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Objective

- “One dose fits all” concept still dominates in clinical development. Pharmacometrics could contribute to implement Personalized Healthcare (PH).
- Over the past decade, several S1P receptor modulators have been brought into clinical development: fingolimod, siponimod, ceralifimod, ponesimod, CS-0777, RPC1063, MT-13-03, GSK2018682.
- S1P (Sphingosine 1-phosphate) receptor modulators prevent the egress of lymphocytes from lymph nodes, reducing the amount of circulating lymphocytes and their potential to transit to the brain and damage neurons in relapsing forms of multiple sclerosis (RRMS).
- In this family of compounds, the extent of drug effect on lesion count is assumed to be correlated to the one on lymphocytes, which represents an excellent biomarker. On average, the disease burden is expected to be reduced in patients with decreased absolute peripheral lymphocyte counts.
- As a consequence of their therapeutic effect, S1P receptor modulators also induce lymphopenia.
- Assessing the variability of lymphocyte response to treatment is critical in order to avoid
 - Severe lymphopenia and infection, if the lymphocytes are too low,
 - Treatment failure due to lack of efficacy, if the lymphocytes remain too high.
- Siponimod, is a S1P receptor modulator currently in Phase 3. Model-based simulations were performed to investigate how dose individualization could improve its efficacy and safety.

Methods

- A simulation framework (Figure 1) using public-domain information was developed to describe the clinical effect of siponimod.
 - A PK model and a drug-specific model linking siponimod concentration to lymphocyte count [1]: an indirect-response, drug effect inhibiting the production rate.
 - A drug-independent model linking lymphocyte count to Gd+ lesion count [2]: a negative binomial model for the log of lesion number.
 - A drug-independent model linking lesion count to relapse rate [3]: regression model.

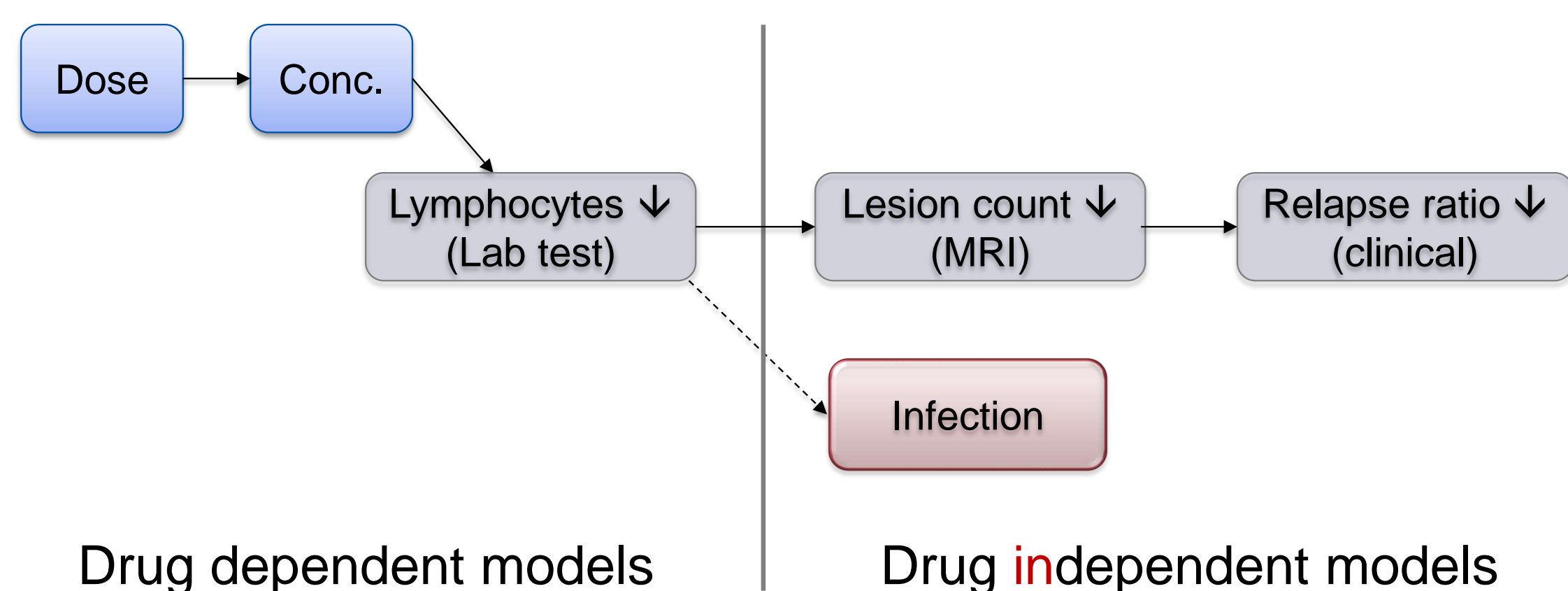


Figure 1: Simulation framework for siponimod

- Using this model, individual lymphocytes time profiles were simulated. A desirable range for lymphocyte counts was defined as being between 0.2 to 0.5.10⁹/L. Indeed, a dose bringing the average lymphocyte count into the window of 0.2 to 0.5.10⁹/L would translate into the appearance of less than 0.5 new Gd+ lesions on average. (i.e. approximately a 80% reduction) [4].
- It can be assumed that patients treated with siponimod could have their lymphocyte level at steady state reached 2 weeks after treatment initiation [4].
- Five different daily siponimod dose regimens were tested (Figure 2):
 - Placebo
 - 1 mg fixed dose
 - 2 mg fixed dose
 - 1 mg starting dose with one dose adjustment (-50% or +100% when above or below the target) 2 weeks after treatment initiation
 - 1 mg starting dose with two dose adjustments 2 and 4 weeks after treatment initiation

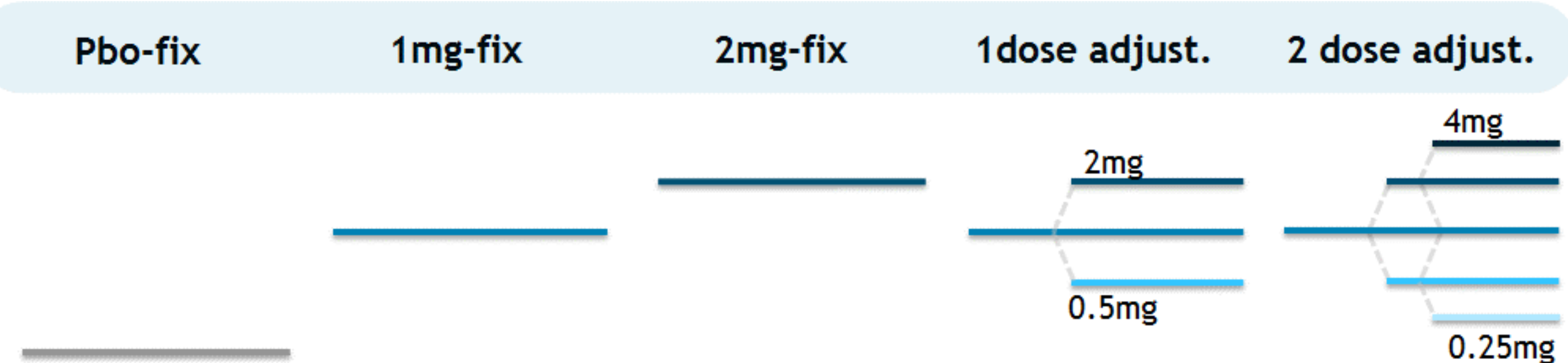


Figure 2: Simulation scenarios

References

[1] Pigeolet E. et al. Population PKPD modeling of dose-response and time course of peripheral lymphocytes after single and repeated administration of the S1P1/5 modulator, BAF312, in healthy volunteers. PAGE 20 (2011) Abstr 2089 [www.page-meeting.org/?abstract=2089].

[2] Hartung H. et al. The selective sphingosine 1-phosphate receptor modulator siponimod (BAF312): magnetic resonance imaging lesion and lymphocyte relationship in a phase 2 study in relapsing-remitting multiple sclerosis. European Committee for Treatment and Research in Multiple Sclerosis (2012).

[3] Sormani M. et al. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. Ann Neurol (2009) 65: 268-275.

[4] Gergely P. et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. Br J Pharmacol (2012) 167:1035-47.

[5] Selmaj K. et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. Lancet Neurol (2013) 12: 756-767.

Results: simulations of individual profiles

- Figure 3 shows three individual lymphocyte count profiles according to each dosing scenario and illustrates the need for dose adjustment in some of them.
- Subject 1 is within the target at 1 mg and would not need dose adjustment, however this subject could be exposed to grade 4 lymphopenia (lymphocyte<0.2.10⁹/L) at 2 mg.
- Subject 2 would need a dose of 4 mg to reach the target, thus 2 dose adjustments.
- Subject 3 would experience grade 4 lymphopenia (lymphocyte<0.2.10⁹/L) at 1 and 2 mg, one dose adjustment would be necessary to reduce the dose at 0.5 mg.

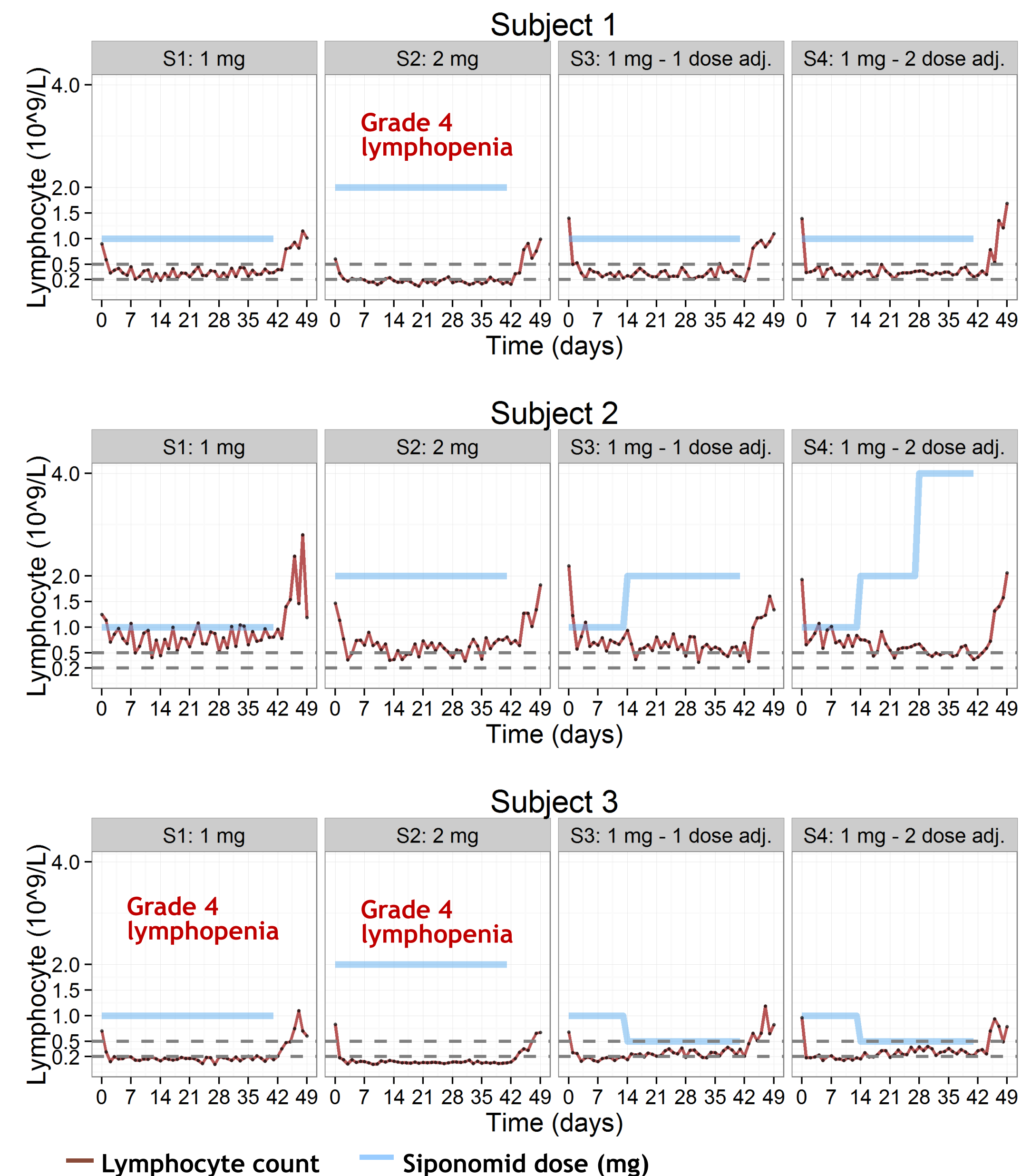


Figure 3: simulations of individual lymphocyte profiles

Results: simulations of a large population

- Simulations of lymphocyte counts and clinical efficacy (lesion count and relapse rate ratio) were simulated on a large population (N=10000) of virtual patients.
- Figure 4 shows:
 - The qualification of the simulation framework against BOLD Phase 2 study.
 - the impact of the different scenarios on lesion count, all scenarios show comparable efficacy though with slightly better results at 2 mg and less variability in dose adjustment scenarios.

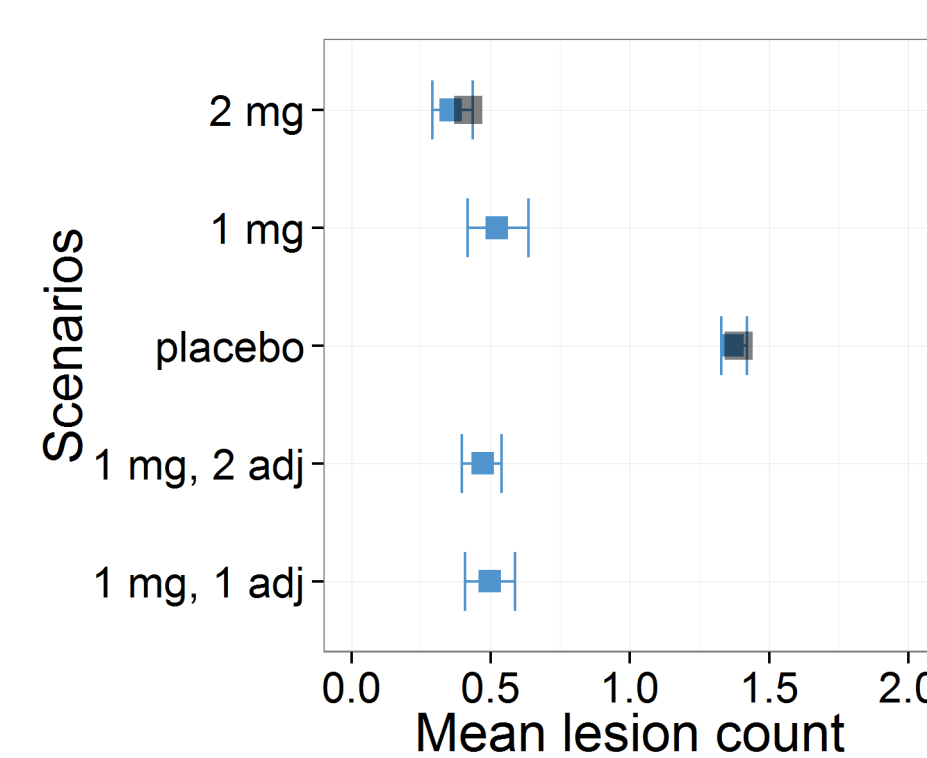


Figure 4: lesion count simulations and qualification of the M&S framework

- Simulation of clinical efficacy and potential safety (Figure 5) showed:
 - A better efficacy with 2 mg.
 - That 1 mg fixed dose can be rejected as it provides the worst risk/benefit ratio.
 - Less potential safety concern with dose adjustment regimens representing the best risk/benefit ratio.

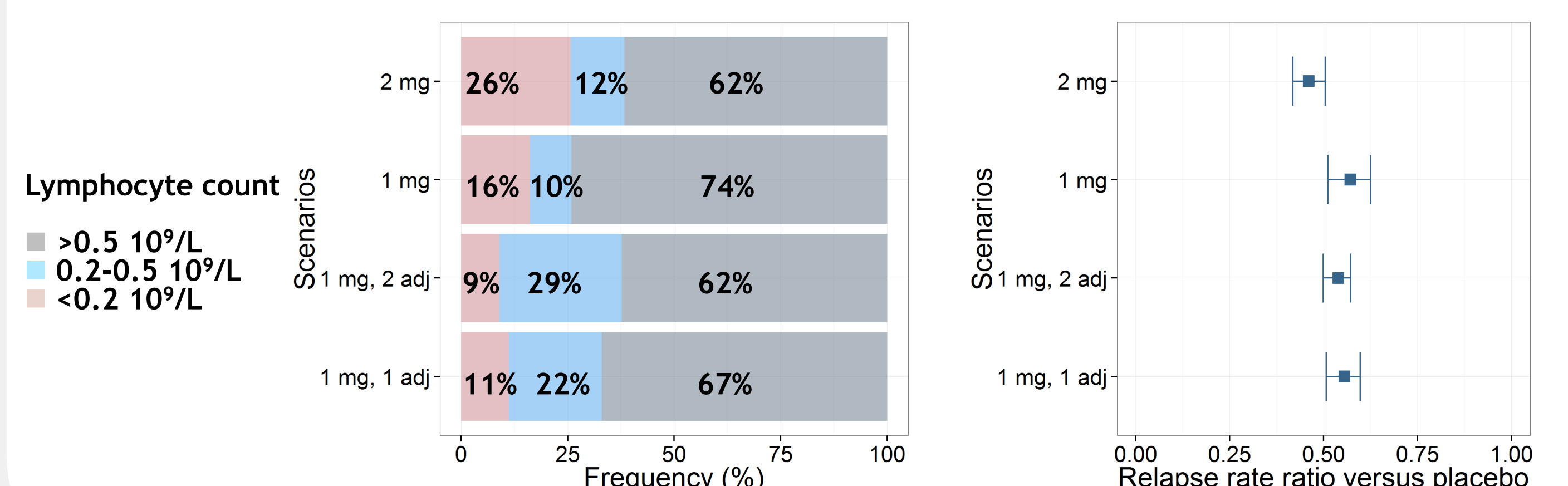


Figure 5: Simulation of lymphocyte count categories and relapse rate (with 90% prediction interval)

Conclusions

- Simulations showed the benefit of dose adjustments during the first weeks of treatment with siponimod using a simple dose adjustment algorithm.
- This approach is particular interesting for drug classes where efficacy and safety can be monitored by the same biomarker.
- Model-based simulations can help delineate best dosing strategies to maximize therapeutic index.