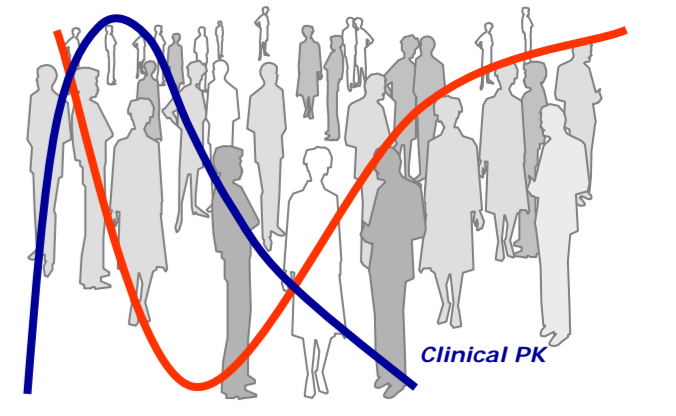


Joint modelling of placebo response and dropout mechanism using clinical data from a trial performed in patients suffering from major depressive disorder



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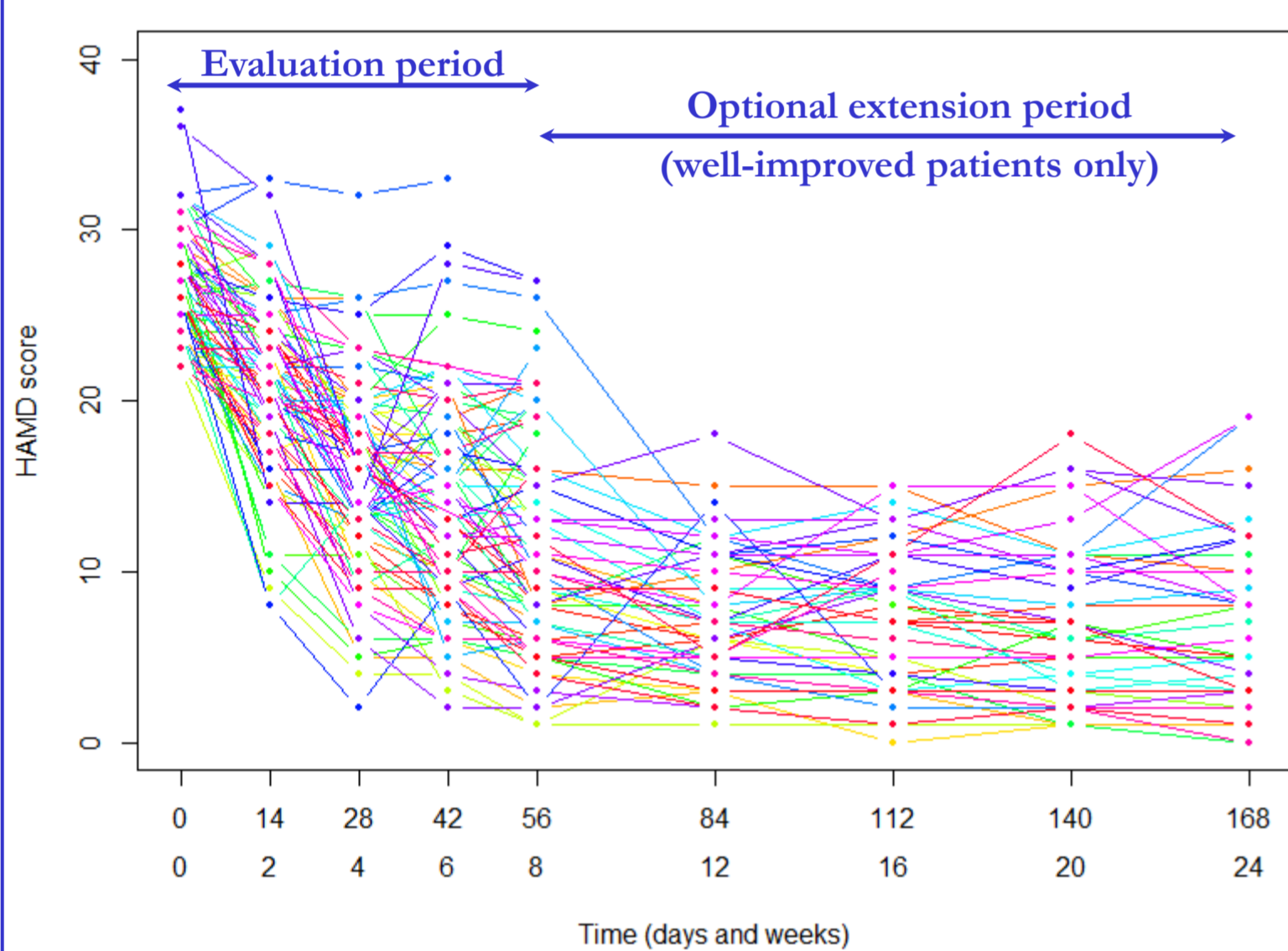
Context

- ✦ Clinical trials evaluating antidepressant agents
 - ✦ Clinical endpoint: Hamilton depression rating scale score (HAMD)
 - ✦ Marked placebo response
 - ✦ High rate of dropout (DO)
 - ✦ Usual statistical analysis
 - ✦ Test on the change from baseline to HAMD value at a predefine visit
 - ✦ Missing data (due to DO): last observation carrying forward, linear mixed effects model (MMRM)
 - ✦ New statistical approach: joint nonlinear mixed effects modelling (NLMEM) of longitudinal and time-to-event (TTE) data^[1-4]
 - ✦ HAMD-time course under placebo (+ antidepressant treatment effect)
 - ✦ Parametric TTE model taking into account the underlying DO mechanism
- ⇒ **Objective: to describe the HAMD-time course under placebo for patients suffering from a major depressive disorder (MDD), using joint NLMEM approach.**

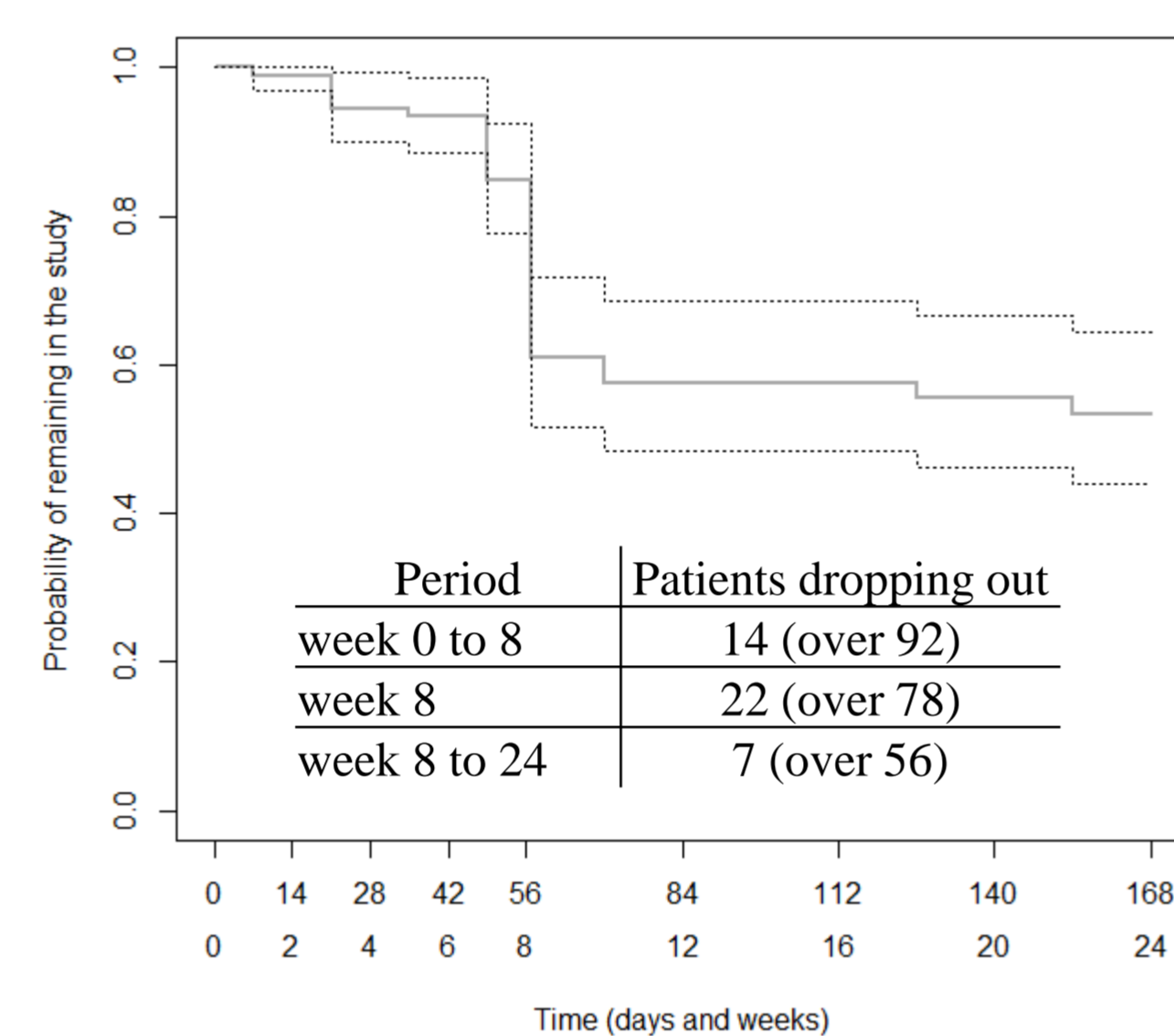
Material and Methods

1. Study design and data

- ✦ 92 MDD patients, with HAMD > 22 at inclusion, in the placebo group
- ✦ 2 study periods
 - ✦ Evaluation period during 8 weeks
 - ✦ Optional extension period for well-improved patients, during 16 weeks (56 patients included)



Plot 1: Individual HAMD versus time profiles



Plot 2: Kaplan Meier plot of observed dropout

2. HAMD-time course modelling

- ✦ Structural model^[2,5,6] (f): Bateman (with relapse or not) and Weibull models
- ✦ Statistical model (NLMEM)
 - ✦ $HAMD_{i,j} = Y_{i,j} = f(t_{i,j}, \mu, \eta_i) + \varepsilon_{i,j}$ with $i=1, \dots, 92$ patients and $j=1, \dots, n_i$ HAMD measures
 - ✦ Inter-individual variability (η_i): full, diagonal and block diagonal matrices
 - ✦ Residual error ($\varepsilon_{i,j}$): additive, proportional and combined model

3. TTE modelling

- ✦ Definition
 - ✦ Instantaneous hazard, cumulative hazard and survivor function: $h(t)$, $H(t)$ and $S(t)$
 - ✦ $H(a,b) = \int_a^b h(u) du$ and $S(a,b) = \exp(-H(a,b))$
 - ✦ Probability of the event (at time T_e)
 - ✦ Right censoring (i.e. no DO): $p(T_e \geq t) = S(0,t)$
 - ✦ Exact time event (i.e. not well-improved patients): $pdf(t = T_e) = S(0, T_e) \times h(T_e)$
 - ✦ Time interval event (between W_{j-1} and W_j visits): $p(t_{j-1} \leq T_e \leq t_j) = S(0, t_{j-1}) \times (1 - S(t_{j-1}, t_j))$
- ✦ Instantaneous hazard model
 - ✦ Missing completely at random (CRD): no time/covariate/HAMD score dependency
 - ✦ $h(t) = \beta_0$
 - ✦ Missing at random (RD): DO influenced by the last observed HAMD ($Y_{i,last}$)
 - ✦ $h(t) = \beta_0 \exp(\beta_{last} Y_{i,last} + \beta_{D56} Y_{i,D56})$ with $\beta_{D56} = 0$ if $t \neq 57$
 - ✦ Missing not at random (i.e. informative, ID): DO influenced by the predicted HAMD
 - ✦ $h(t) = \beta_0 \exp(\beta_{pred} f(t_{i,j}, \mu, \eta_i))$

4. Parameter estimation by maximization of the likelihood

- ✦ Longitudinal model (HAMD data alone): FOCE algorithm
- ✦ Joint model (HAMD + TTE data): Laplacian method
 - ✦ Simultaneous estimation of parameters from HAMD-time course and TTE models
- ✦ Software: NONMEM V1.2

5. Model evaluation

- ✦ HAMD: parameter estimate precision, goodness-of-fit plots, visual predictive checks (VPC)
- ✦ TTE: parameter estimate precision, Kaplan-Meier VPC comparing $S(0,t)$ estimated from observed and simulated data

Results

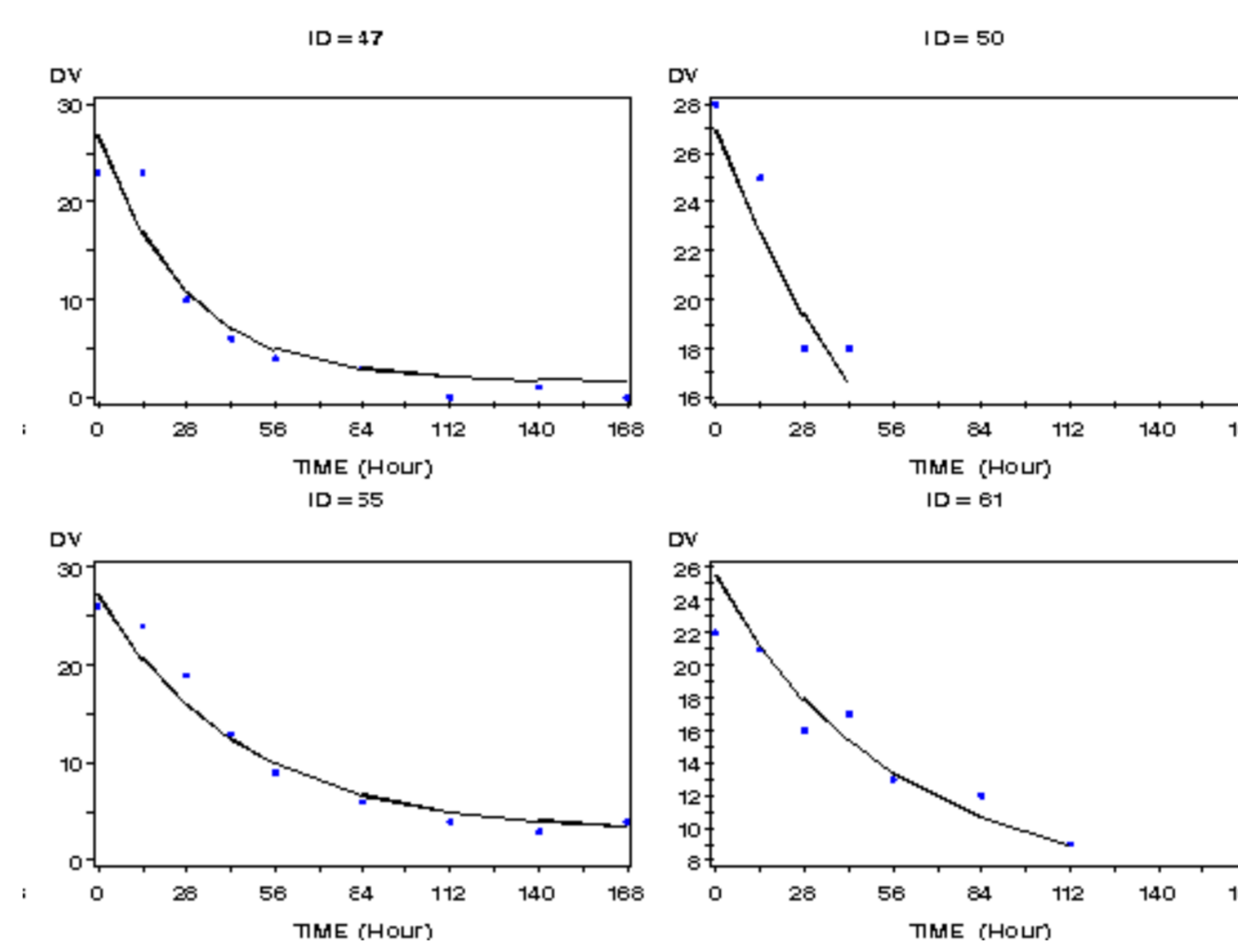
1. NLMEM of HAMD data alone

- ✦ Structural model: Bateman model with $f(t) = S_0 - (S_0 - S_{min}) \times \left[1 - \exp\left(-\frac{\log(2)}{T_{rem}} \times t\right) \right]$
- ✦ IIV on all parameters, combined error model
- ✦ Good precision of parameter estimates, correct prediction at individual level
- ✦ Bias of the prediction at the population level

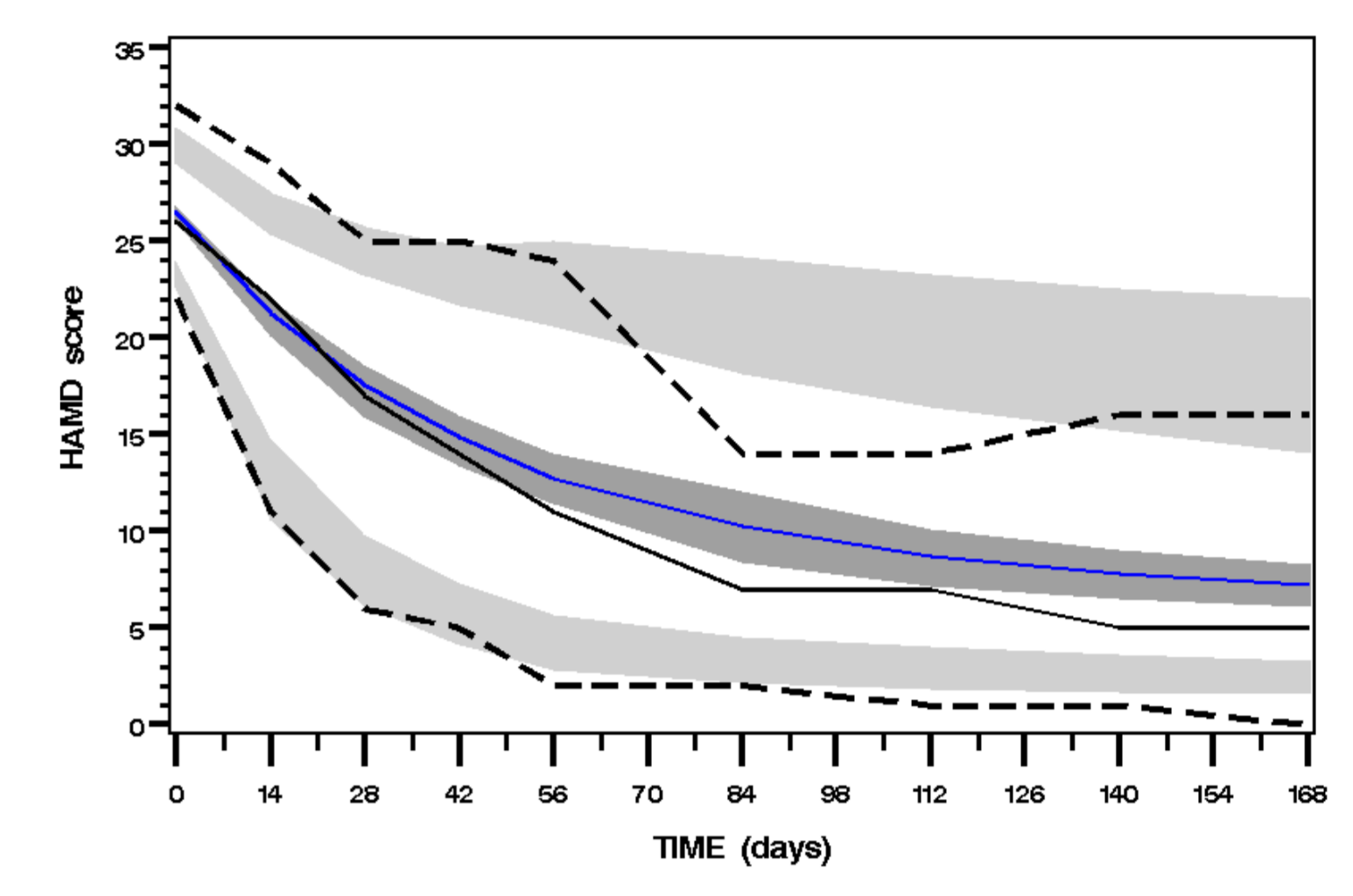
Parameter	Fixed effects (RSE %)	Random effects		Proportional error (-)	Additive error (-)
		ω^2 (RSE, %)	CV (%)		
S_0 (-)	27 (1.4)	$5.3 \cdot 10^{-3}$ (58)	7.3	14%	(31)
S_{min} (-)	5.3 (8.5)	0.44 (11)	67		
T_{rem} (day ⁻¹)	33 (8.5)	0.59 (11)	77		1.88 (28)

RSE: relative standard error, ω^2 : IIV variance, CV: coefficient of variation

Table 1: Parameter estimates of the NLMEM of HAMD data alone



Plot 3: Individual fits of HAMD versus time



Plot 4: VPC of HAMD-time course

⇒ **Need to take into account the dropout to correctly predict the HAMD score**

2. Joint modelling of HAMD and dropout data

- ✦ HAMD data: same NLMEM as previously except for the residual error model (no successful run with the combined model)
- ✦ TTE data: RD model
 - ✦ Importance of taking into account the design: great likelihood decrease when estimating β_{D56}
 - ✦ Convergence issue with the ID model (no successful run)

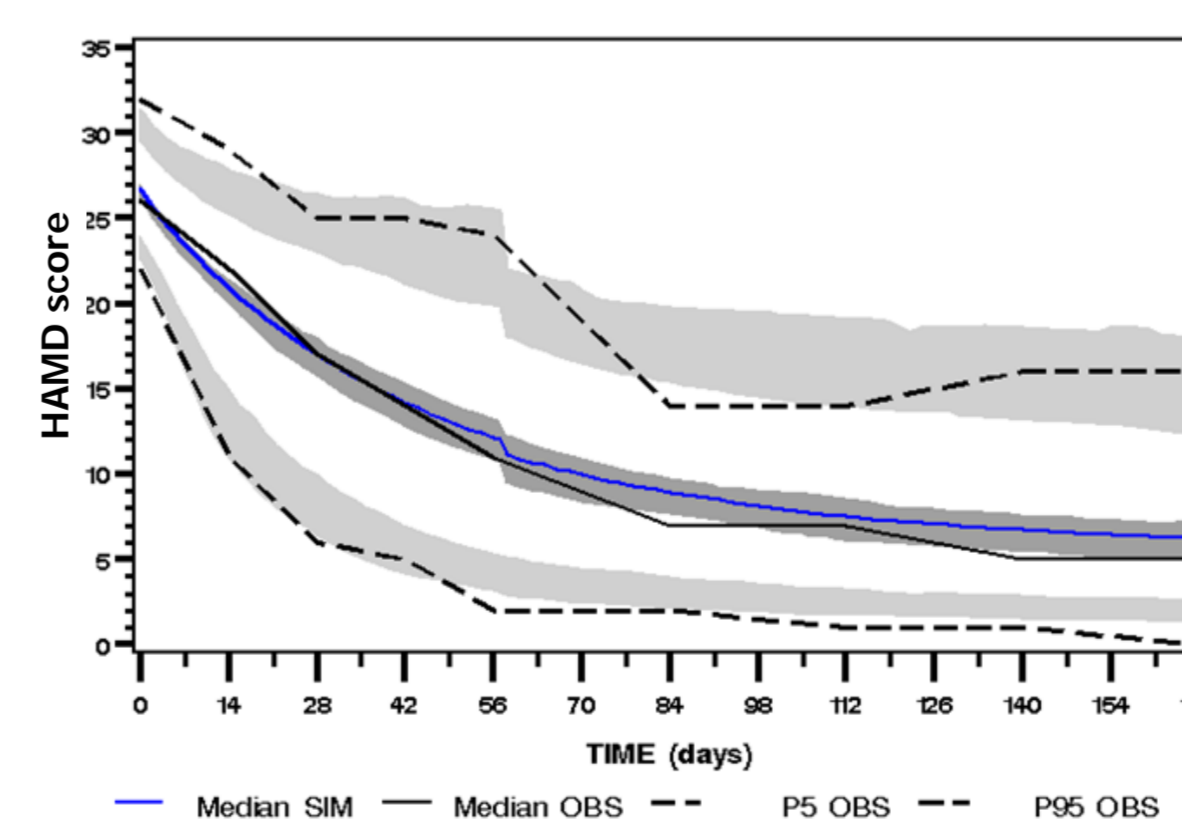
Parameter	Fixed effects (RSE %)	Random effects		Parameter	Estimate (RSE %)
		ω^2 (RSE, %)	CV (%)		
S_0 (-)	26.7 (1.3)	$6.5 \cdot 10^{-3}$ (36)	8.1	β_0 (events/week*10 ³)	8.9 (40)
S_{min} (-)	5.43 (13)	0.52 (20)	72	β_{last} (-)	$40 \cdot 10^{-3}$ (59)
T_{rem} (day ⁻¹)	29.3 (8.1)	0.44 (14)	66	β_{D56} (-)	$243 \cdot 10^{-3}$ (8.1)
				Additive error (-)	2.8(5.6)

RSE: relative standard error, ω^2 : IIV variance, CV: coefficient of variation

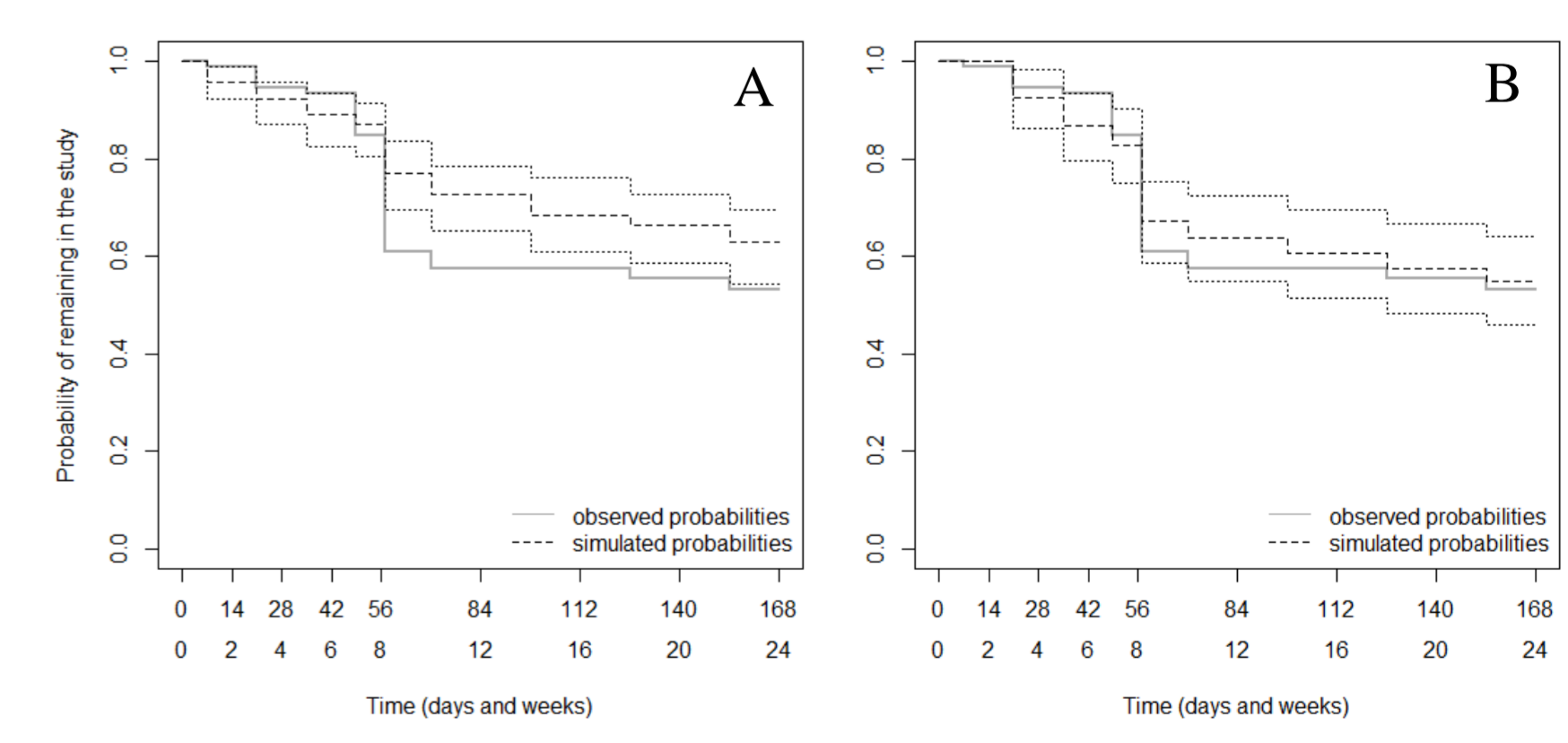
Table 2: Parameter estimates of the joint NLMEM (HAMD + TTE data)

Model evaluation

- ✦ Simulation process using the final joint model parameter estimates
 - Simulation of HAMD-time course data
 - For each simulated patient, simulation of dropout (yes/no with T_e): at time $t_{j-1} < t \leq t_j$, simulation of TTE data using simulated HAMD at (j-1)th visit (i.e. $Y_{i,last}$)
 - At time t , deletion of HAMD data from simulated patients dropping out before t
 - ✦ HAMD-time course VPC taking into account the simulated DO
 - ✦ Great decrease of the 95th percentile of the simulated (and observed) HAMD after day 56 (i.e. beginning of the extension period with well-improved patients only)
- ⇒ **Better prediction at the population level when taking into account the DO**
- ✦ TTE: Kaplan-Meier VPC taking into account the simulated HAMD
 - ✦ Under prediction of DO: due to HAMD-time course or/and TTE models?
 - ✦ Better prediction if taking into account the observed HAMD (instead of the simulated)



Plot 5: VPC of HAMD-time course taking into account dropout



Plot 6: Kaplan-Meier VPC of TTE data using simulated (A) or observed (B) HAMD score of the last visit

⇒ **Influence of correctly modelling HAMD data to better predict dropout (and vice versa)**

Perspectives

- ✦ Algorithm convergence issues
 - ✦ NONMEM VII implementing new algorithms (SAEM...)
 - ✦ Parameter estimation with other software (MONOLIX...)
- ✦ Better predict the HAMD-time course to better predict the dropout mechanism
 - ✦ Semi mechanistic model, mixture model for relapse, adding placebo data from other studies
- ✦ Importance and issue of evaluating joint NLMEM^[7]

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 [3] Hu and Sale. *Journal of Pharmacokinetics and Pharmacodynamics*. 2003.

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