CLADRIBINE TABLETS DOSING RULES

Simulation analysis of absolute lymphocytes counts (ALC) and relapse rate (RR) following cladribine treatment rules in subjects with relapsing-remitting multiple sclerosis (RRMS)

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PAGE 2017
Budapest, Hungary

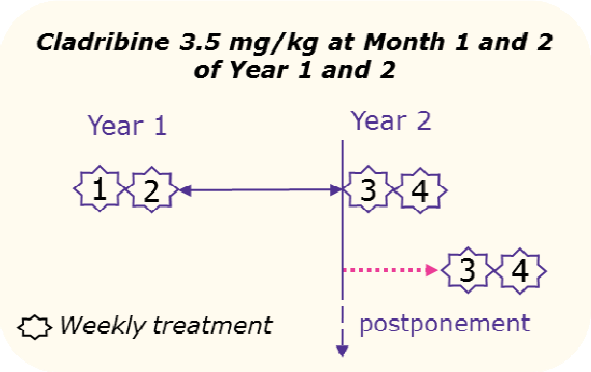
Outline

1. Objective
2. Clinical Trial Simulation workflow
3. Evaluation of alternative treatment rules
4. Conclusions

Treatment guidelines proposed to manage the risk of lymphopenia expected due to cladribine MoA

- Cladribine exerts sustained effects in RRMS by selective depletion of lymphocytes.
- A minority of patients develop Grade 3/4 lymphopenia at any time (25%, CLARITY study). Most of these occurred in patients receiving cladribine treatment when their absolute lymphocyte counts (ALC) were at Grade 2 or worse.

Proposed Risk Minimization: treatment guidelines



Alternative rules*:*

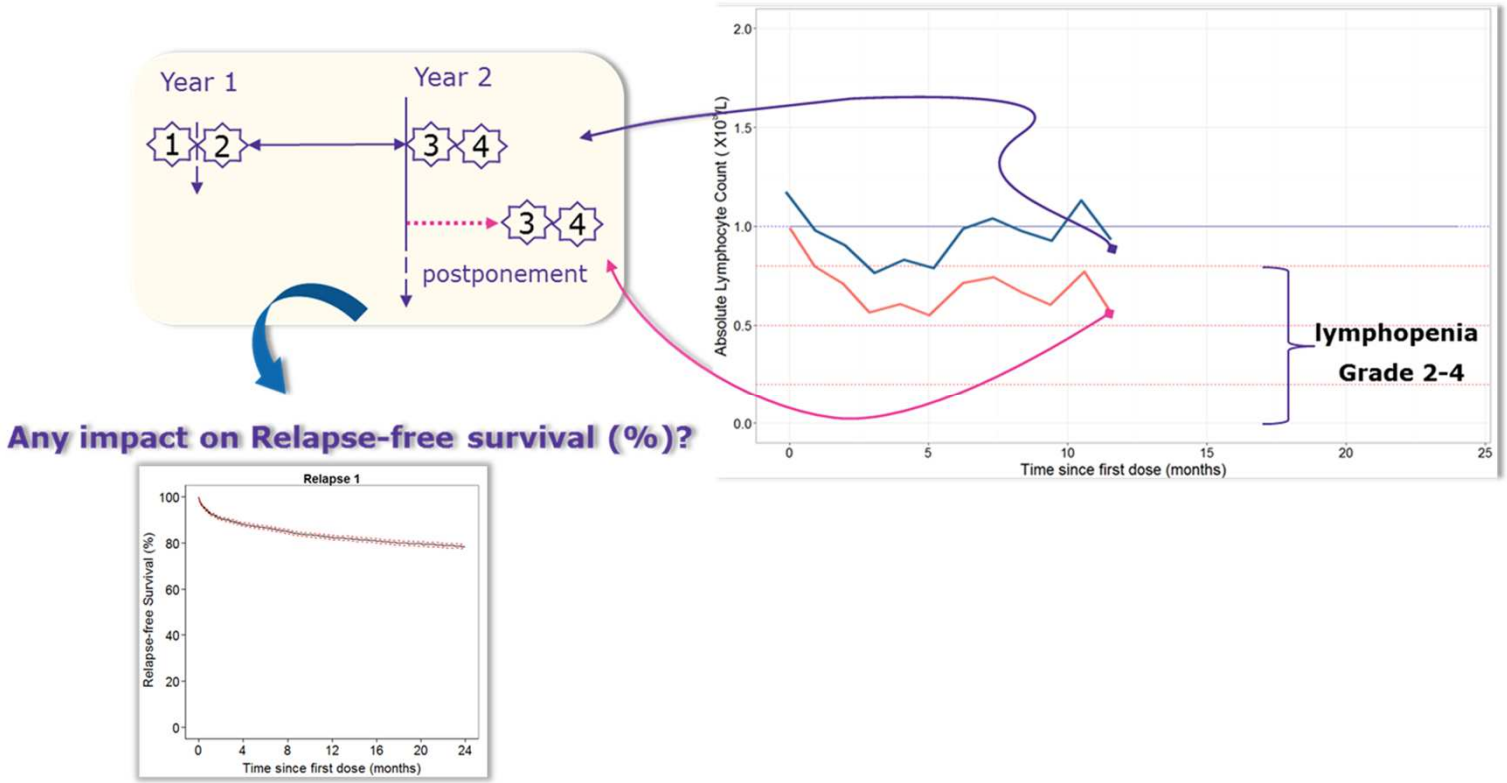
Treatment postponements during Year 2 allowed in blocks of 1/2/3 months in patients with lymphopenia Grade 2-4 or 3-4.

- *If, after three postponements, a patient's ALC value had not recovered to Grade 0/1, the treatment would stop*

Assessing the impact of treatment guidelines on the occurrence of relapses requires clinical trial simulations

- Obtain projections for **Relapse Rate** (RR) and the **Absolute Lymphocyte Counts** (ALC) dynamics by accounting for treatment delays or cancellations in patients presenting lymphopenia of Grade 2-4.

- Investigate the **impact of postponement of dosing or cancellation of treatment** with cladribine tablets on the probability of being relapse free over time in RRMS subjects.



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1 Objective

2 **Clinical Trial Simulation workflow**

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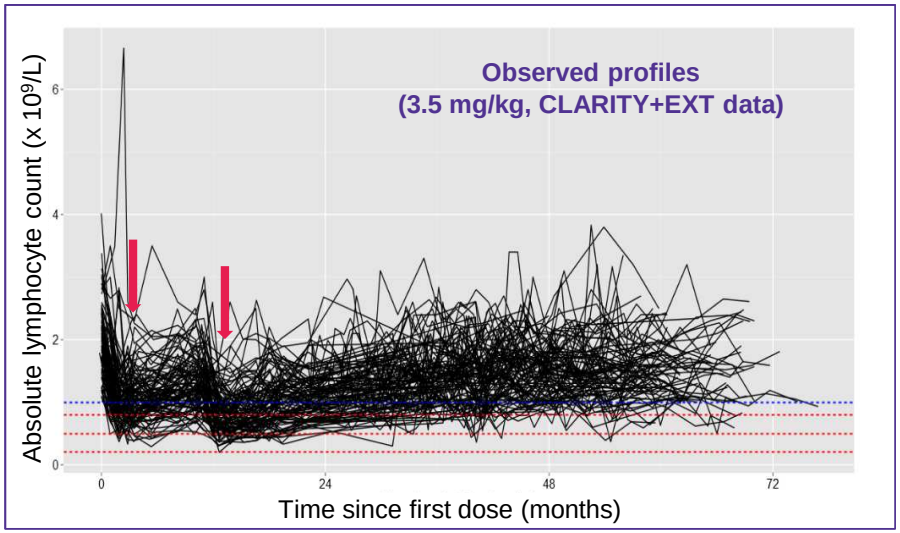
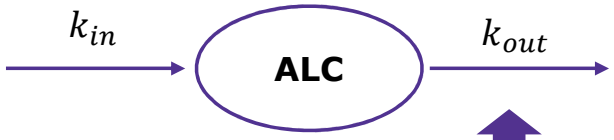
Satisfactory model of ALC *vs.* time and exposure
Prior ALC modeling information

Population PD modeling approach*

Indirect response model with cladribine stimulating the loss function (lymphocyte perish rate) through an E_{max} drug-effect relationship to cladribine exposure



*CLARITY, CLARITY Extension and Oracle Studies



Stimulation function: $1 + \frac{E_{max} * C_P}{C_{50} + C_P}$

dependent on the time-varying cladribine concentration C_P

- Renal clearance proportional to the individual $CR_{CL_i}(t)$
- IIV on *ALC0,* MRT (mean residence time), and C_{50}
- Covariate SEX on cladribine potency parameter C_{50}

Good **description of ALC dynamics** following treatment with cladribine according to different schedules

Good capabilities in **predicting different CTCAE grades** of lymphopenia

Credits: Pharmacometrics group at Uppsala University

Modelling shows that 3.5 mg/kg dose is already at the shoulder of exposure-efficacy curve

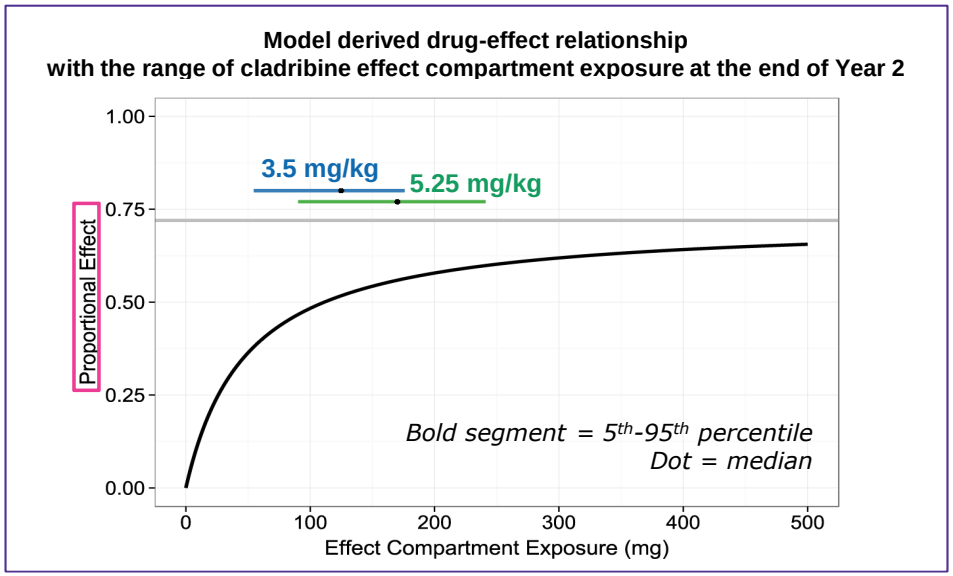
Prior RR modeling information

Population Repeated Time-to-Event (RTTE) model of qualifying relapses*

- Weibull hazard function with decreasing hazard over time
- Inhibitory Emax dose-effect relationship on hazard, using cumulative dose with implemented decay as effect driver

$$h(t) = h_0(t) * (1 - \frac{E_{max} * Exps(t)}{D_{50} + Exps(t)})$$

Effect compartment exposure, linking the short systemic exposure to the long-lasting effect



*CLARITY, CLARITY Extension and Oracle Studies

- Baseline hazard (h_0) given by: $h_0(t) = \lambda\gamma(\lambda t)^{\gamma-1}$
- Dose adjusted for $CR_{CL_i}(t)$ centered on population median
- IIV and covariate EXNB (number of exacerbation prior to study entry) on λ

Good **description of the time to occurrence (and re-occurrence) of qualifying relapses**

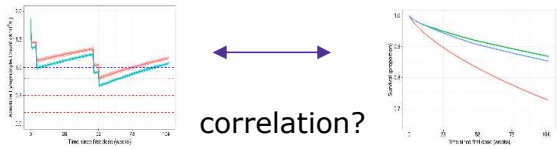
Showed that the **3.5 mg/kg cumulative dose is truly appropriated** in reducing the risk of relapses

Credits: Pharmacometrics group at Uppsala University

Simulation strategy relies on a complex workflow

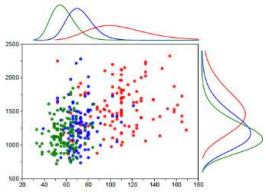
1. Exploratory and Graphical Analysis

ALC model **RTTE model for RR**



correlation?

2. Virtual subjects generation

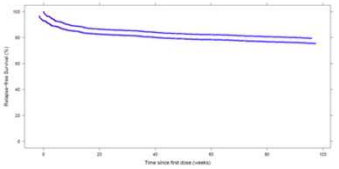


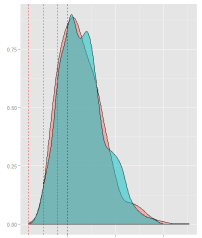
Covariate resampling

3. Clinical Trial Simulation to reproduce CLARITY scenario

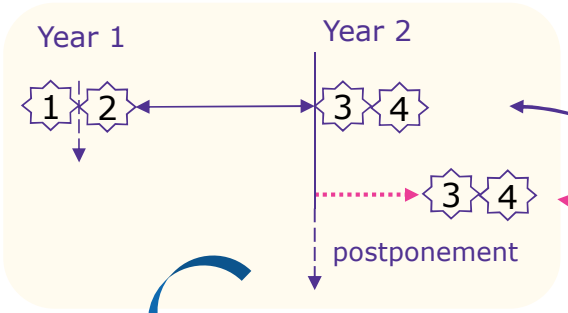
ALC distributions at Week 49

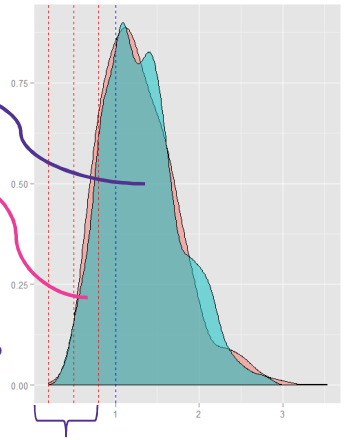
Relapse-free survival (%)





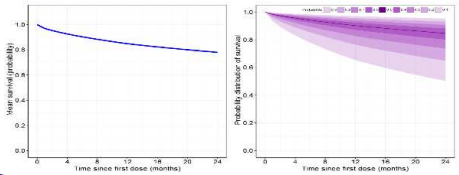
4. Simulation of alternative treatment rules





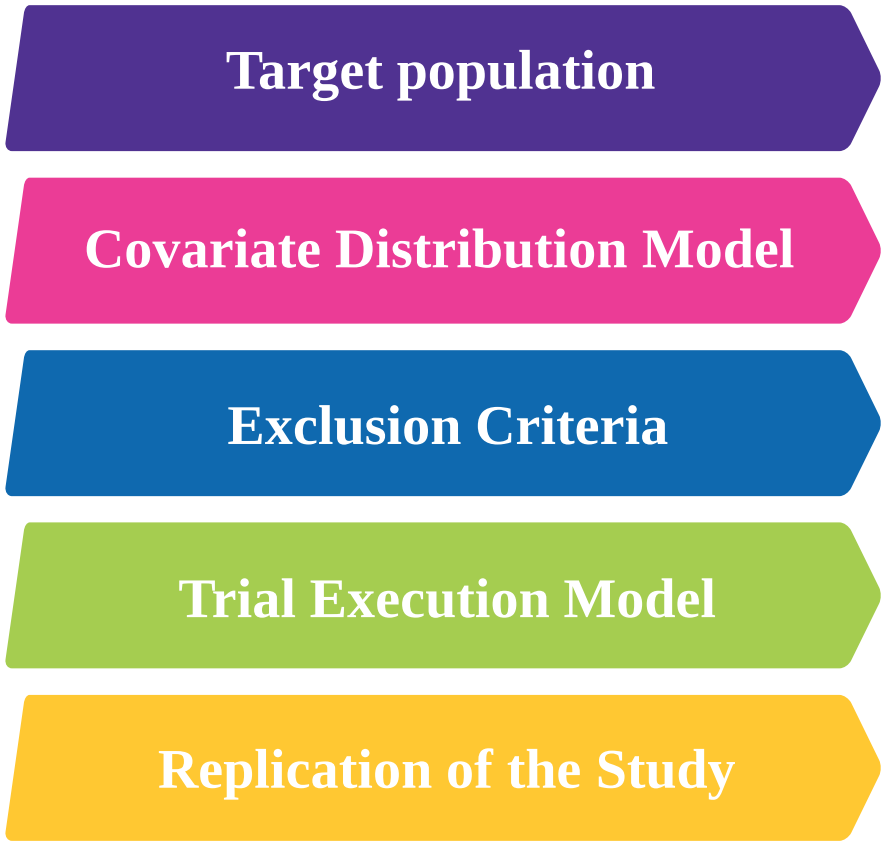
lymphopenia Grade 2-4

Any impact on Relapse-free survival (%)?



Simulx *was employed for simulations, with models encoded in MLXTRAN*
http://lixoft.com/products/simulx/

CLARITY was considered as the clinical trial to be simulated
Covariate and execution models



- **Subjects with RRMS** from the Phase III cladribine trial **(CLARITY)**
- **Sampling** of model covariates from **observed** distributions by accounting for their relationships (**covariance**), and assignment to each virtual subject
- Covariates considered as constant (no time-varying)
- Patients with **baseline lymphopenia** Grade 1-4 (as part of the risk minimization plan)
- **Cladribine** total cumulative dose of **3.5 mg/kg** over 4 or 5 days at **Month 1 and 2 of Year 1 and 2**
- No randomization rules or deviations from the protocol
- Initial virtual population of **5000 subjects**
- Study **size increase** by blocks of 2000 subjects until model **output comparable** with observations

Holford N, et al. *Clin Pharmacol Ther* (2010)
Tannenbaum SJ, et al. *J Pharmacokinet Pharmacodyn* (2006)

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Generating individual virtual subjects representative of subjects in CLARITY study

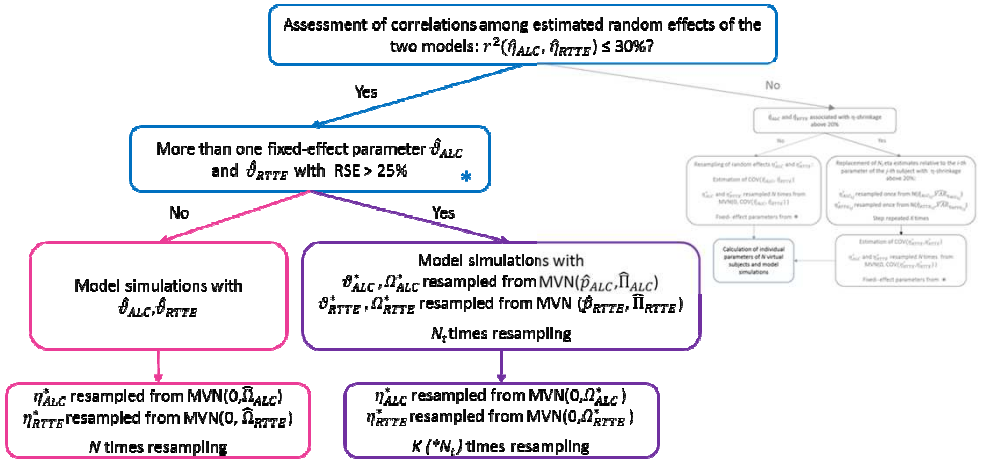
Input-Output Model

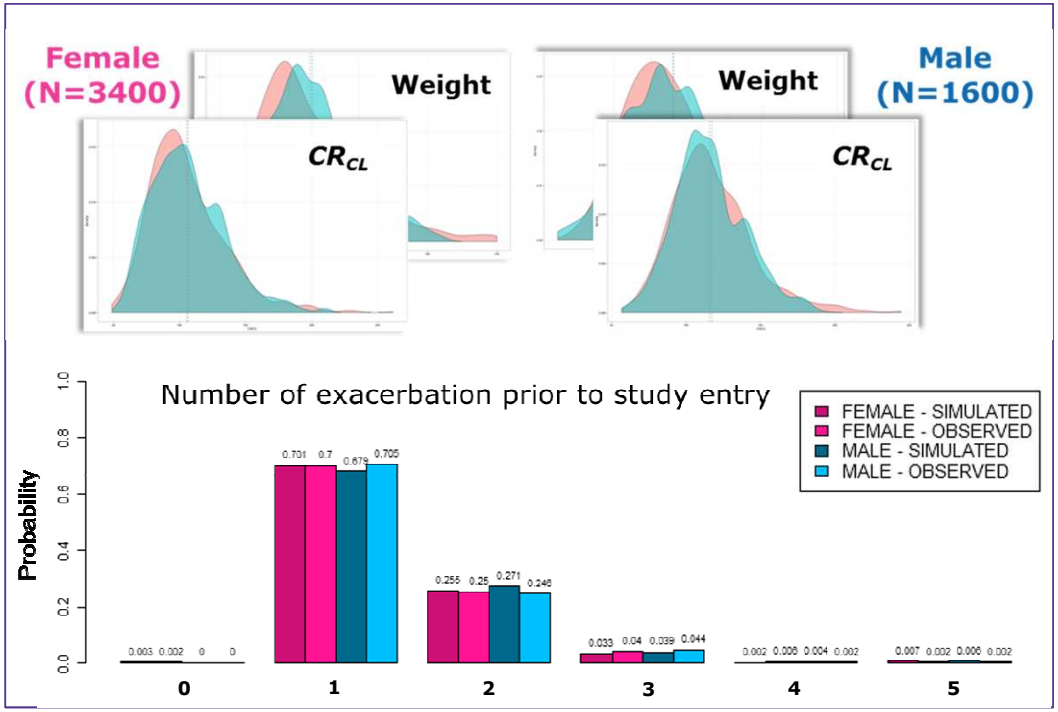
Individual model parameters

Covariate Model

Physiologically reasonable covariate distributions

Decision tree for virtual population generation

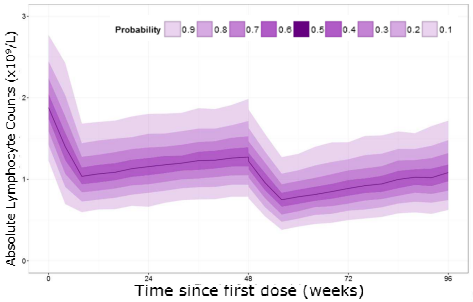


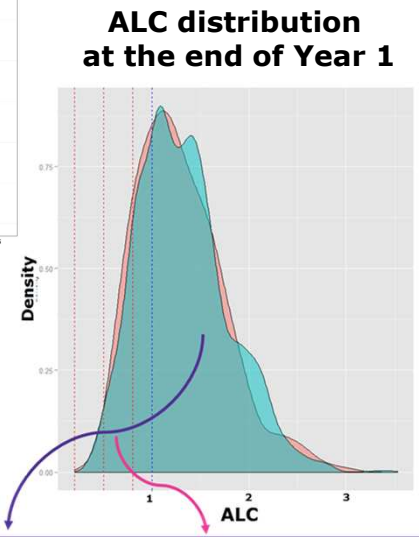


Using 5000 virtual patients, the simulation workflow could be validated, reproducing CLARITY scenario

ALC model simulations

Reproducing subject distributions within lymphopenia grades

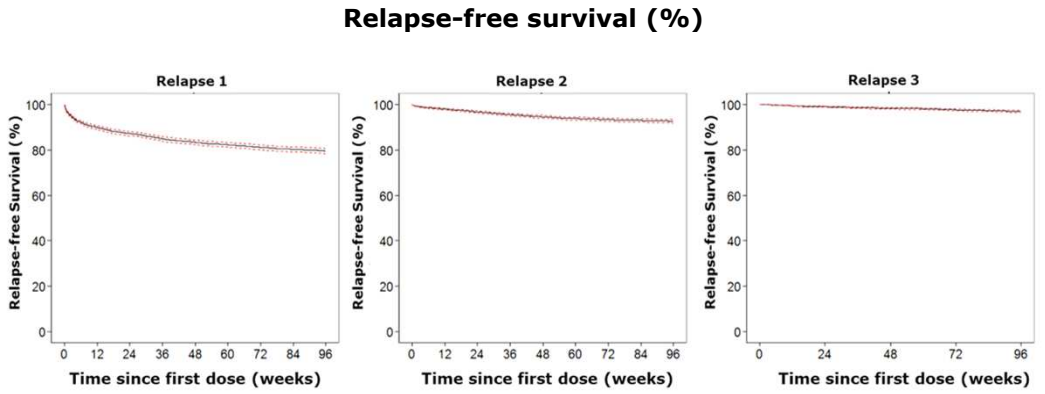




	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
observed %	72.4	15.7	11.4	0.5	0
simulated %	74.7	14.4	10.0	0.9	0

RTTE model simulations

Reproducing proportions of subject not experiencing 1-6 relapses

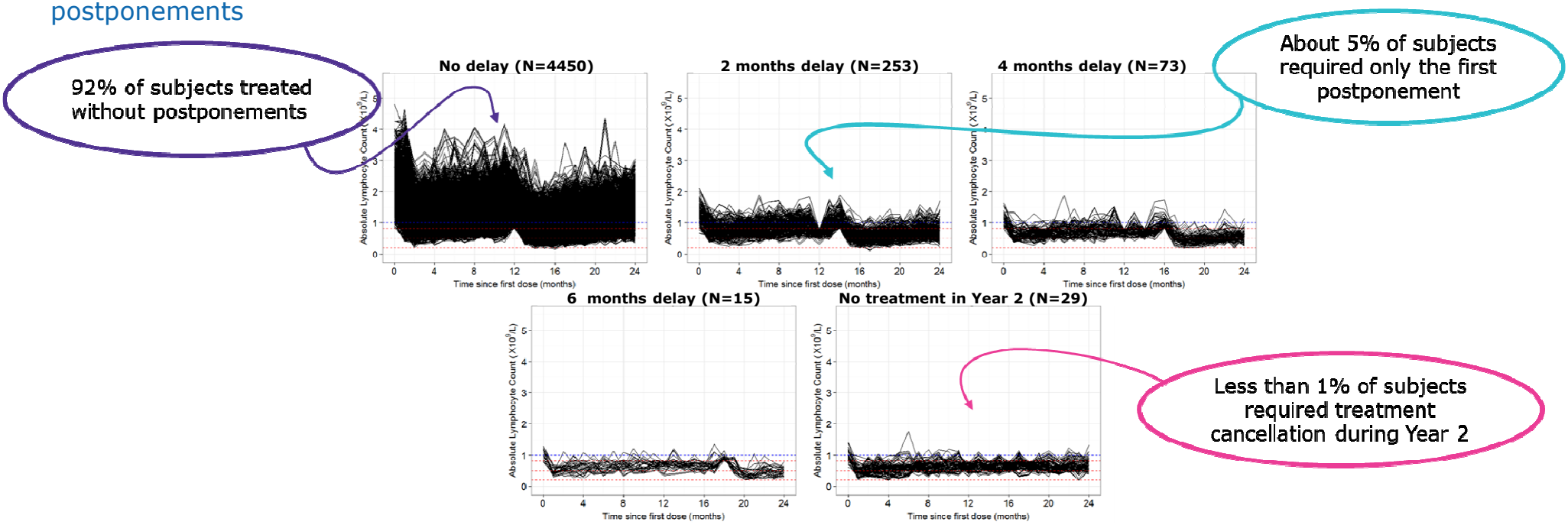


		Relapse 1	Relapse 2	Relapse 3	Relapse 4	Relapse 5	Relapse 6
End of Year 1	observed %	86.9	98.3	100	100	100	100
	simulated %	83.5	94.7	98.5	99.7	99.8	99.9
End of Year 2	observed %	79.3	94.9	98.6	99.8	100	100
	simulated %	79.6	92.7	97.0	99.2	99.7	99.9

Virtual patients treated with cladribine total cumulative dose of 3.5 mg/kg according to the CLARITY trial protocol

The simulation allowed to identify those virtual patients requiring postponement, based on their ALC observed at the end of Year 1

- Regardless of block definition (1, 2 or 3 months) only 3% of virtual subjects required two or more treatment postponements



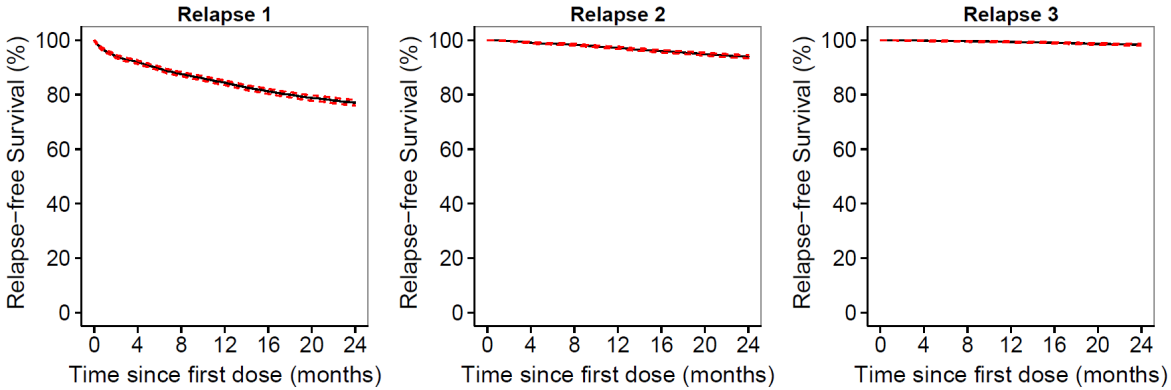
Alternative scenario 2:

Treatment postponements during Year 2 allowed in blocks of two months in patients with lymphopenia Grade 2-4

- Of those who qualified for postponements (lymphopenia Grade 2-4), less Grade 3-4 lymphopenia was observed at anytime during Year 2 when applying the postponement rules.

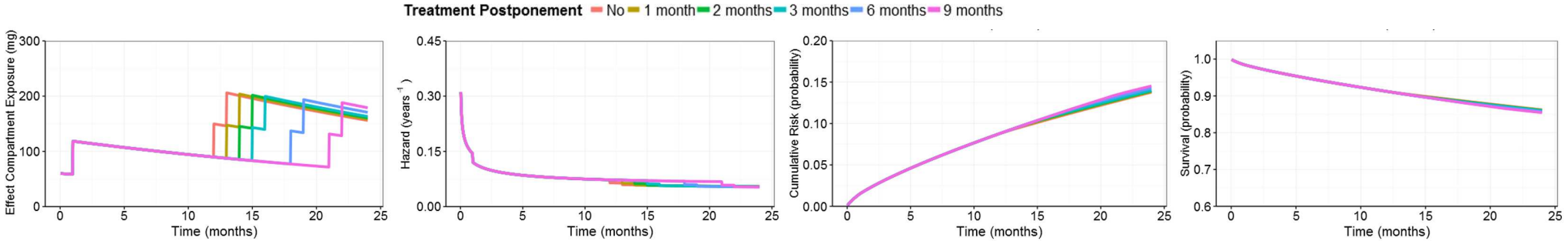
The dosing algorithms had no impact on the probability of having a relapse over the 2-year treatment duration

- **No impact** of treatment rules was observed (in the virtual population) on the probability of having 1-6 relapses within 24 months treatment window



- Differences in the clinical relevant outcome appear small, suggesting that treatment postponements during Year 2 do not lead to loss of efficacy

Model predictions for a typical subject



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Postponing the Year 2 treatment is an appropriate risk mitigation measure for patients with lymphopenia Grade 2-4 at the end of Year 1

- **Alternative treatment rules** were investigated by obtaining projections for the Absolute Lymphocyte Counts (ALC) dynamics and Relapse Rate (RR) and in different scenarios.

- Results from this simulation analysis **support treatment guidelines** proposed to decrease risk of developing severe lymphopenia following cladribine treatment, while preserving cladribine efficacy on the considered clinical endpoint.

- As part of the **risk minimization strategy** to reduce the risk of lymphopenia, it is proposed to postpone cladribine treatment in year 2 until ALC have recovered to Grade 1 or better; should this not happen within 6 months, the treatment should be discontinued.
  - Very few subjects (1% or less) would not recover to Grade 1 or 0 within an additional 6 months.
  - In those who qualified for postponements (8% of virtual subjects), the proportion reaching Grade 3/4 lymphopenia at some time in the study is decreased (from 85% to 76%) when the mitigation rule is applied.
  - Such a delay of up to 6 months has essentially no effect on the probability of experiencing relapses during the second year of cladribine treatment.

Acknowledgements

Merck colleagues

- Clinical Team and Project Team
- Pascal Girard

Externals

- Prof. Marc Lavielle
- Pharmacometrics group at Uppsala University, especially Prof. Mats O. Karlsson, Siv Jönsson, Ana Novakovic, Emilie Schindler and Anders Thorsted