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Population Pharmacodynamics of Cladribine Tablets Therapy in Patients with Multiple Sclerosis: Relationship between Magnetic Resonance Imaging and Clinical Outcomes

Rada Savic[1]
Alain Munafo[2], Mats Karlsson[1]

(1) Dept of Pharmaceutical Biosciences,
Uppsala University, Sweden

(2) Modeling and Simulation,
Merck Serono S.A. – Geneva, Switzerland*

*An affiliate of Merck KGaA, Darmstadt, Germany

Background

Relapsing forms of multiple sclerosis (MS) are characterized by:

- Unpredictable periods of remission
- Slow disease progression
- Substantial inter-patient variability
- Poorly-understood relationship with biomarkers (MRI)

Making it a challenge to quantify effects of therapies on disease progression dynamics

MRI, magnetic resonance imaging

Aim

- We previously developed NLME models to characterize the effect of cladribine tablets on clinical outcomes in patients with relapsing–remitting multiple sclerosis[1–2]
- These models allow predictions of relapse rate dynamics and disability progression based on an individual's disease activity, baseline characteristics, renal clearance and cladribine dose

- AIM
  - To integrate key MRI readouts into models relating cladribine exposure to clinical efficacy, and delineate the poorly-understood relationship between MRI and clinical markers of MS progression

NLME, nonlinear mixed-effects

1. Savic R *et al*. ECTRIMS 2010 (Poster P477);
2. Savic R *et al*. ACoP 2011 (Poster M-9-5)

Data, clinical endpoints, biomarkers

- Data
  - (i) CLARITY trial (96 weeks)
    - 1,326 patients with relapsing–remitting MS
    - 3 arms (placebo or cladribine tablets at cumulative doses of 3.5 and 5.25 mg/kg over 96 weeks, given as 4 and 6 short 4–5-day courses)
  - (ii) OWIMS trial (48 weeks) and PRISMS trial (96 weeks)
    - Additional 287 placebo patients with relapsing–remitting MS
- Clinical endpoints
  - Expanded Disability Status Scale (EDSS) score
    - Categorical variable (0–10 scale, with 0.5-point increments)
  - Relapse rate
    - Repeated time-to-event variable (up to 6 relapses, over 96 weeks)
- MRI Biomarkers
  - I. T2 lesion volume – burden of disease (BOD) (continuous variable)
  - II. Combined unique (CU) lesion count (count variable)

Modeling strategy

- (i) Develop population models for time course of biomarkers (with covariates)
  - CU model
  - BOD model
- (ii) Link the time course of biomarkers with the time course of clinical endpoints

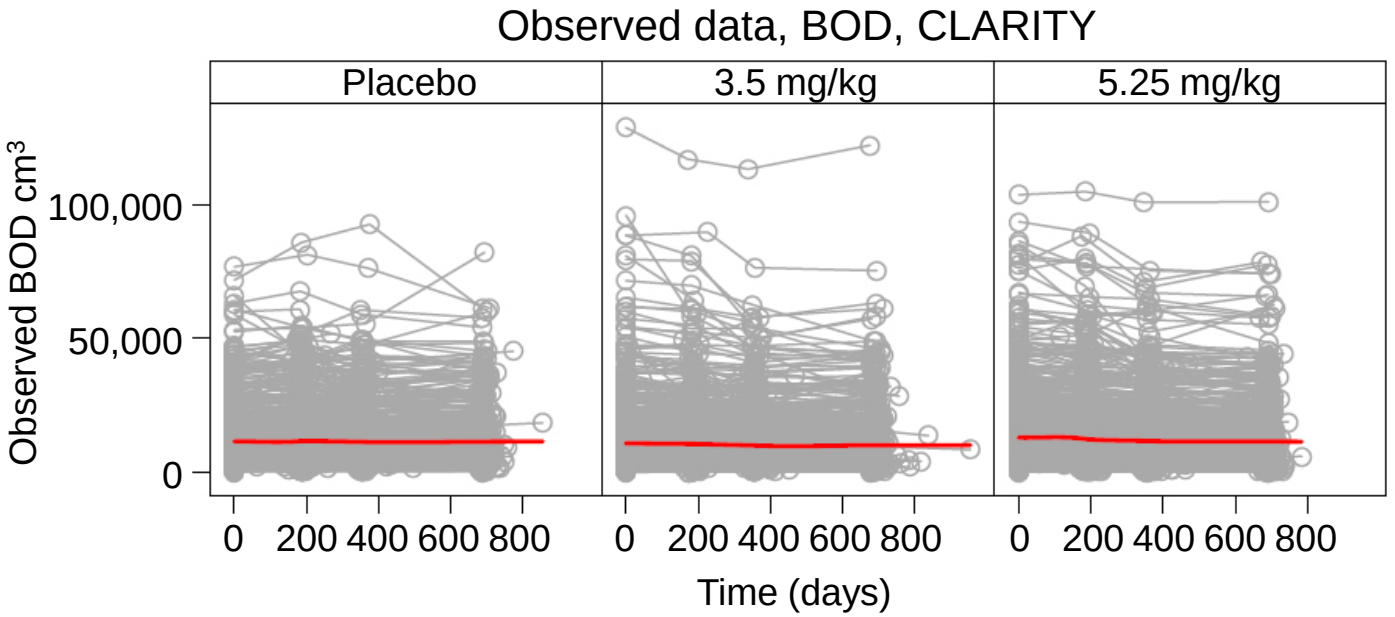
Final aim: establish predictive models for 2 major clinical endpoints:

1) Exposure – MRI BOD – EDSS
2) Exposure – MRI CU lesions – relapse rate (RR)

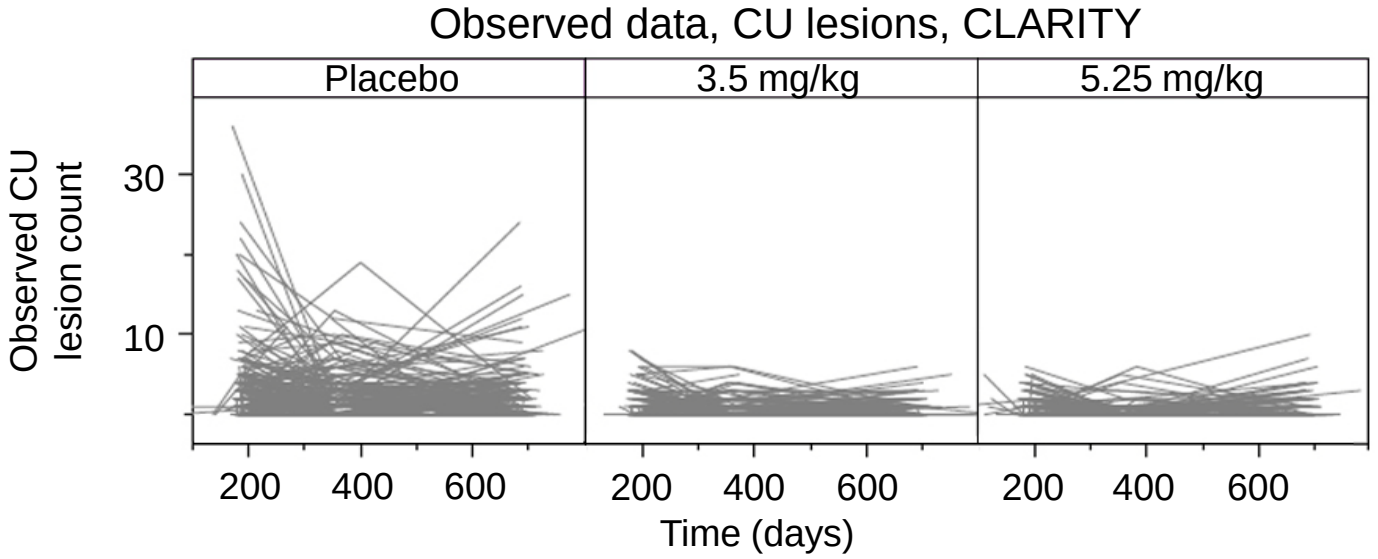
STEP I: MODEL DEVELOPMENT FOR BIOMARKERS

Raw data

Large variability, skewed baseline



Large variability in placebo group, variability decreased with cladribine



Modeling strategy

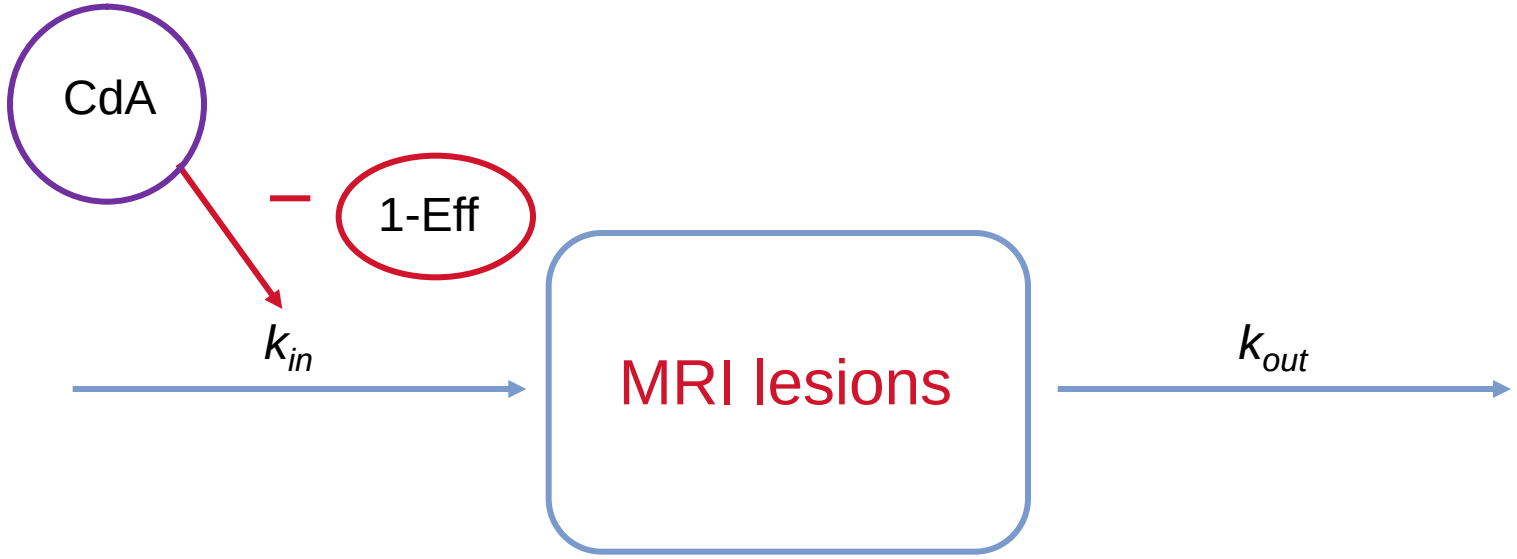
- Development of the placebo model
  - Constant vs time changes
  - CU lesions: choice of count data model (overdispersion)

Count model	Data	# of parameters	Parameters	OFV
Poisson	Placebo	2	λ, IIV (λ)	9209
Zero inflated	Placebo	4	λ, IIV (λ) p, IIV (p)	8327
Generalized Poisson	Placebo	4	λ, IIV (λ) δ, IIV (δ)	8479
Inverse binomial	**Placebo**	**4**	**λ, IIV (λ)** **OVDP, IIV (OVDP)**	**7732**

- Development of the drug model

OVDP, overdispersion factor

General MRI model



$$Eff = \frac{E_{max} \times Exps}{Exps_{50} + Exps}$$

$$Exps = \frac{CD \times CL_{CR\_median}}{CL_{CR}}$$

CD	= cumulative dose
$Exps$	= exposure
k_{in}	= production rate constant
k_{out}	= elimination rate constant
CL_{CR}	= creatinine clearance
CL_{CR_median}	= median creatinine clearance
Eff	= drug effect
$Exps_{50}$	= exposure needed for half maximal effect

CdA, cladribine

Covariate model for biomarkers

BOD

1. Baseline EDSS, MSD and age on baseline BOD (ΔOFV=95, 35 and 26)

- BOD increases with greater baseline EDSS and duration of disease, and decreases with greater age

$$BOD_0 = \theta_1 \bullet (1 + 0.185 \bullet (BASE - 2.5)) \bullet (1 + 0.0364 \bullet (MSD - 6.22)) \bullet (1 - 0.15 \bullet (Age - 38))$$

2. Age on Emax (ΔOFV=22)

- Emax decreases with greater age

$$Emax = \theta_2 \bullet (1 - 0.027 \bullet (Age - 38))$$

CU lesions

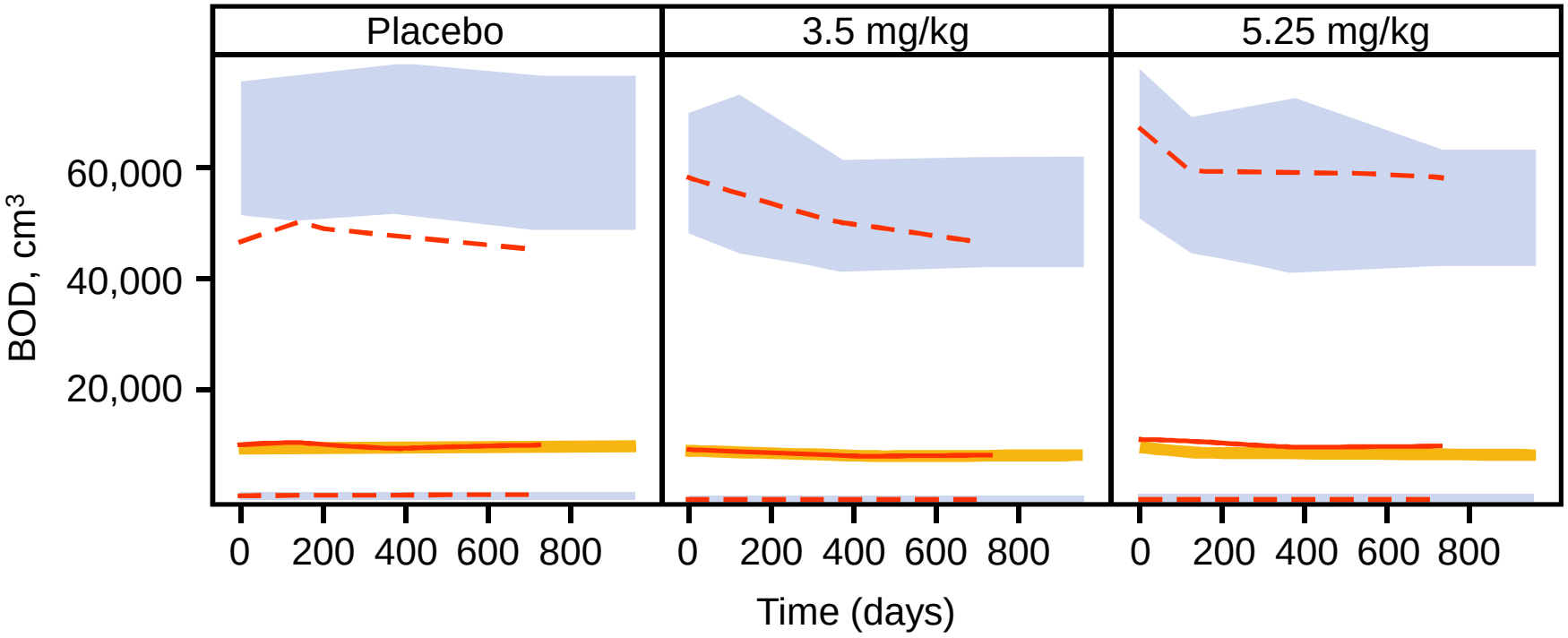
1. AGE on mean count (ΔOFV=110)

$$\lambda = \theta_1 \bullet (1 - 0.0348 * (Age - 38))$$

2. SEX on EC50 (ΔOFV=8): lower EC50 in men

MSD, duration of disease

Diagnostics: visual predictive check (BOD)



STEP II: BIOMARKER – CLINICAL ENDPOINTS MODELS

Clinical endpoint I: EDSS disease progression model for MS

DISEASE PROGRESSION MODEL

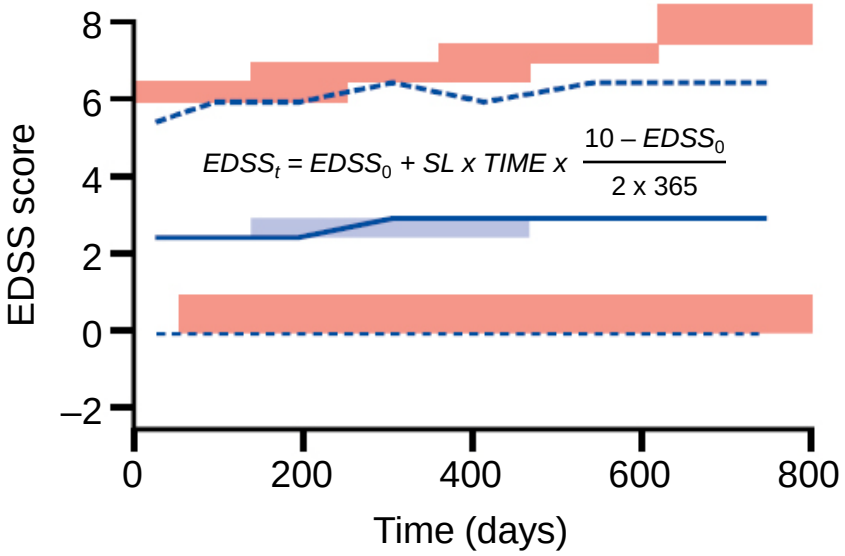
- Linear model where baseline ($EDSS_0$) and disease progression rate (SL) are estimated from the data
- Strong correlation $EDSS_0$ ~SL
- $EDSS_0$ related to patient age and disease duration

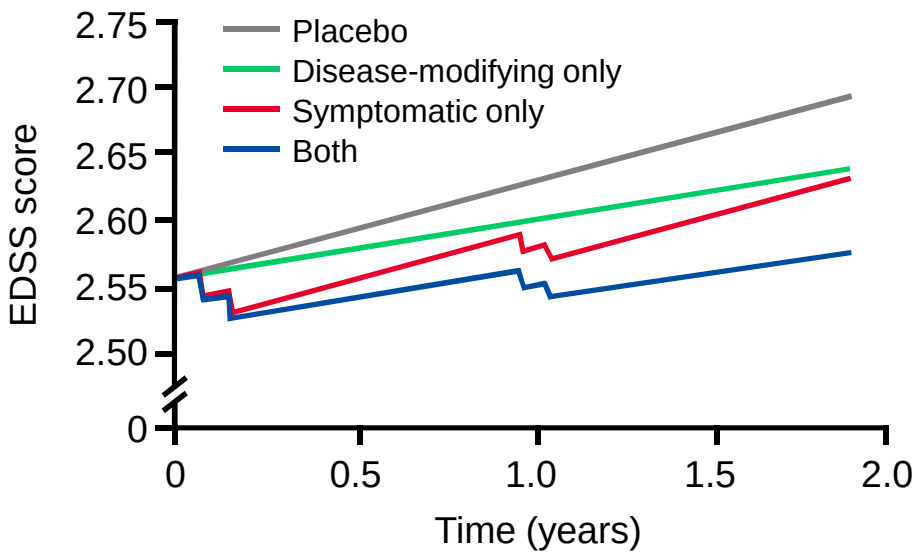
EXPOSURE – RESPONSE MODEL

- Dual effect: disease-modifying and symptomatic

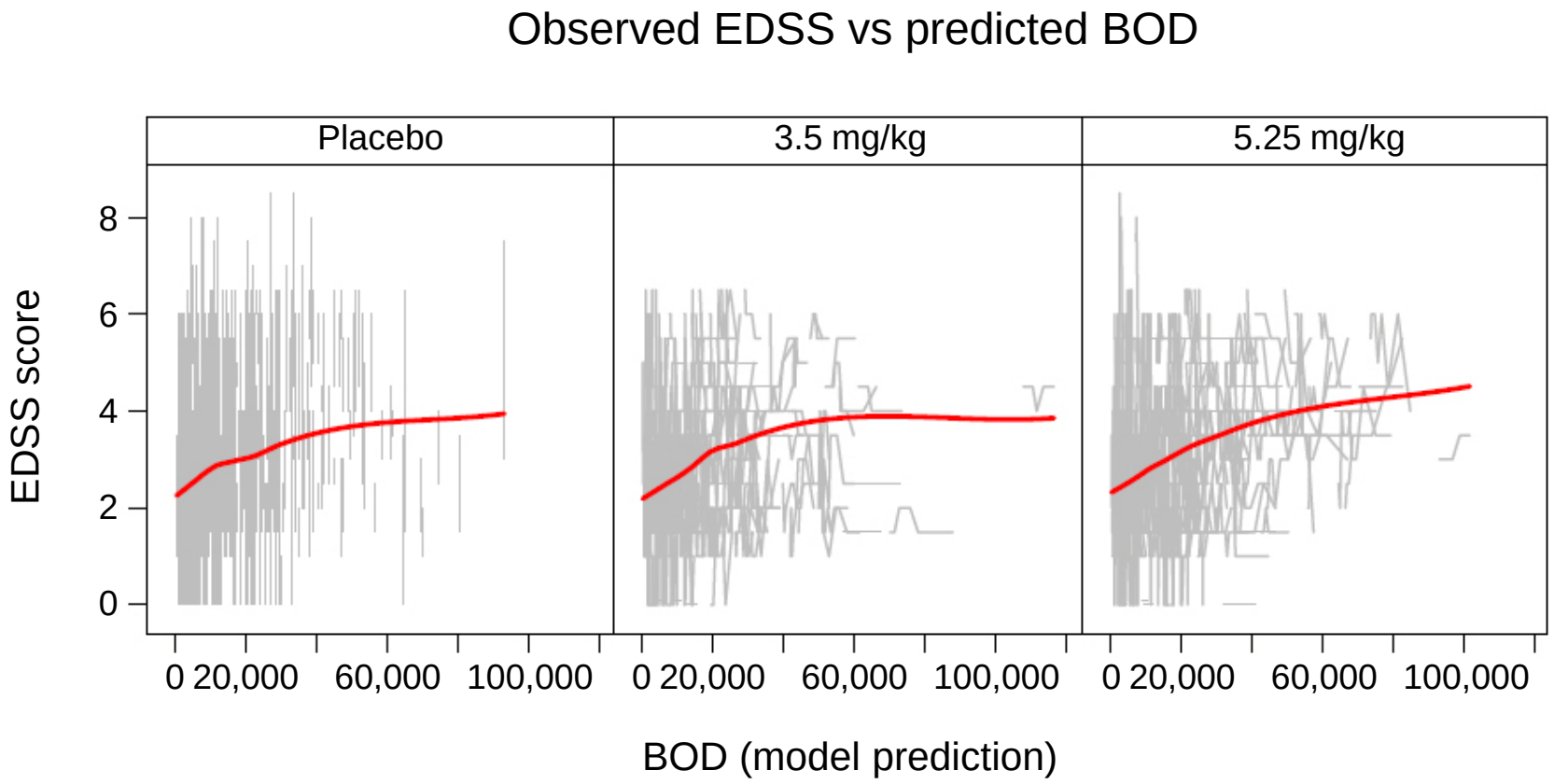
$$EDSS_t = EDSS_0 + ((1 - EffP) \times SL \times \frac{10 - EDSS_0}{2 \times 365} \times TIME) \times (1 - EffS)$$

$$EffS = \frac{E_{max} \bullet Exps_i}{Exps_{50} + Exps_i} \qquad Exps = \frac{CumDose \times CL_{CR\_median}}{CL_{CR}}$$

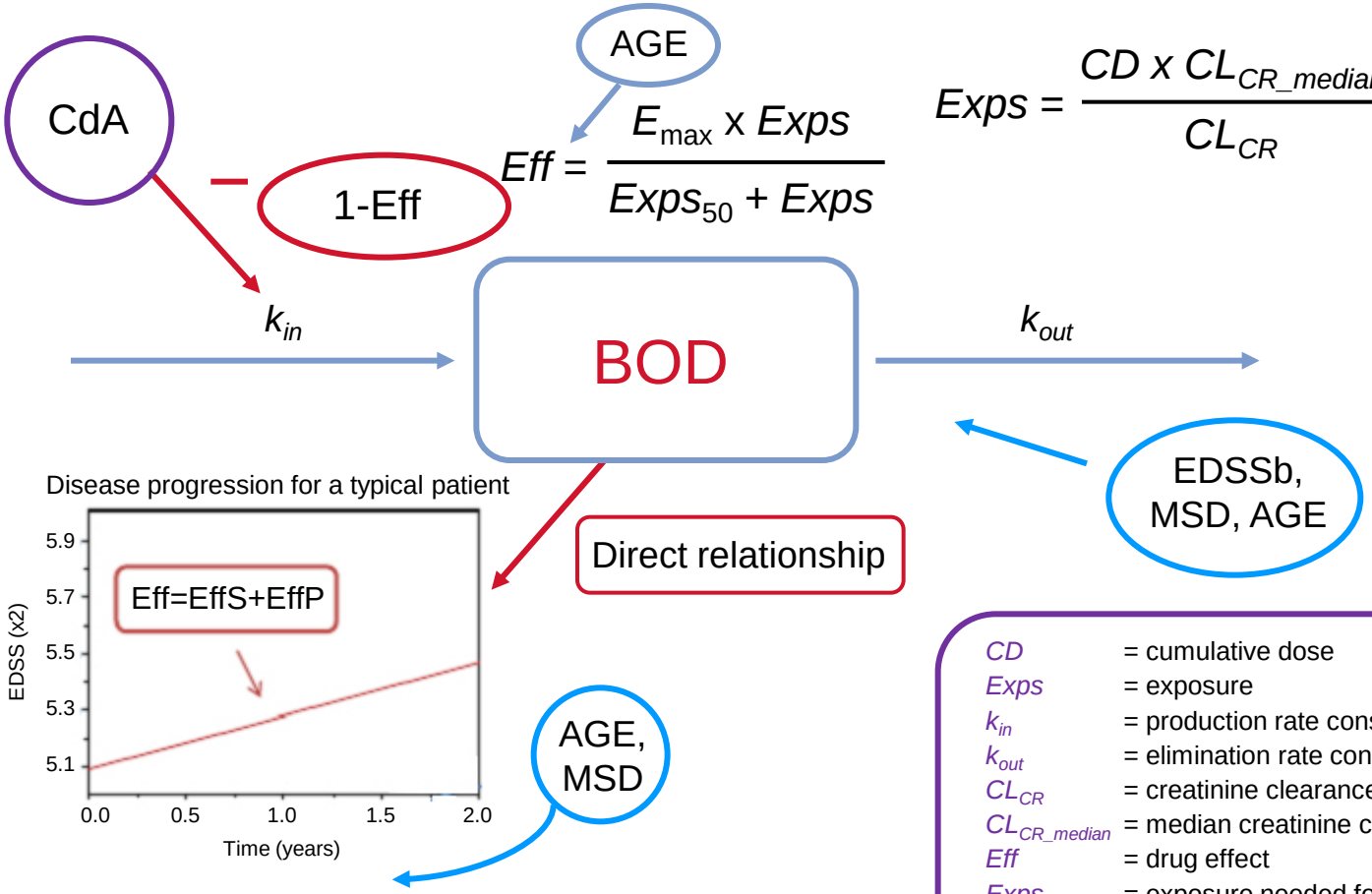




Exploratory analysis



Joint MRI burden of disease – EDSS model



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$Exps$	= exposure
k_{in}	= production rate constant
k_{out}	= elimination rate constant
CL_{CR}	= creatinine clearance
CL_{CR_median}	= median creatinine clearance
Eff	= drug effect
$Exps_{50}$	= exposure needed for half maximal effect
LNK	= coefficient of BOD – EDSS relationship

$$EDSS_t = \left(EDSS_0 \bullet S0MRI + (1 - EffP) \bullet \frac{SL \bullet (10 - EDSS_0) \bullet TIME}{2 \times 365} \right) \bullet (1 - EffS)$$

$$S0MRI = 1 + LNK \bullet \left(Ln(BOD) - 9.21 \right)$$

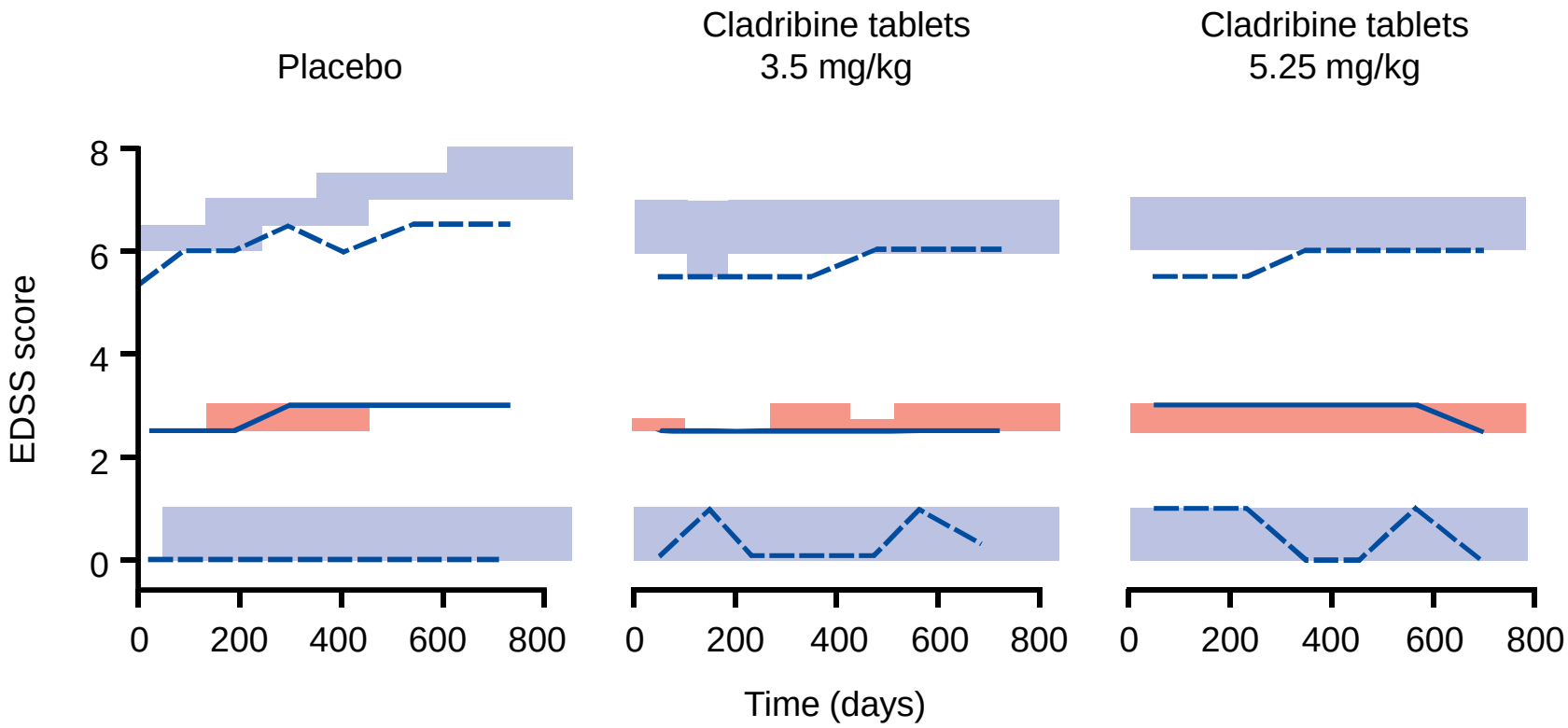
CdA, cladribine; MSD, duration of disease

Overview of key models

The overview of likelihood comparison for some of the tested models

Model	-2*log(likelihood)
EDSS model, with drug exposure	5961
EDSS model, with BOD	5929
EDSS model, with BOD and drug exposure	5878

Disease progression model with BOD and drug effect



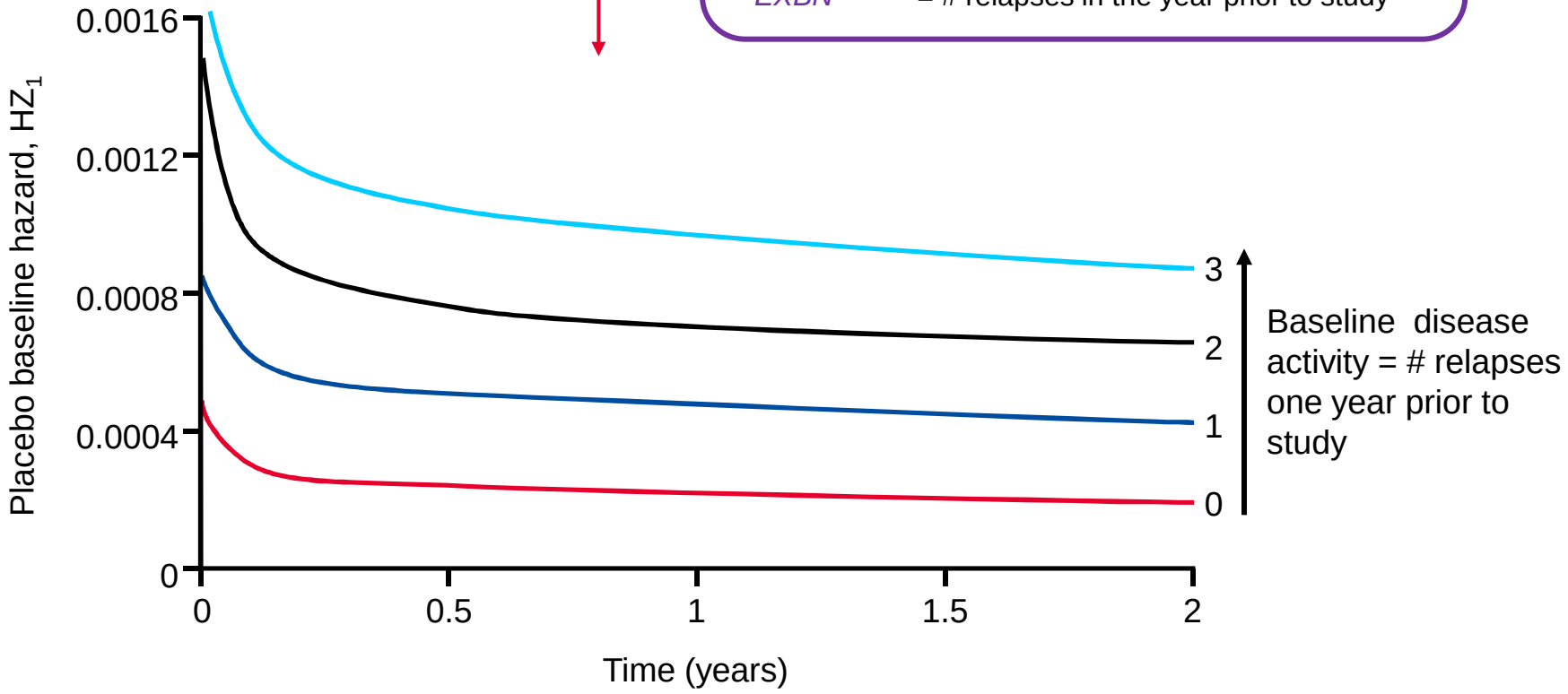
Clinical endpoint II: relapse rate

Baseline hazard (placebo model with covariate effect)

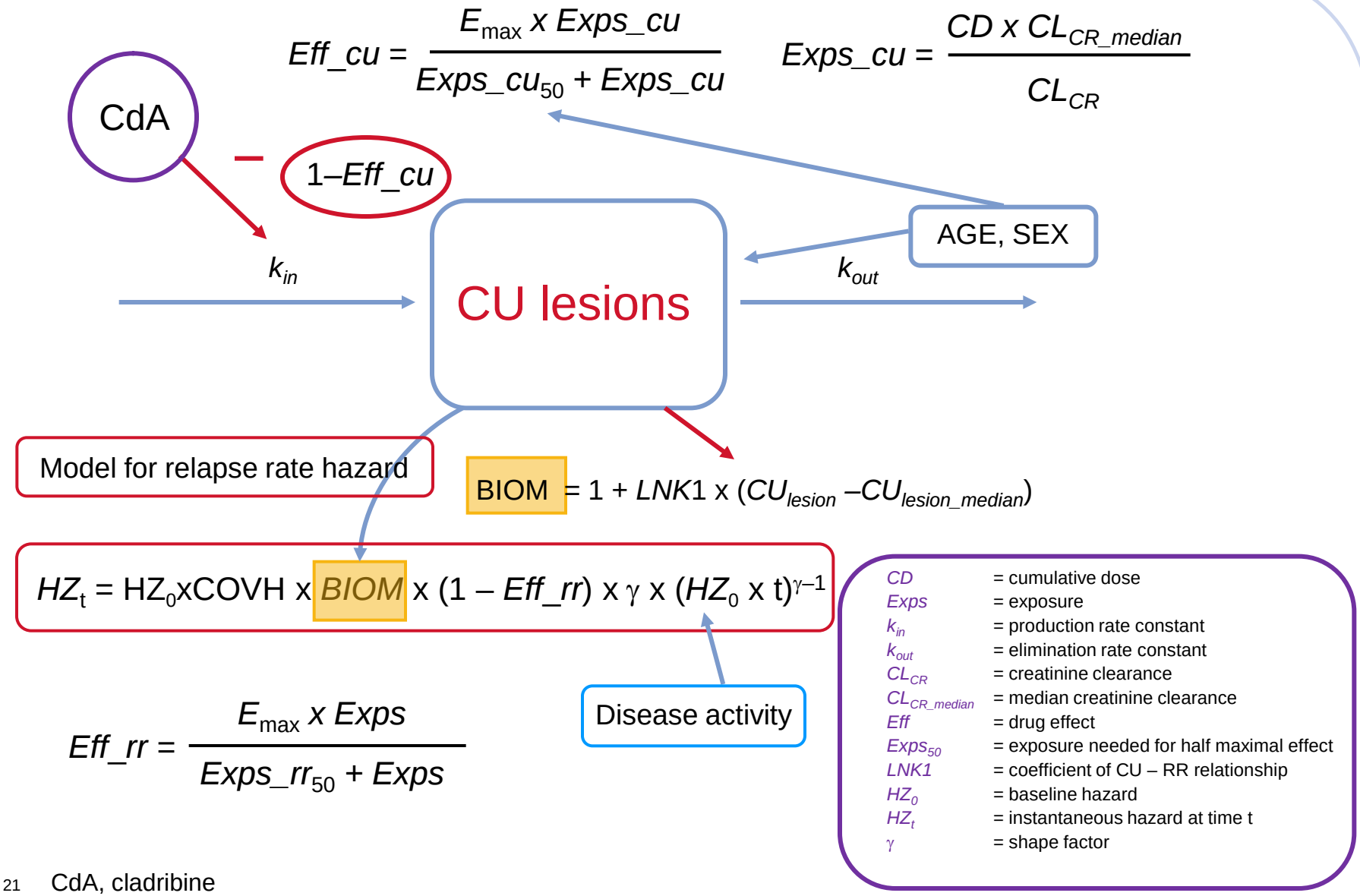
$$HZ_t = HZ_0 \times COVH \times \gamma \times (HZ_0 \times t)^{\gamma-1}$$

$$COVH = 1 + SI \times (EXBN - EXBN_{median})$$

HZ_0	= baseline hazard
HZ_t	= instantaneous hazard at time t
γ	= shape factor
SI	= slope of EXBN – HZ_t relationship
$EXBN$	= # relapses in the year prior to study



Joint MRI CU lesions – relapse rate model

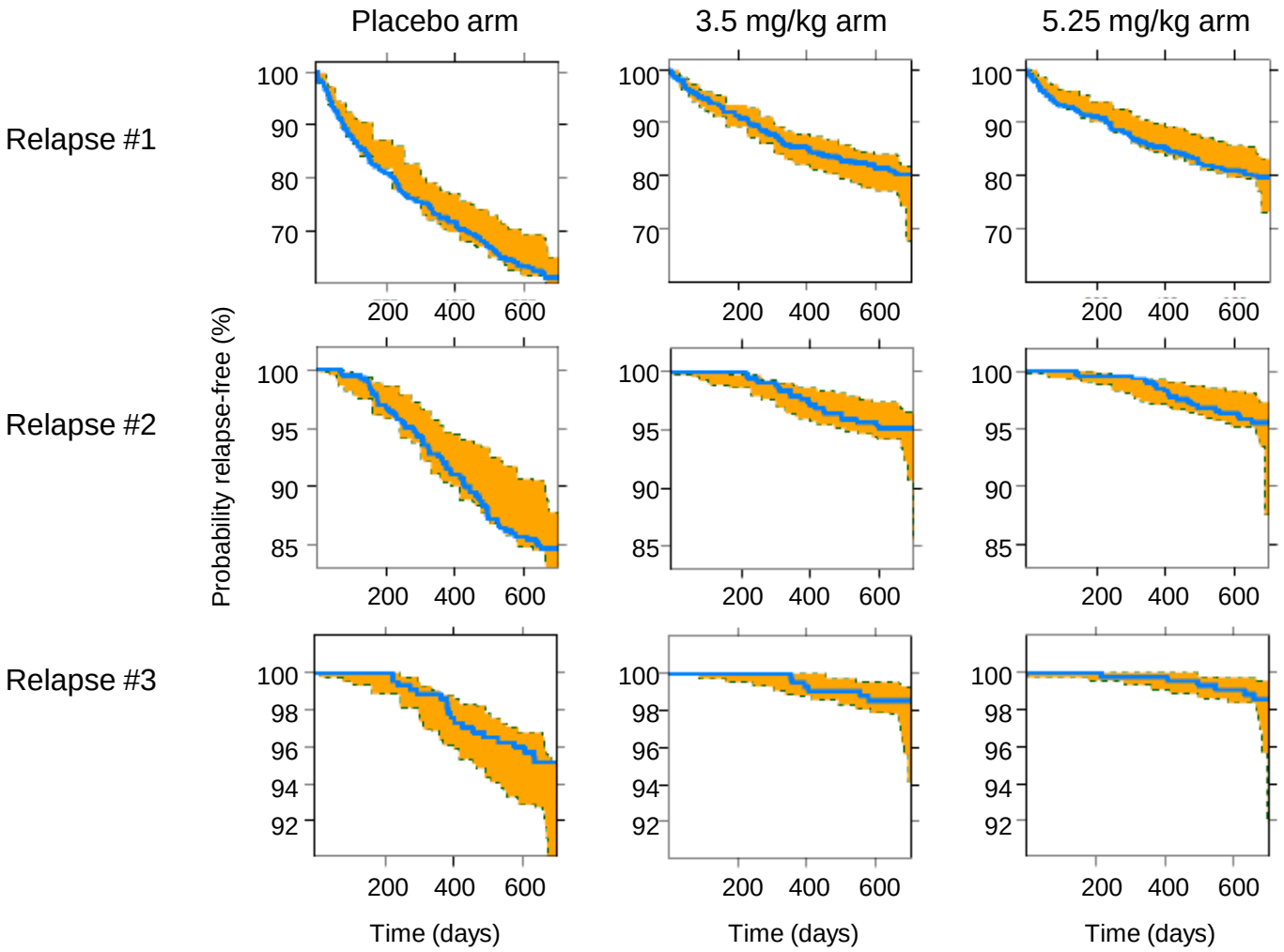


CdA, cladribine

Overview of key final RR and CU models

Model	-2*log(likelihood)
Final RR model, without CU lesions	7816
Final CU lesion model	7070
Joint CU and RR model with link	14850 <7070+7816=14886

Visual predictive check: joint CU and RR model



The blue line represents the observed Kaplan-Meier curve; the orange shaded area displays 90% prediction intervals derived from model simulations. Probability relapse-free is defined as percentage of patients not experiencing 1 (upper), 2 (middle), or 3 (lower) relapses

Conclusions

- Despite major technical challenges and poor mechanistic understanding about MRI–clinical outcome relationships, links between MRI lesion dynamics and clinical endpoints were established

- The proposed exposure–biomarker–clinical endpoints models integrate a significant amount of knowledge and data, representing a useful platform for quantitative understanding of the MS time course

Disclosures and acknowledgments

- This study was funded by Merck Serono S.A. – Geneva, Switzerland*

- R Savic and M Karlsson are paid consultants for Merck Serono S.A.*

- A Munafo is an employee of Merck Serono S.A.*

- Cladribine tablets treatment is not approved in the USA. Marketing authorization for the use of cladribine tablets in patients with RRMS has been granted in Russia and Australia (2010). Please refer to full prescribing information for further details on use.

*An affiliate of Merck KGaA, Darmstadt, Germany

BOD predictions w/ and w/o EDSS0 as covariate