# Genetic effect on a complex parent-metabolite joint pharmacokinetic model developed with NONMEM and MONOLIX

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## Objectives

### Pharmacological modelling

- To develop a joint population PK model for an antipsychotic from SERVIER research and its active metabolite
  - to investigate the existence of a back-transformation of the metabolite into the parent drug (process known for numerous amines [1])
  - to test for the effects of the *CYP2D6*3, *4, *6, *7*, and **8* allele polymorphisms

### Methodological issues

- To address the identifiability problems and numerical difficulties
  - to encode the model in ordinary differential equations (ODE) system and closed form solutions (CF)
  - to build the model using both linearisation-based and exact estimation algorithms, in parallel

## Methods

### Drug concentration data

- Phase II study including 120 schizophrenic patients
- Four samples at steady state in two occasions : W4 and W8
- Oral administration o.d.

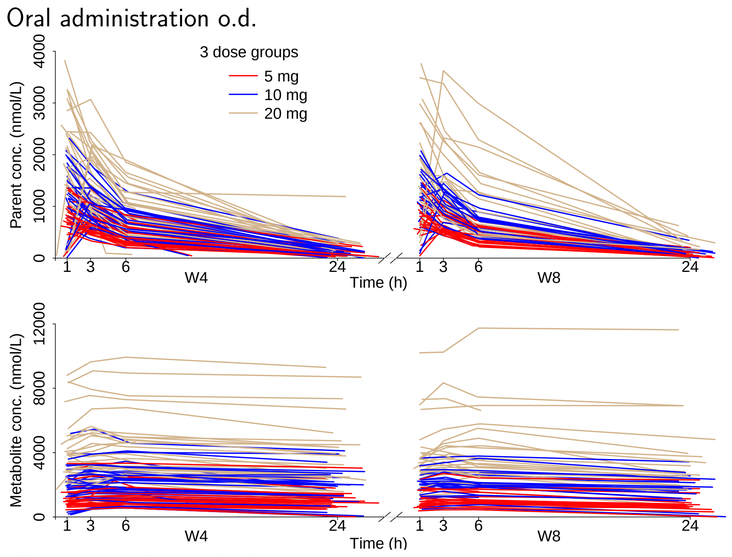



Figure 1: Model building data set

### Model building

- Structural model
  - determination on data at W4
  - four different structural models investigated (see Figure 3)
    - hypotheses to ensure global identifiability : $f$=1 and $V_p = V_m$
  - model selection on Bayesian information criteria (BIC) [2, 3]
    - FOCE-I in NONMEM version V for ODE and VI for CF
    - SAEM in MONOLIX version 2.4
- Variability model
  - between and within-subject variances
    - Gaussian random effects on the log-parameters except for $F_p$ where logit transformation (between 0 and 1)
  - proportional error model for the parent and the metabolite
- Covariate model
  - linear dose effect investigated on $f$ and $F_p$
    - dose analyzed as a continuous covariate using Wald test
  - *CYP2D6* polymorphisms
    - phenotypic binary categorization (PM versus EM) [4]
    - forward selection using Wald test
    - final p-values assessed using permutations [5]

### Model evaluation

- External evaluation
  - phase I study in 30 healthy volunteers, intermediate or extensive metabolizer for CYP2D6
  - ten samples collected at W2 after repeated administrations
  - oral administration o.d.

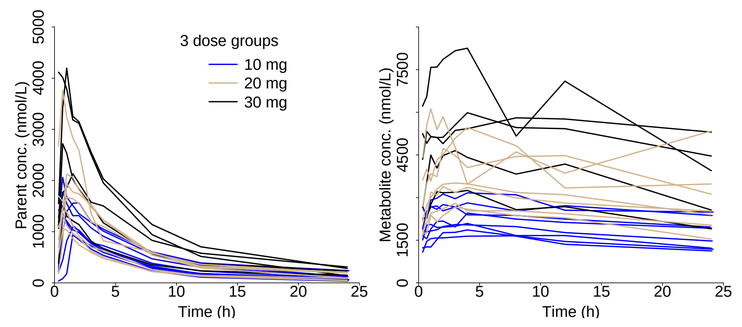
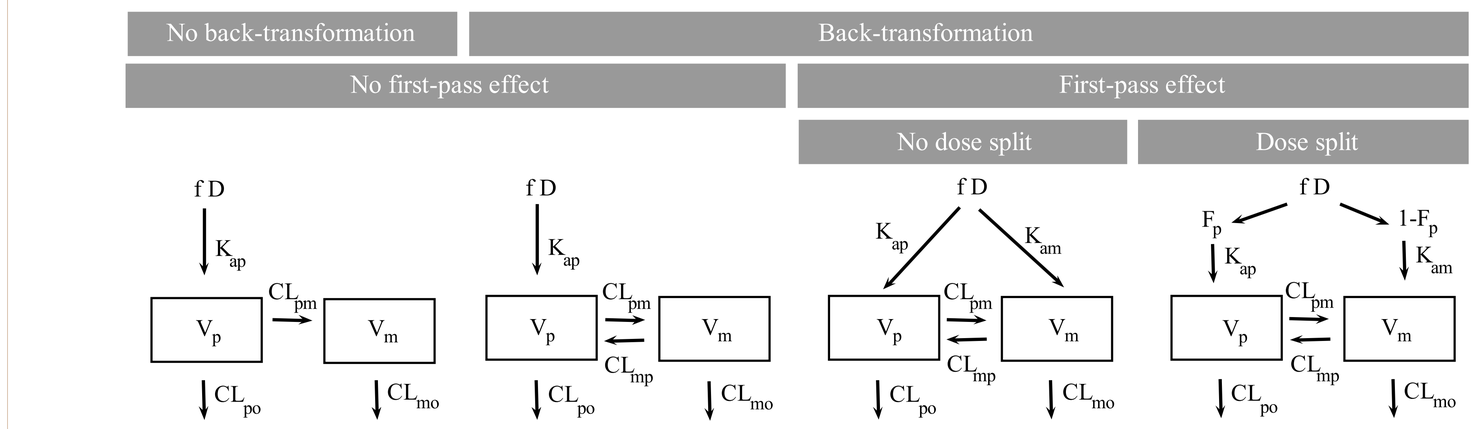



Figure 2: External evaluation data set

- Graphical evaluation
  - normalized prediction distribution errors (npde) [6] plotted *versus* time
  - 1000 data sets simulated using the covariate model




f = fraction of dose after absorption
D = dose
$F_p$ = fraction of parent reaching systemic circulation after absorption
$K_{ap}$ = absorption constant for the parent
$K_{am}$ = absorption constant for the metabolite
$V_p$ = volume of distribution for the parent
$V_m$ = volume of distribution for the metabolite
$CL_{po}$ = clearance of the parent by other pathways
$CL_{pm}$ = clearance of the parent into the metabolite
$CL_{mo}$ = clearance of the metabolite by other pathways
$CL_{mp}$ = clearance of back-transformation of the metabolite into the parent drug

Figure 3: Schematic representation of the four tested structural models

## Results

### Structural model selection

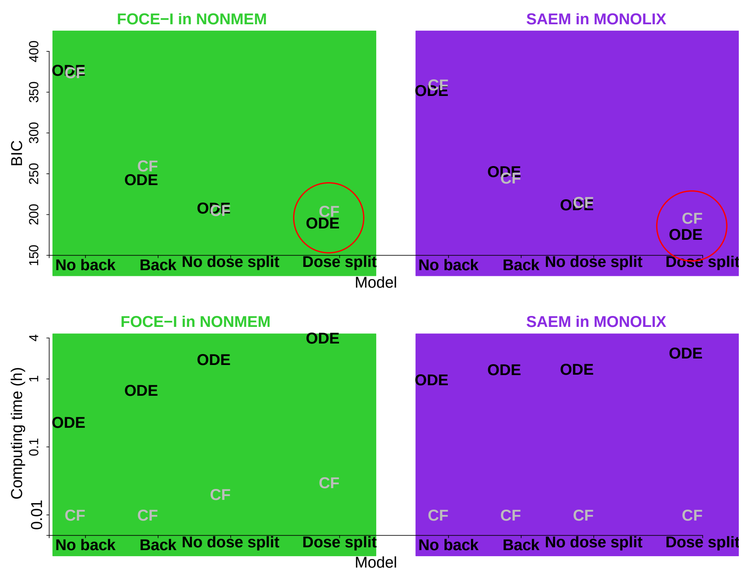



Figure 4: Bayesian information criteria (BIC) and computing time (log-scale) for the four investigated models encoded in CF and ODE using FOCE-I in NONMEM and SAEM in MONOLIX

- Similar population parameter estimates across coding and estimation algorithms
  - inversion in clearances ratio between NONMEM and MONOLIX on models with first-pass
- Back-transformation = 14% of metabolite total clearance
- No standard errors obtained with NONMEM in contrast with MONOLIX
- Low estimation errors on all parameters using SAEM in MONOLIX

### Genetic covariate model

- Ninety nine patients with available genotype
  - covariate model building using SAEM in MONOLIX in CF
  - $f$ and $Fp$ : 10 and 22% higher for 5mg and 19 and 33% lower for 20mg
  - $CL_{mo}$ decreased by 34% in *CYP2D6* PM patients (p-value=0.015)

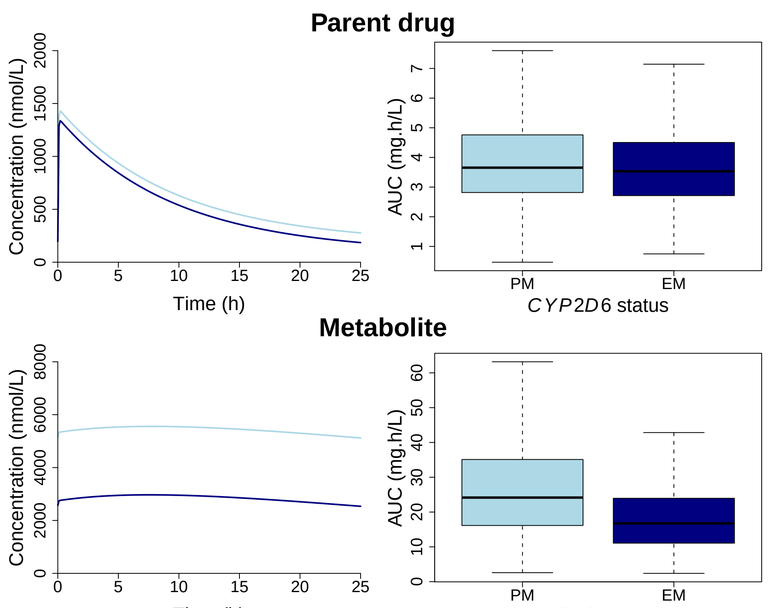



Figure 5: Mean concentration *versus* time curve and area under the curve distribution from 1000 simulated subjects, given the CYP2D6 metabolizer status for a dose of 10mg

### Internal evaluation

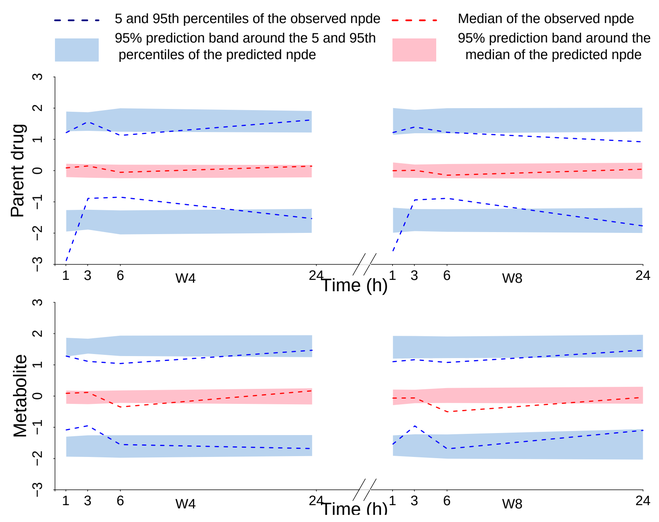



Figure 6: npde *versus* time for the model building data set

### External evaluation

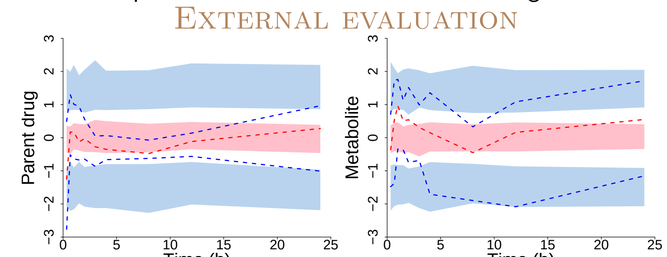



Figure 7: npde *versus* time for the external evaluation data set

- Satisfactory prediction for the model building data set, less for the external evaluation data set (homogeneity, food effect, extended sampling)

## Conclusions

- Joint population PK model of the novel antipsychotic and its active metabolite
  - mechanism-based explanation for the long terminal plasma half-life observed for the parent drug without accumulation at steady-state
  - impact of *CYP2D6* polymorphisms on the metabolite and to a less extent on the parent drug due to a small back-transformation
- Performance of the estimation algorithms
  - both algorithms and coding led to the selection of the same structural model
  - important gain of time using CF, especially for the continuation of the analysis

⇒ As regulatory authorities encourage the use of new estimation algorithms, this work provides interesting insight on the use of both software and codings on such a complex model

## References

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