Population pharmacokinetics of ibrutinib and its dihydrodiol metabolite in patients with lymphoid malignancies

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BACKGROUND

- Ibrutinib is a **targeted therapy** which alters the B cell antigen receptor signalling pathway by irreversibly inhibiting the Bruton Tyrosine Kinase. It is used for the treatment of **chronic lymphocytic leukaemia** (CLL), **mantle cell lymphoma** (MCL) and other lymphoid malignancies.
- **Pharmacokinetics (PK)** of ibrutinib is **highly variable between patients**. Its bioavailability is very low (around 3%) due to high first-pass hepatic metabolism (FPHM).
- One of its metabolites, dihydrodiol-ibrutinib (DHD-ibritunib), is 15 times less active but has concentrations up to twice as high as ibrutinib's [1].

Objective : Develop a population PK (POPPK) model for ibrutinib and its dihydrodiol metabolite, quantify and explain PK interindividual variability (IIV)

METHODS

DATA

- PKE3i study initiated in 2016.
- Daily dose of ibrutinib : 140mg to 560mg.
- **PK sampling** :
  - M1 Visit : Complete kinetic profile (6 samples : 0, 0.5, 1, 2, 4, 6h after administration) done after 1 month of treatment (steady-state).
  - M2, M3, M6 Visits : Single sample before drug intake at months 2, 3 and 6 (trough concentrations).
- Drug dosage done by UHPLC-MS/MS.

POPPK MODEL DEVELOPMENT

Software : NONMEM 7.4.1

a. POPPK model of **ibrutinib** : search of the best model to describe complex absorption phase.
b. POPPK model of **ibrutinib and DHD-ibrutinib** : structural model obtained in (a) kept for ibrutinib, simultaneous modelling of parent and metabolite concentrations, search of the best model to describe FPHM [2].
c. Estimation of inter-occasion variability (IOV) between patient hospital visits.
d. Testing of available **covariates** on the parameters of the model to explain interindividual variability.
e. **External evaluation** of the final model on a similar and independent population. Prediction bias and accuracy were assessed through median prediction error (MPE) and median absolute prediction error (MAPE) respectively. Prediction error was calculated as $PE(\%) = \frac{C_{obs} - C_{pred}}{C_{obs}} * 100$.

RESULTS

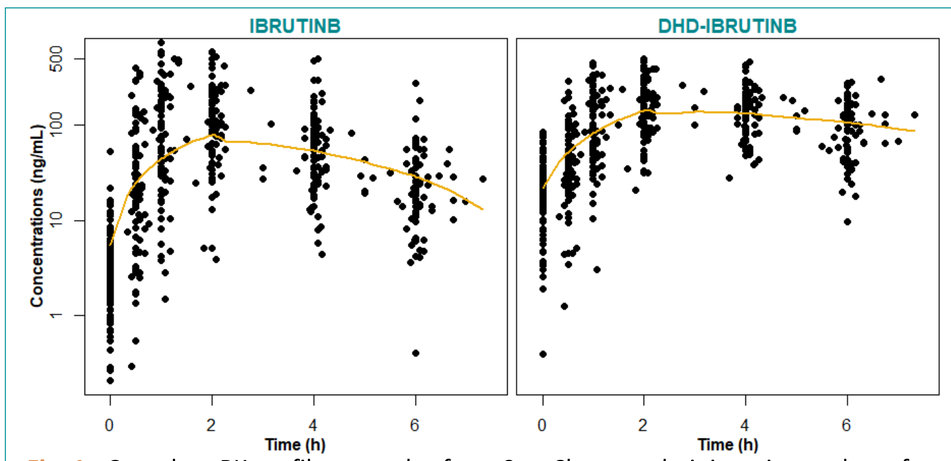


Fig. 1 : Complete PK profile : samples from 0 to 6h post administration, taken after one month of treatment (M1 Visit). High interindividual variability is observed.
A total of **89 patients and 1501 concentrations** were included in the analysis.

Continuous covariate	Mean (range)	Continuous covariate	Mean (range)
Age (years)	68.7 (31.1 – 84.5)	Haemoglobin (g/dL)	11.1 (1.4 – 16.2)
Weight (kg)	72.3 (40 – 112)	Platelets (G/L)	141.5 (7 – 343)
Height (cm)	169.8 (148 – 187)	AST (UI/L)	25.3 (9 – 71)
Leucocytes (G/L)	106.5 (1.8 – 441.2)	ALT (UI/L)	29.4 (11 – 109)
Neutrophils (G/L)	4.3 (0.1 – 14.5)	Creatinine Clearance (mL/min)	63.9 (27 – 81)
Lymphocytes (G/L)	99.8 (0.3 – 429.7)	LDH (g/L)	274.2 (108 – 892)
CD4+ T cells (/mm3)	1667.3 (94 – 7571)	Bilirubin (µmol/L)	12.6 (4 – 228)
CD8+ T cells (/mm3)	1269.8 (66 – 6814)	GGT (g/L)	6.4 (1.2 – 28.4)

Categorical covariate	Patients, n (%)
Disease (CLL / MCL / Waldenström)	77 (87%) / 10 (11%) / 2 (2%)
Sex (F/M)	27 (30%) / 62 (70%)
Prior treatment (Yes / No)	70 (79%) / 19 (21%)
Performance status (0 / 1 / 2)	22(25%) / 50 (56%) / 16 (18%) *(NK=1)*
Smoking (Yes / No)	18 (20%) / 70 (79%) *(NK=1)*
Alcohol (Yes / No)	9 (10%) / 79 (89%) *(NK=1)*
CYP3A4*22 (*1/*1 - *1/*22)	80 (90%) / 9 (10%)
CYP3A5*1 (*3/*3 - *1/*3)	84 (94%) / 5 (6%)

Tab. 1 Description of the population at inclusion. *(NK : Not Known)*

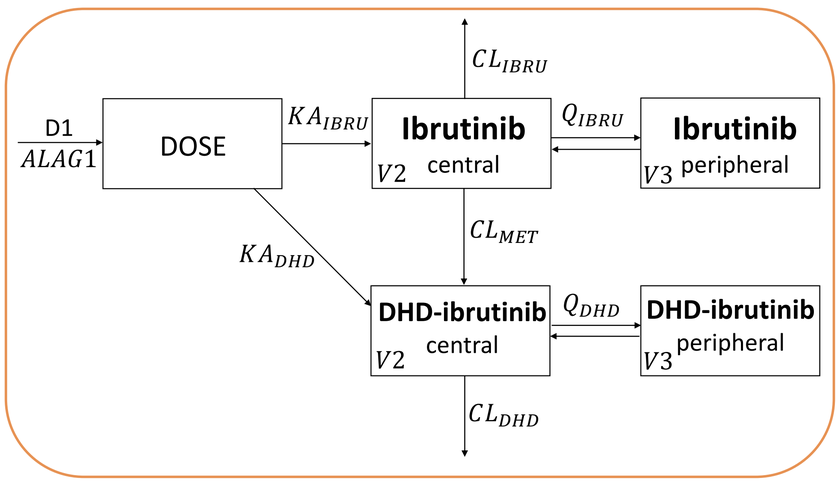
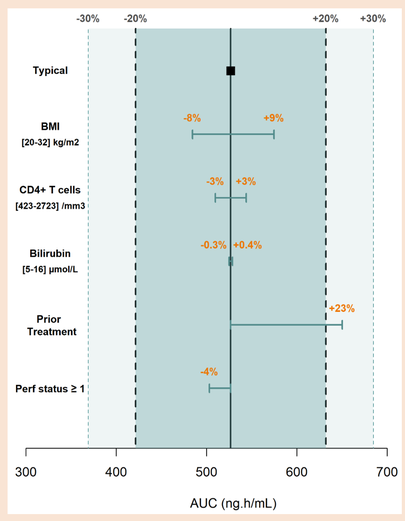


Fig. 2 : Final POPPK model. Ibrutinib absorption is delayed ($ALAG1$). It is modelled by two sequential processes ($D1$, KA_{ibru}). FPHM is modelled by parameter KA_{DHD}. Ibrutinib is either excreted (CL_{ibru}) or metabolized into DHD-Ibrutinib (CL_{met}) which is then excreted (CL_{DHD}).

PK parameter	Estimation (SE%)	IIV (SE%)	IOV (SE%)
D1 (h)	0.989 (19%)	115.2% (16%)	*NE*
ALAG1 (h)	0.238 (16%)	80.6% (16%)	*NE*
KA_{ibru} (h^{-1})	1.56 (18%)	*NE*	*NE*
$KA_{DHD}{}^{a}$ (h^{-1})	1.21 (20%)	64.2% (24%)	*NE*
$CL_{IBRU}{}^{a}$ (L/h)	242 (11%)	66.5% (24%)	46.7% (13%)
Q_{IBRU}(L/h)	171 (16%)	*NE*	*NE*
$CL_{DHD}{}^{a}$(L/h)	181 (9%)	50.7% (12%)	25.7% (8%)
Q_{DHD}(L/h)	50 (13%)	*NE*	*NE*
$CL_{MET}{}^{a}$(L/h)	150 (19%)	64.4% (21%)	*NE*
$V2^{a}$ (L)	1010 (9%)	81.8% (19%)	*NE*
$V3^{a}$ (L)	1480 (9%)	76.9% (20%)	*NE*
Residual variability : Estimation (SE%)			
σ_{IBRU}	37% (13%)	σ_{DHD}	25.7% (8%)

Tab. 2 : Final estimations of model parameters. Non-zero covariance terms were estimated between $D1$ and $ALAG1$, and between parameters a. *(IIV : interindividual variability, IOV : inter-occasion variability, SE : standard error, NE : not estimated)*

Covariate analysis



- Analysis on model with no covariance terms (due to lack of stability)
- **Univariable analysis** on CL_{ibru}, CL_{met}, KA_{DHD}
  → BMI, CD4+ T cells, bilirubin, prior treatment, performance status
- **Multivariable analysis** : prior treatment on CL_{ibru}

Fig. 3 : **Clinical relevance** of significant covariates was tested by simulating ibrutinib AUC with each covariate value varying from its 10th to 90th percentile.

None of the tested covariates led to a change of ibrutinib AUC greater than 30%. Therefore, they were not kept in the final PK model.

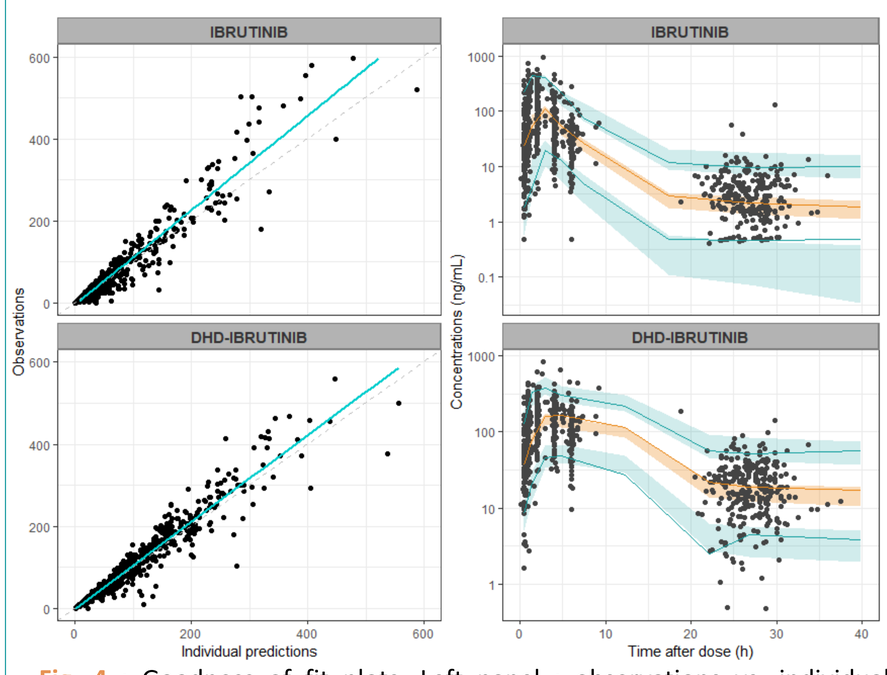


Fig. 4 : Goodness of fit plots. Left panel : observations vs. individual predictions. Right panel : prediction corrected VPCs (1000 simulations)

External evaluation

✓ **Independent population** :

28 patients (11 women / 17 men) with a mean age of 69 y.o. treated by ibrutinib for CLL or MCL.

- **Bias was under 10%** for both molecules for PRED and IPRED
- More than 80% and 90% IPRED had $PE < 30\%$ for ibrutinib and DHD-ibrutinib respectively.
- PRED are not very accurate (only 23% and 40% PRED had $PE < 30\%$ for ibrutinib and DHD-ibrutinib respectively.
- Prediction corrected visual predictive checks are satisfactory.

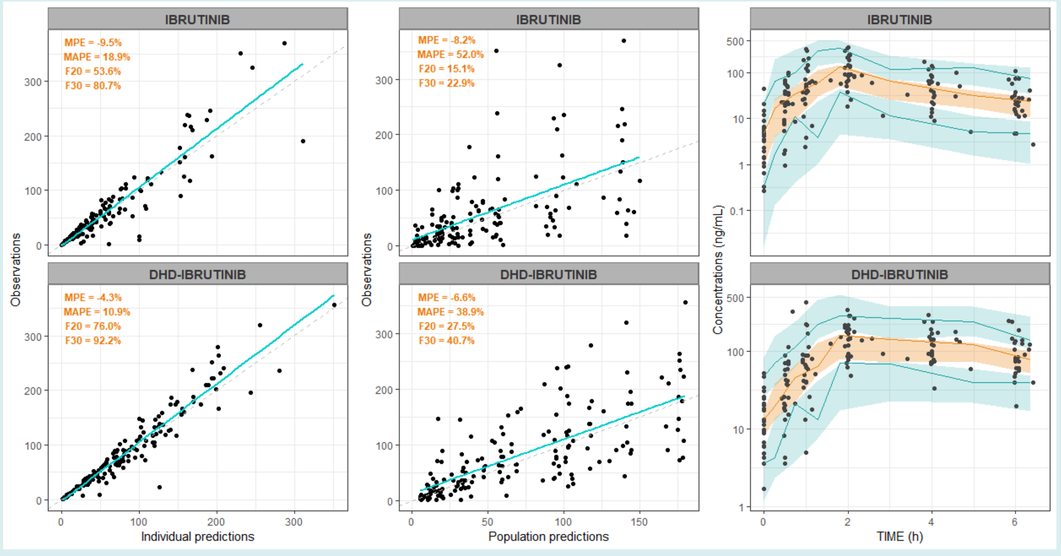


Fig. 5 : External evaluation of the model. From left to right : observations vs. individual predictions, observations vs. population predictions, prediction corrected VPCs (1000 simulations). MPE is median of prediction errors (bias), MAPE is median of absolute prediction errors (accuracy), F20 and F30 are the percentages of PE inferior to 20% and 30% respectively. All metrics were calculated for both molecules using individual and population predictions.

DISCUSSION

- **First POPPK model** taking simultaneously into account **ibrutinib and its metabolite** observations, results for ibrutinib structural model are in agreement with [3]. The final model fits the data well. Interindividual variability was quantified for most PK parameters.
- Our model shows **good prediction performance** on external population. Satisfactory results with individual predictions and VPCs demonstrate that the structural model is correct. **No clinically relevant covariate** was found in our analysis.
- This PK model is a first step towards building a **pharmacokinetic-pharmacodynamic model.** The aim of this model will be to understand the relationship between **ibrutinib pharmacokinets and reponse to treatment** which is assessed by **lymphocyte dynamics over time**.

References

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[2] Bertrand J. et al. AAPS J. sept 2011;13(3):390-404

[3] Marostica E. et al. Cancer Chemother Pharmacol. jan 2015;75(1):111-21.