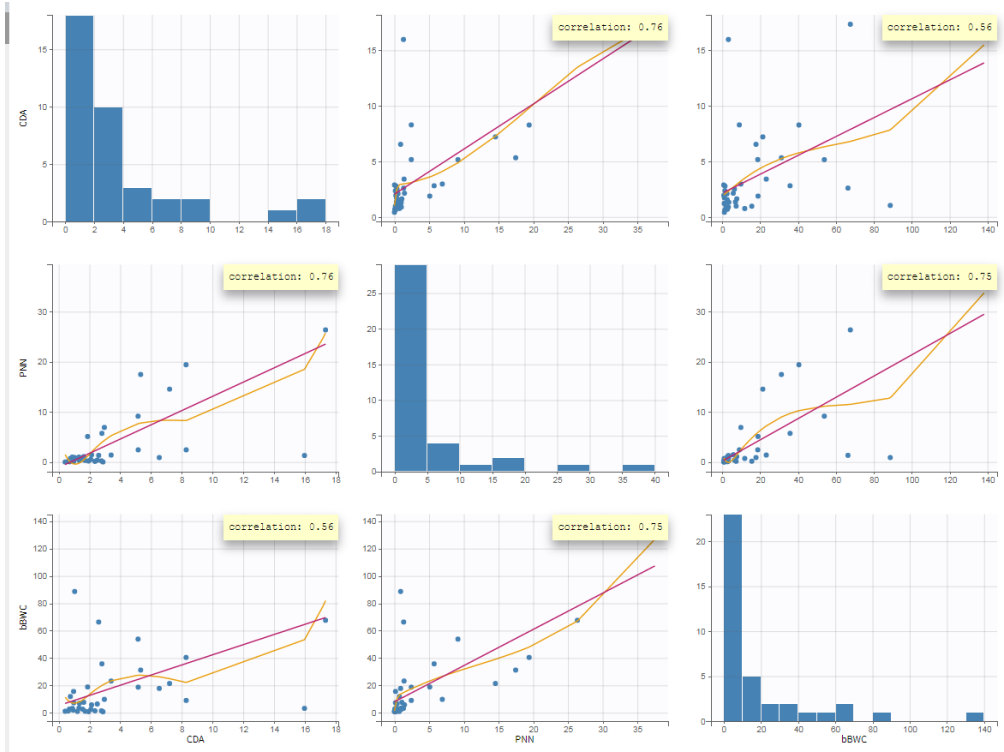
PGx

ID	OC(	REGIMEN	rs602950	rs32154	rs20726	rs12059	rs4889	rs144224977	rs37381	rs77158	rs61781	rs61781	rs61735	rs10489	rs99977	rs138544	rs11544	rs14862	rs72553
001	1	Low-dose	AG	C -	AC	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
003	1	Low-dose	AG	--	AC	GG	AA	-	TC	AA	AA	TT	GG	TT	GG	AA	CC	TT	AA
008	1	Low-dose	AG	--	AC	AG	AA	[16477-16178insTCAA]+[=]	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
011	3	Low-dose																	
011	3	Low-dose																	
012	1	Low-dose	AA	CC	AA	GG	AA	-	TC	AG	AG	TC	GG	TC	GG	AA	CT	AA	AA
013	1	Low-dose	GG	--	CC	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	AT	AA
015	1	Low-dose	AA	C -	AC	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AG	CC	AA	AA
017	1	Low-dose	AA	CC	AC	GG	AA	-	TC	AG	AG	TC	GG	TC	GG	AA	CC	TT	AA
018	1	Low-dose	AA	CC	AA	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	AA	AA
020	1	Low-dose	AA	CC	AC	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
022	1	Low-dose	AA	CC	AA	GG	AA	-	TC	AG	AG	TC	GG	TC	GG	AA	CC	TT	AA
023	1	Low-dose	AA	CC	AC	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
024	1	Low-dose	AA	CC	AC	GG	AA	-	TC	AG	AG	TC	GG	TC	GG	AA	CC	TT	AA
025	1	Low-dose	AG	C -	AA	GG	AA	-	TC	AG	AG	TC	GG	TC	GG	AA	CC	TT	AT
026	1	Low-dose	AG	--	AC	GG	AA	-	TT	GG	CC	CC	GG	CC	GG	AA	CC	AA	AA
028	1	Low-dose	AA	CC	AA	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
029	1	Low-dose																	
030	1	Low-dose	AG	C -	AC	GG	AA	-	TT	AG	AG	TC	GG	TC	GG	AA	CC	TT	AA
031	1	Low-dose	AA	CC	AA	GG	AA	[16477-16178insTCAA]+[=]	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
032	1	Low-dose	AA	CC	AA	GG	AT	-	TT	AG	AG	CT	GG	CT	GG	AA	CC	AA	AA
033	1	Low-dose																	
034	1	Low-dose	GG	--	CC	GG	AA	-	TC	GG	GG	TT	GG	TT	GG	AA	CC	TT	AA
035	1	Low-dose	AG	C -	AC	GG	AA	-	TT	GG	GG	CC	GG	CC	GG	AA	CC	TT	AA
036	1	Low-dose	AVIS MEDICAL + TTT PAR MEC																
037	1	Low-dose																	
038	1	Low-dose	AA	--	AA	GA	AA	-	TT	AG	AG	CT	GG	CT	GG	AA	CC	AA	AA
039	1	Low-dose																	
040	1	Low-dose	AG	--	AC	GG	AA	-	TC	AG	AG	CT	GG	CT	GG	AA	CC	AA	AA
041	1	Low-dose																	
042	1	Low-dose																	
043	1	Low-dose																	
044	1	Low-dose	ECHUTE MIS SOUS V2																
045	1	Low-dose	AA	--	AA	GG	AA	-	TT	GG	GG	CC	GG	CC					
046	1	Low-dose																	
047	1	Low-dose																	
048	1	Low-dose																	
049	1	Low-dose	AA	C -	AA	GG	AA	-	TT	GG	GG	CC	GG	CC					
050	1	Low-dose																	
051	1	Low-dose	e blastes mais MRD positive																

PGx > 40%
➔ Excluded

Covariate sub-models building: analysis plan

3 Data reduction and collinearity issues



- ✓ **Covariates** effects to be included in the model should be independent (e.g., they carry unique information).
- ✓ Rule of thumb:
  be cautious when **|corr. coef| > 0.3**

The Effect of Collinearity on Parameter Estimates in Nonlinear Mixed Effect Models (Perer L. Bonate., 1999)

Covariate sub-models building: analysis plan

4 Covariate evaluation methodology

✓ The classic stepwise covariate modeling (SCM) method

- Forward selection (significant at p = 0.05 level ; ΔOFV > 3.84)
- Backward deletion (significant at p = 0.01 level; ΔOFV > 6.63)
- Reduction in unexplained variability
- Mechanistic plausibility

PK VARIABILITY SOURCES

Table 1. Summarized covariate sub-models building steps

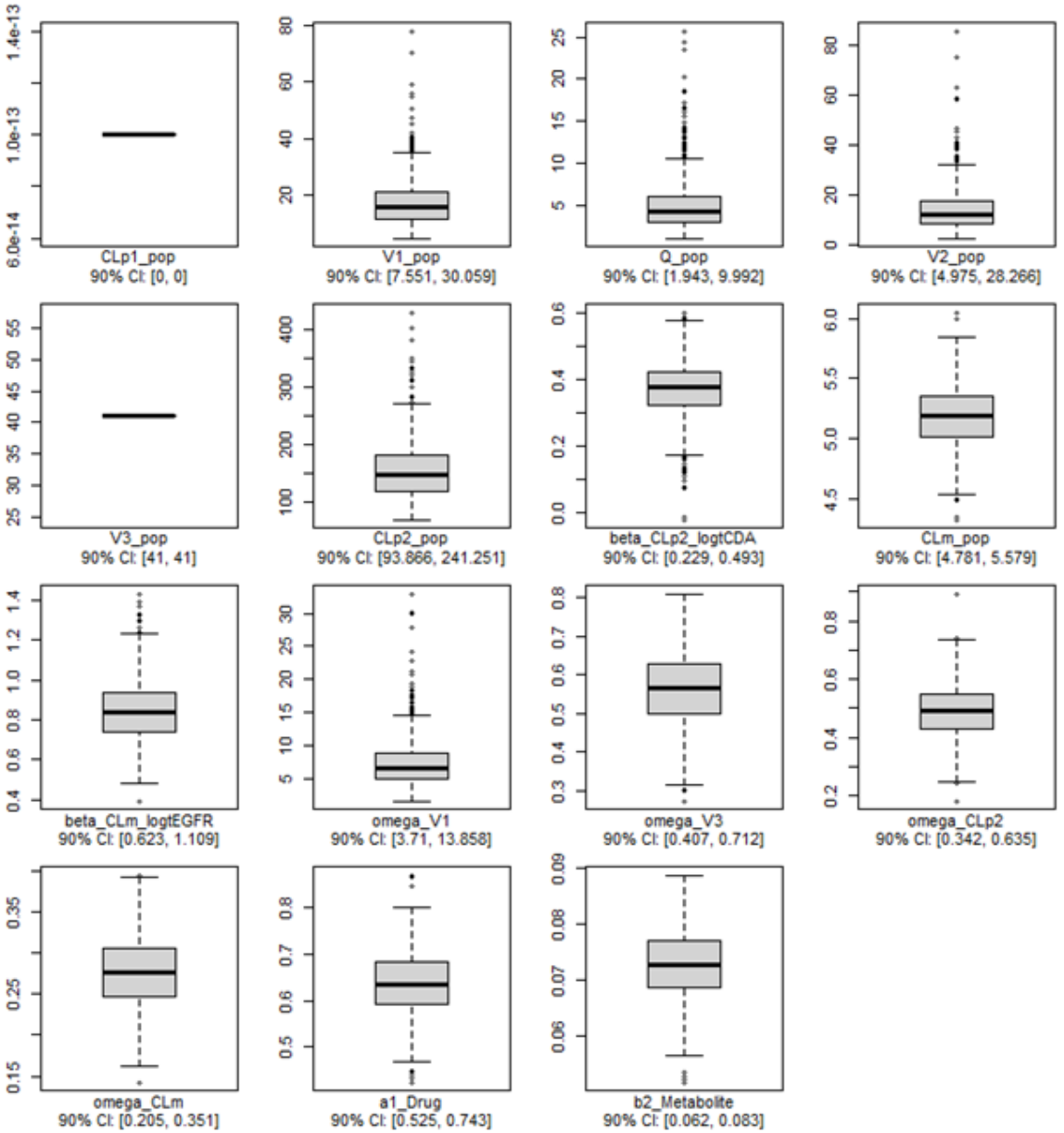
Model N°	Description	OFV (-2LL)	Δ_{OFV}	LRT (υ, p-Value)	Wald test (p-Value)	Δ_{BSV}
1	Base model	3854				
2	eGFR on CL_{Ara-U}	3835	19	<0.05	<0.0001	**0.29 vs 0.37 (21.6%)**
3	Model 2 + CDA on $CL_{m, Ara-C}$	3823	12	<0.05	<0.0001	**0.51 vs 0.62 (17.7%)**
4	Model 3 + Blasts on $CL_{m, Ara-C}$	3818	5	<0.05	<0.001	**0.49 vs 0.51 (3.90%)**
5	Model 4 + LDH on $V_{c, Ara-U}$	3812	6	<0.05	<0.001	**0.53 vs 0.58 (8.60%)**
Full Multivariable Model (Model N° 5)	$CL_{m, Ara-C} = 151 * (CDA/2.4)^{0.31} * (Blasts/45)^{-0.28} e^{\eta CLm, Ara-C}$ (L/h) $CL_{Ara-U} = 5.2 * (eGFR/165)^{0.84} * e^{\eta CL Ara-U}$ (L/h) $V_{c, Ara-U} = 41 * (LDH/424)^{0.12} * e^{\eta Vc Ara-U}$ (L)					
6	Model 5 - without Blasts	3816	4.53	p > 0.01		
7	Model 6 - without LDH	3823	6.35	p > 0.01		
Final Model	$CL_{m, Ara-C} = 130 * (CDA/2.4)^{0.36} * e^{\eta CLm, Ara-C}$ (L/h) $CL_{Ara-U} = 5.2 * (eGFR/165)^{0.84} * e^{\eta CL Ara-U}$ (L/h)					

Δ_{IAV}: Relative reduction in variance for the inter-animal unexplained variability ($\frac{\Omega_{Base}-\Omega_{Full}}{\Omega_{Base}}$)

Abbreviations: υ, degrees of freedom; LRT, likelihood-ratio test.

Final MODEL VALIDATION

Bootstrapping results




Thank you
For
your interest in our work