Electronic Supplementary Material (Online Resource)

Journal *Clinical Pharmacokinetics*

Original Research Article

Exposure-bleeding count modeling of emicizumab for the prophylaxis of bleeding in persons with hemophilia A with / without inhibitors against factor VIII

Running Heading

Exposure-bleeding count modeling of emicizumab in hemophilia A

Authors

Fredrik Jonsson[1], Christophe Schmitt[2], Claire Petry[2], Francois Mercier[2], Nicolas Frey[2], Sylvie Retout[2]

[1]qPharmetra, Cary, NC, USA; [2]Roche Pharma Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center, Basel, Switzerland

Corresponding Author

Fredrik Jonsson

Address: qPharmetra, 506 Grant Forest Lane, Cary, NC 27519, USA

Email: Fredrik.Jonsson@qpharmetra.com; Tel: +46 73 800 37 01

Supplementary Material

Dropouts

The number of dropouts was small: a total of 7 PwHA withdrew from the studies due to adverse events (n=4), investigator decision (n=1), personal reason (n=1) and lost to follow-up (n=1). At the clinical cut-off date used for this analysis, no participant withdrew the study for lack of efficacy.

Distributional assumptions

The distributions of the estimated individual mean daily bleed frequency versus estimated individual variance are given in **Figure S1**. Because of the log-log scale, the graph does not include the individuals who did not experience any bleeds. A modest over dispersion (i.e. variance> mean) can be observed. There is substantial inter-individual variability for both means and variances.

The generalized Poisson performed better than the other distributions tested, based on likelihood-based comparisons (ΔAIC=-15.0 when compared with the Poisson distribution) and was therefore used as a starting point for the exposure-response model building.

Estimation concerns

Modeling count data, especially count data whose distribution deviates from the standard Poisson distribution, is generally not robust when using first order conditional estimation with Interaction (FOCE-I). In contrast, resampling methodology like stochastic approximation of the EM algorithm (SAEM) followed by Monte Carlo-Markov chain Bayesian estimation (MCMC BAYES) have been proven successful [S1,S2]. However, in our experience the MCMC BAYES method tends to be unstable (frequent premature termination of the estimation steps). Hence, it was decided to first run a SAEM step before running a MCMC BAYES step using the output of the SAEM step as initial estimates for the MCMC BAYES step. The SAEM started with 50 burn-in samples with convergence test (CTYPE=3) and 50 stochastic posterior samples, and the subsequent MCMC BAYES run consisted of 2,000 burn-in samples with the same convergence test, followed by at least 500 samples of the posterior distribution. Parameter estimates were obtained using at least 500 samples from the posterior distribution.

Structural model building

The introduction of a treatment effect of any sort provided a considerable improvement in the model fit. Compared to a model that did not include any sort of treatment effect, the mode of the objective function value decreased by 343.2, 739.6 and 1585.2 points, respectively, when adding a single parameter denoting either a linear effect of last given dose, a linear effect of emicizumab concentration or an effective concentration (EC_{50}) under the assumption of a maximum effect (E_{max}) of 1 (a so-called "I_{max}" model).

A full E_{max} model, where the maximum effect was estimated, provided the lowest objective function value mode. Models that included any sort of effect sustainment, either as in an effect of time after dose on E_{max}, or using a K-PD model that allowed for an effect offset that was slower than the elimination of drug from the plasma, were also tested. These models did indeed improve the distribution of the objective function value. However, the estimated rate constants of the estimated effect offset tended to approach infinity and their precision were lacking. In contrast, when the E_{max} value was fixed to 1, thus reducing the model to an I_{max} model, the objective function distribution overlapped considerably with that of the full E_{max} model (see **Figure S10**). Since the I_{max} model encompassed one parameter less, it was selected over the E_{max} model. In addition, this model is similar to the model used in the emicizumab RTTE model published previously [24]. Addition of a Hill factor to the I_{max} model was tested, and, while marginally improving the objective function distribution, the resultant IC_{50} was conspicuously low (0.091 μg/ml) and highly uncertain. It was concluded that the I_{max} model with added Hill factor was over-parameterized, and the I_{max} model was selected as final.

Covariate model building strategy

One objective of the analysis was to use covariate information in order to identify sensitive groups that may differ in their exposure response profiles. One attractive option for investigating potential covariate effects would be to use the so-called "full model" approach, by including all possible covariates in the model. However, in this specific context, with the exposure response model being

fit to count data using computationally demanding techniques, and also considering the identifiability issues that could be encountered, we opted for a stepwise approach.

The effect of adding a covariate is dependent on which covariates that were added previously, which again poses a problem in this analysis as computation times in MCMC BAYES runs are generally long, and there are no generally accepted criteria for model selection in this context. This was addressed by performing a stepwise covariate modeling (SCM) procedure, as implemented in Perl-speaks NONMEM (PsN) [S1] using SAEM estimation. The one-sided type I error rate was set to α=0.01 for the forward inclusion step and α=0.001 for the backwards exclusion. The SCM was performed using the generally recommended approach for model selection in a SAEM setting, which encompasses running a last estimation step using a single replicate of importance sampling. This practice provides a point estimate that could be used for model selection in the SCM procedure. Once the SCM was completed, potential covariates would be added to the base model in order of inclusion in the SCM, and models (re-) fit using MCMC BAYES. We thus implemented SCM more as a screening procedure than as a final criterion for model selection. In this later step of the covariate selection procedure, the same criteria for model selection were used as when the basic structural model was developed, i.e. objective function distribution, Akaike information criterion, parameter precision, visual predictive check performance, in addition to clinical significance of covariate inclusion.

Possible impact of FVIII prophylaxis

Prophylaxis with FVIII was forbidden in HAVEN studies, with the exception of the first week of treatment with emicizumab for PwHA without FVIII inhibitors who were previously treated with FVIII prophylaxis. Only episodic use of FVIII was allowed during the study to treat a bleed. The use of FVIII did therefore not prevent the occurrence of a bleed, limiting its impact on the exposure-response of emicizumab. It is however conceivable that the treatment of a bleed with FVIII in a given PwHA may decrease the likelihood of occurrence of the next bleed and indirectly impact the exposure response of emicizumab. This influence is however thought to be minimal as the model

nicely described the exposure-responses in different emicizumab treated populations, as seen by the VPCs, including those who did not receive FVIII to treat a bleed or those who had previously received FVIII prophylaxis.

Supplementary Figures

Fig. S1 Individual variances versus individual mean daily bleed counts among all persons with hemophilia A experiencing bleeds.

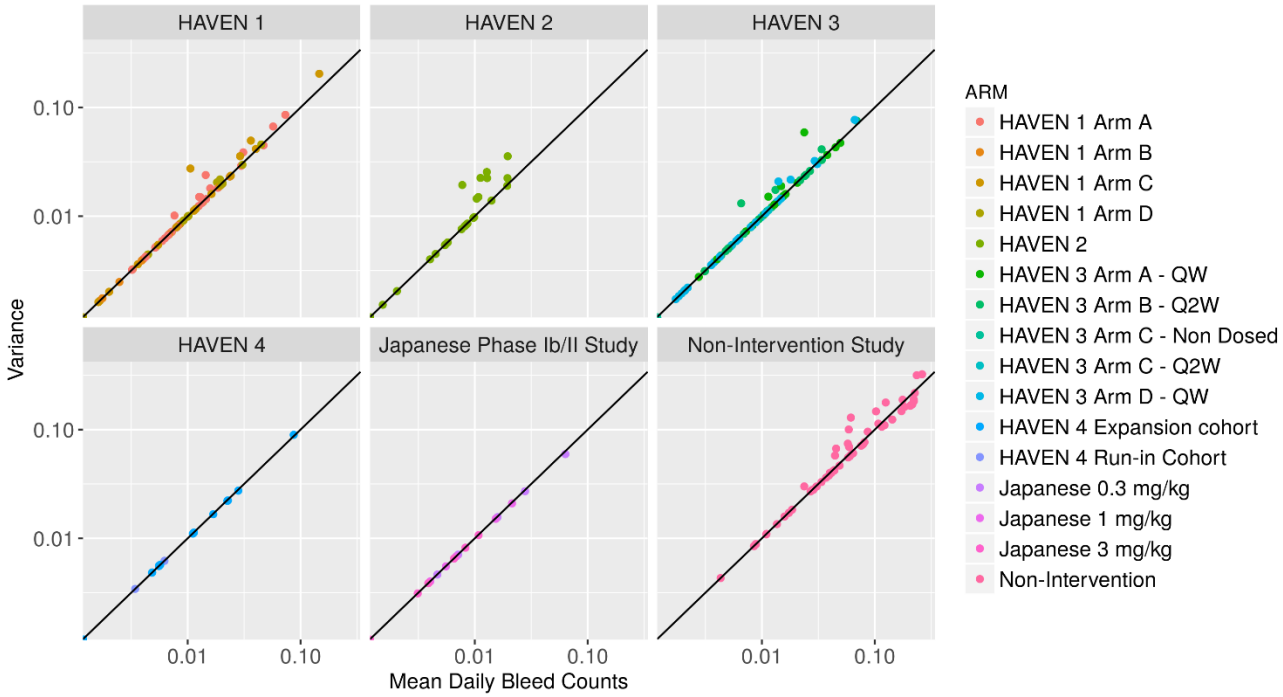


Fig. S2 Visual predictive check plots for the count data model – HAVEN 1 study, 1.5 mg/kg QW – (**top**) Arm A (**bottom**) Arm B. *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

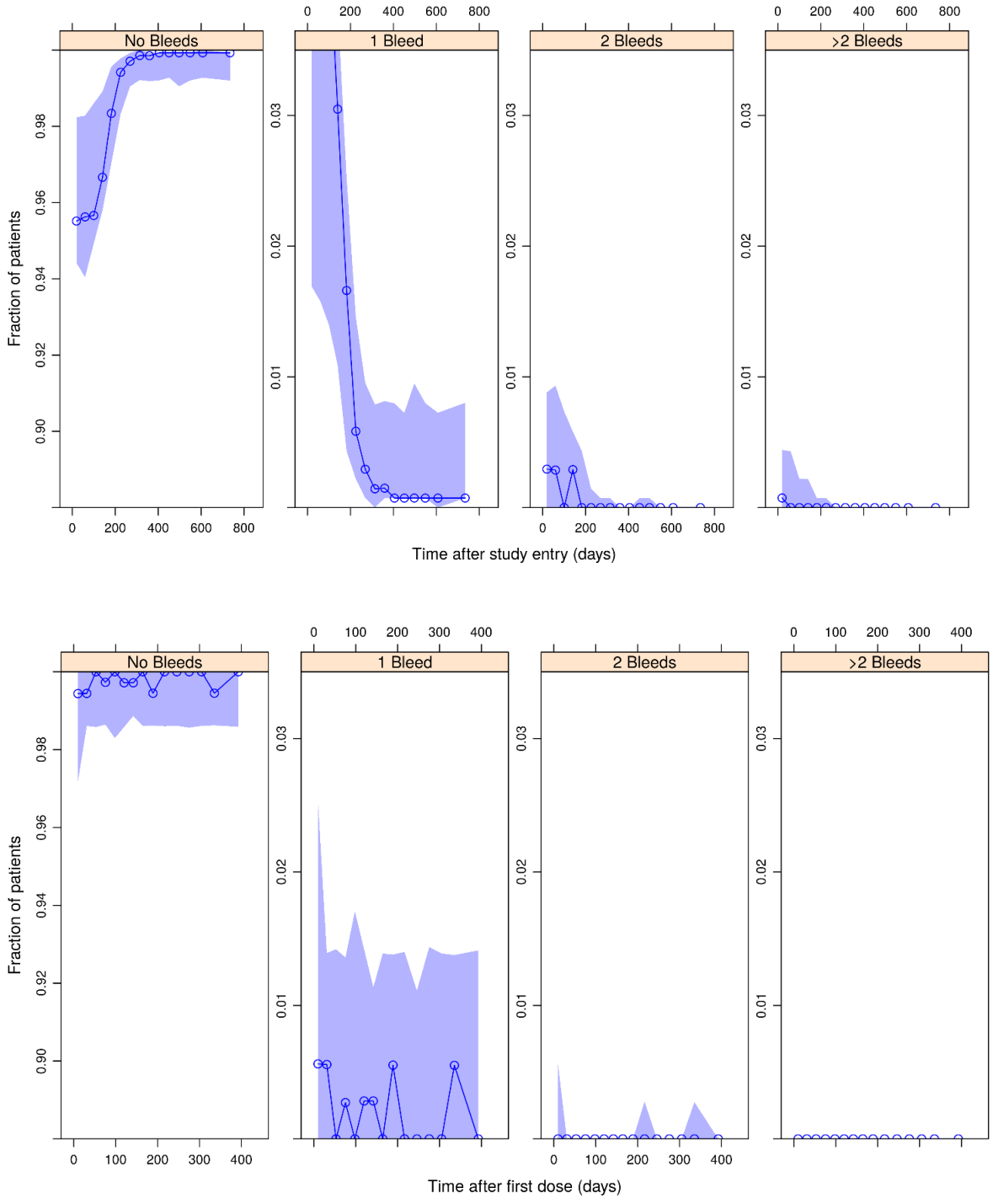
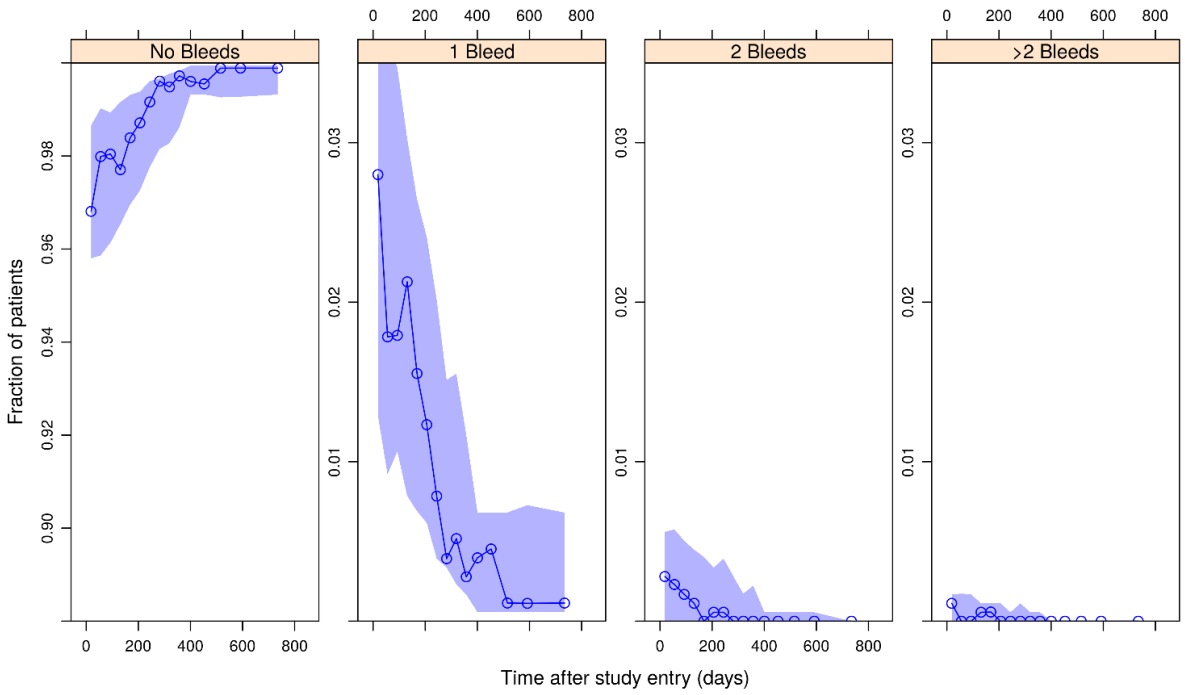


Fig. S3 Visual predictive check plots for the count data model – HAVEN 1 study, 1.5 mg/kg QW – (**top**) Arm C (**bottom**) Arm D *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.



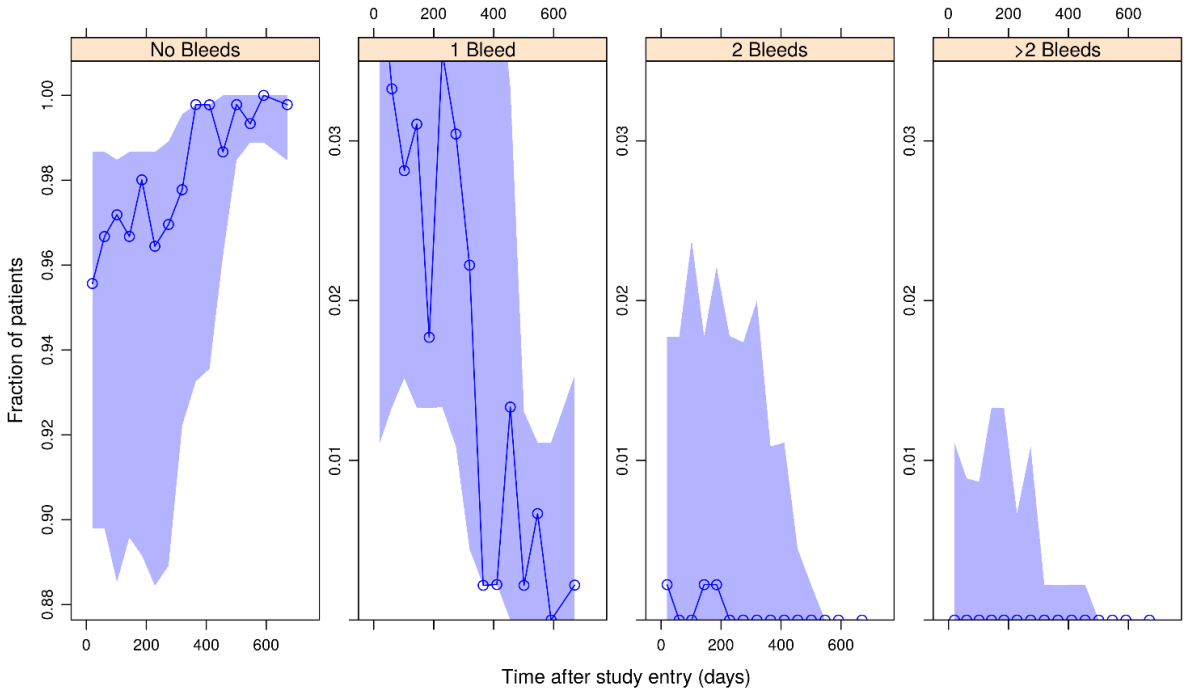


Fig. S4 Visual predictive check plots for the count data model – Japanese phase Ib/II study - (**top**) 0.3 mg/kg QW (**bottom**) 1 mg/kg QW. *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

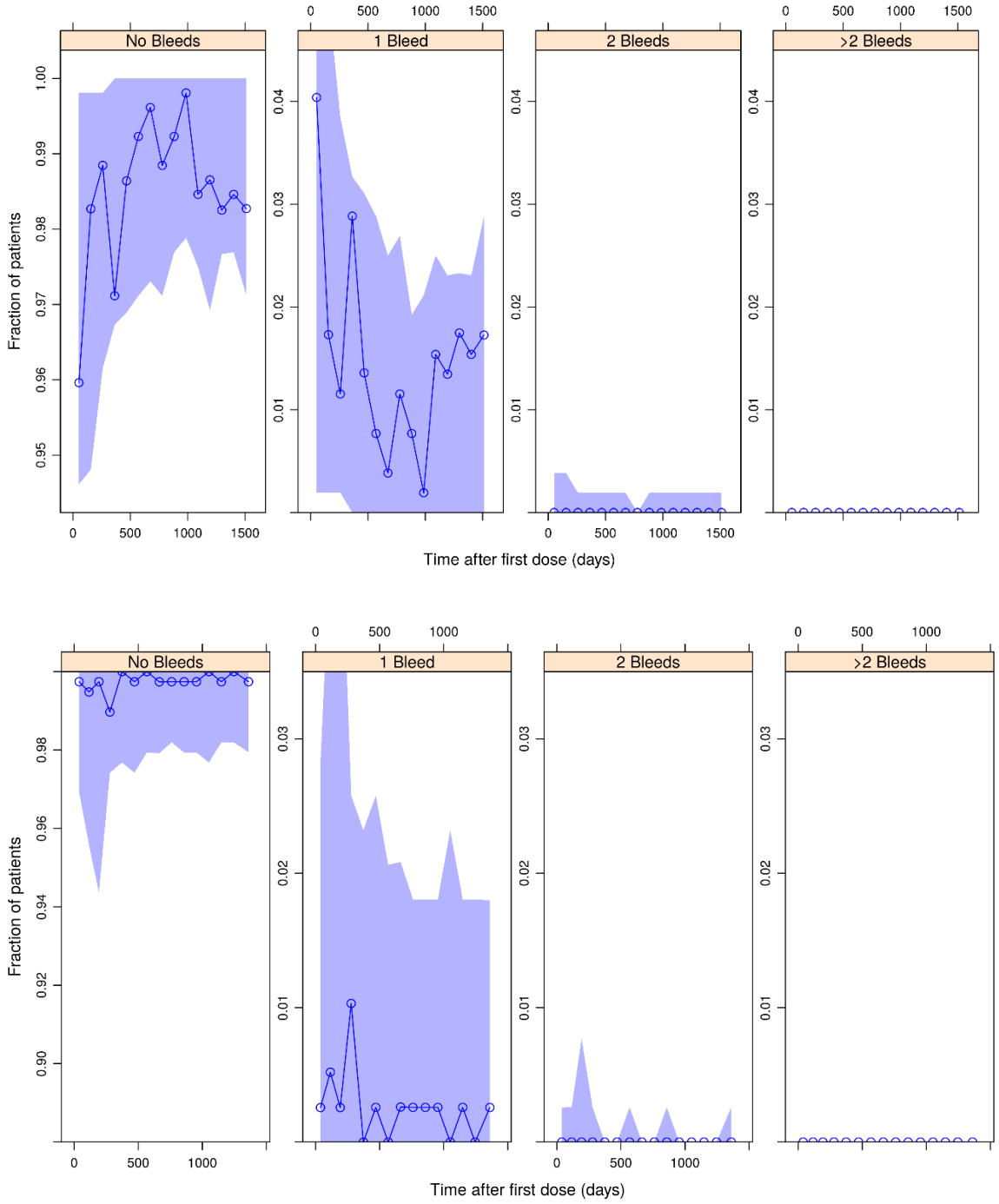


Fig. S5 Visual predictive check plots for the count data model – Study ACE001JP Part C/ACE002JO 3.0 mg/kg QW. *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

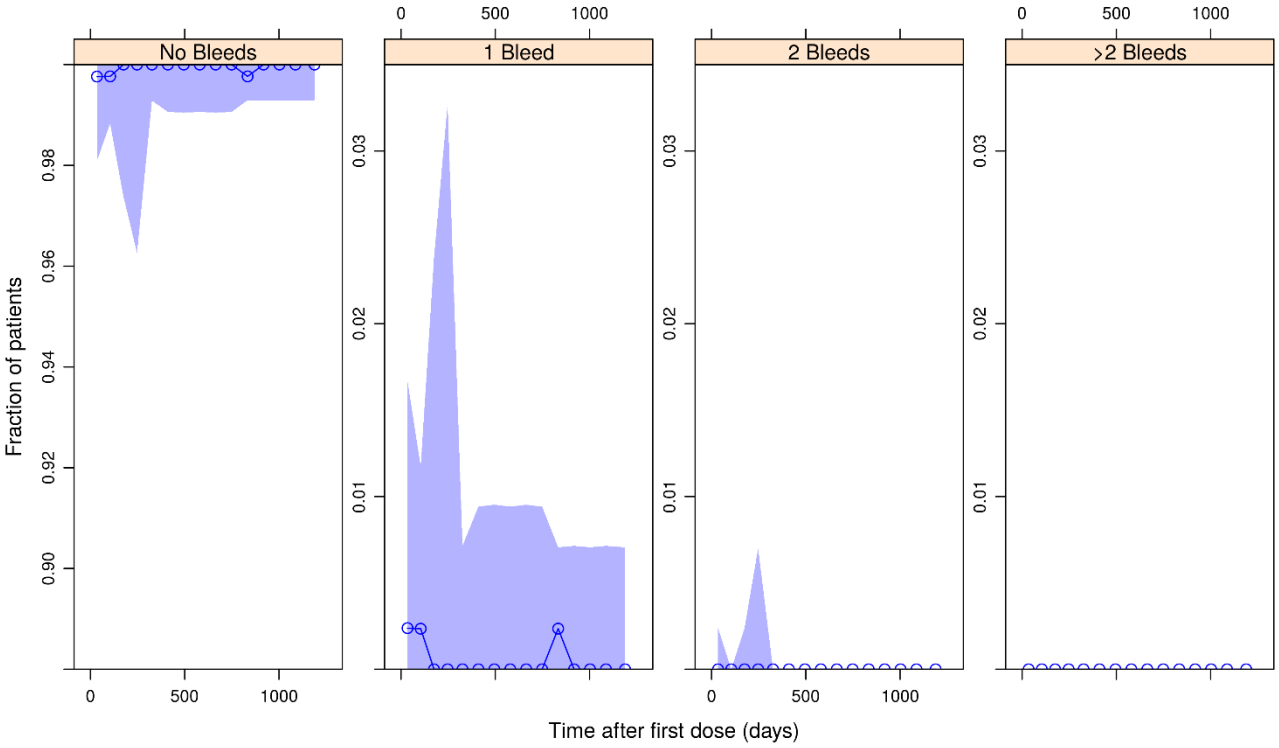

No Bleeds
1 Bleed
2 Bleeds
>2 Bleeds
Fraction of patients
Time after first dose (days)
0.90
0.92
0.94
0.96
0.98
0.01
0.02
0.03
0
500
1000

Fig. S6 Visual predictive check plots for the count data model – HAVEN 3 study, 1.5 mg/kg QW – (**top**) Arm A (**bottom**) Arm D. *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

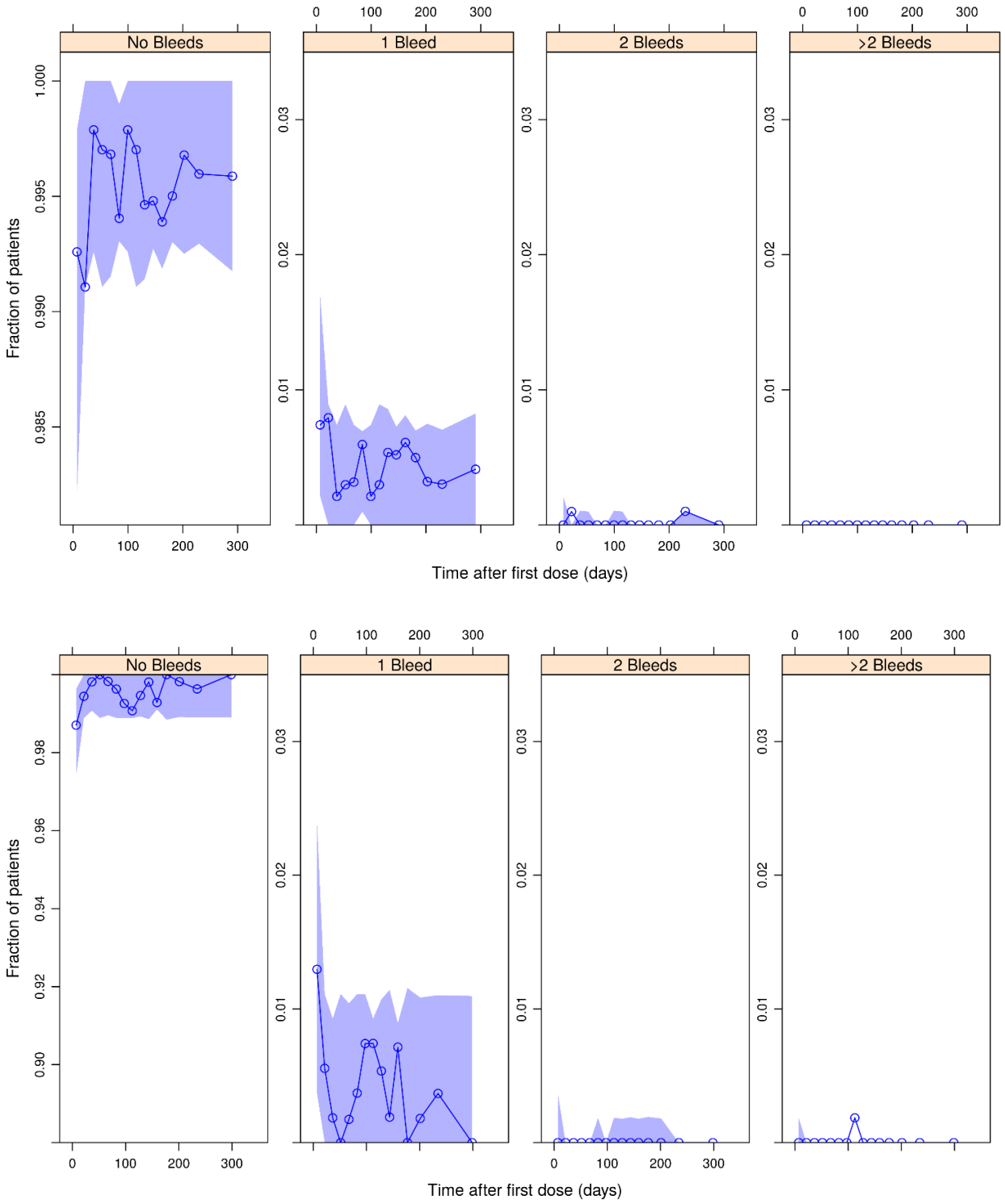


Fig. S7 Visual predictive check plots for the count data model – HAVEN 3 study, 3 mg/kg Q2W – (**top**) Arm B (**bottom**) Arm C. *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

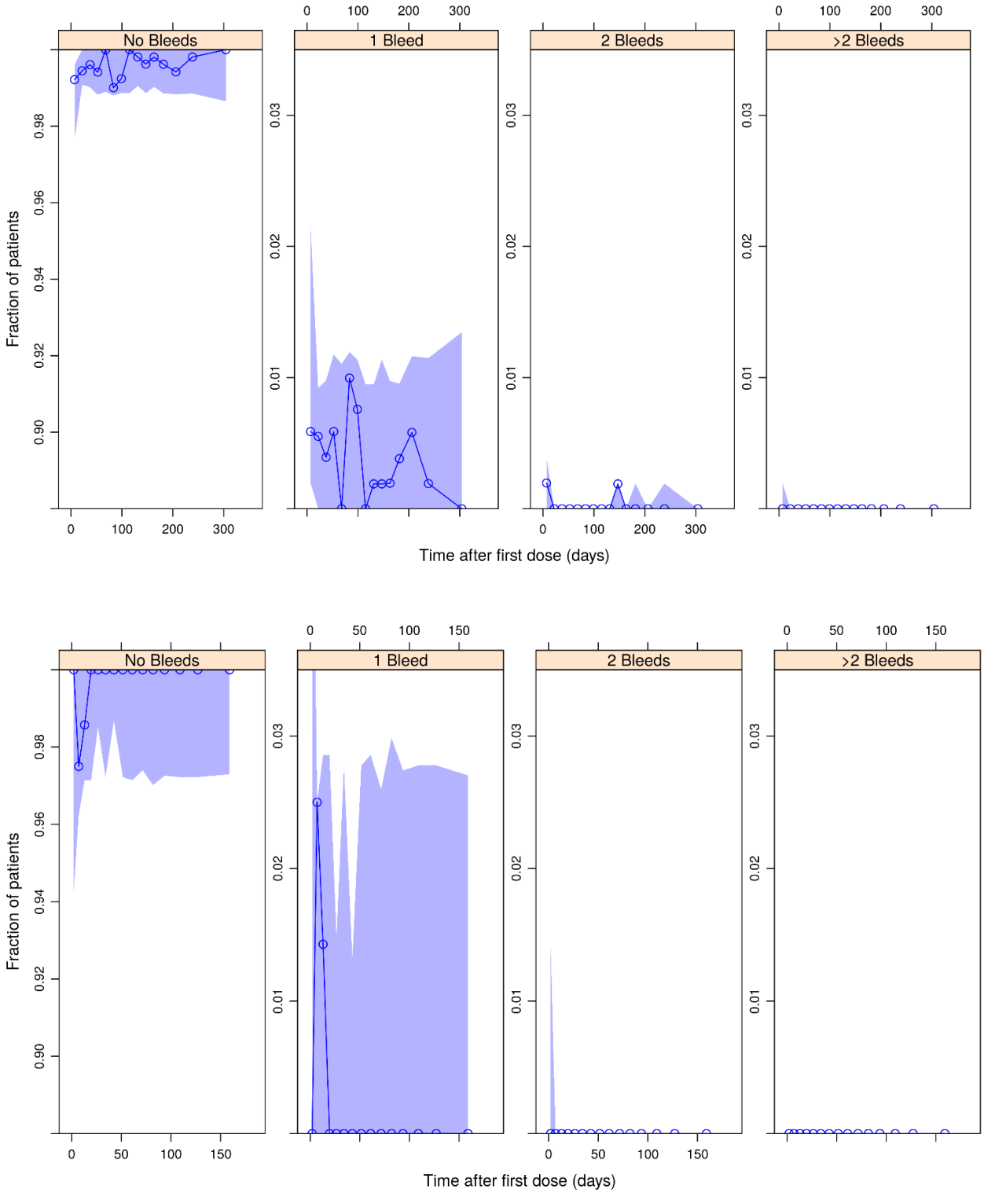


Fig. S8 Visual predictive check plots for the count data model – HAVEN 4 study, 6 mg/kg Q4W – (**top**) run-in Arm (**bottom**) expansion Arm. *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

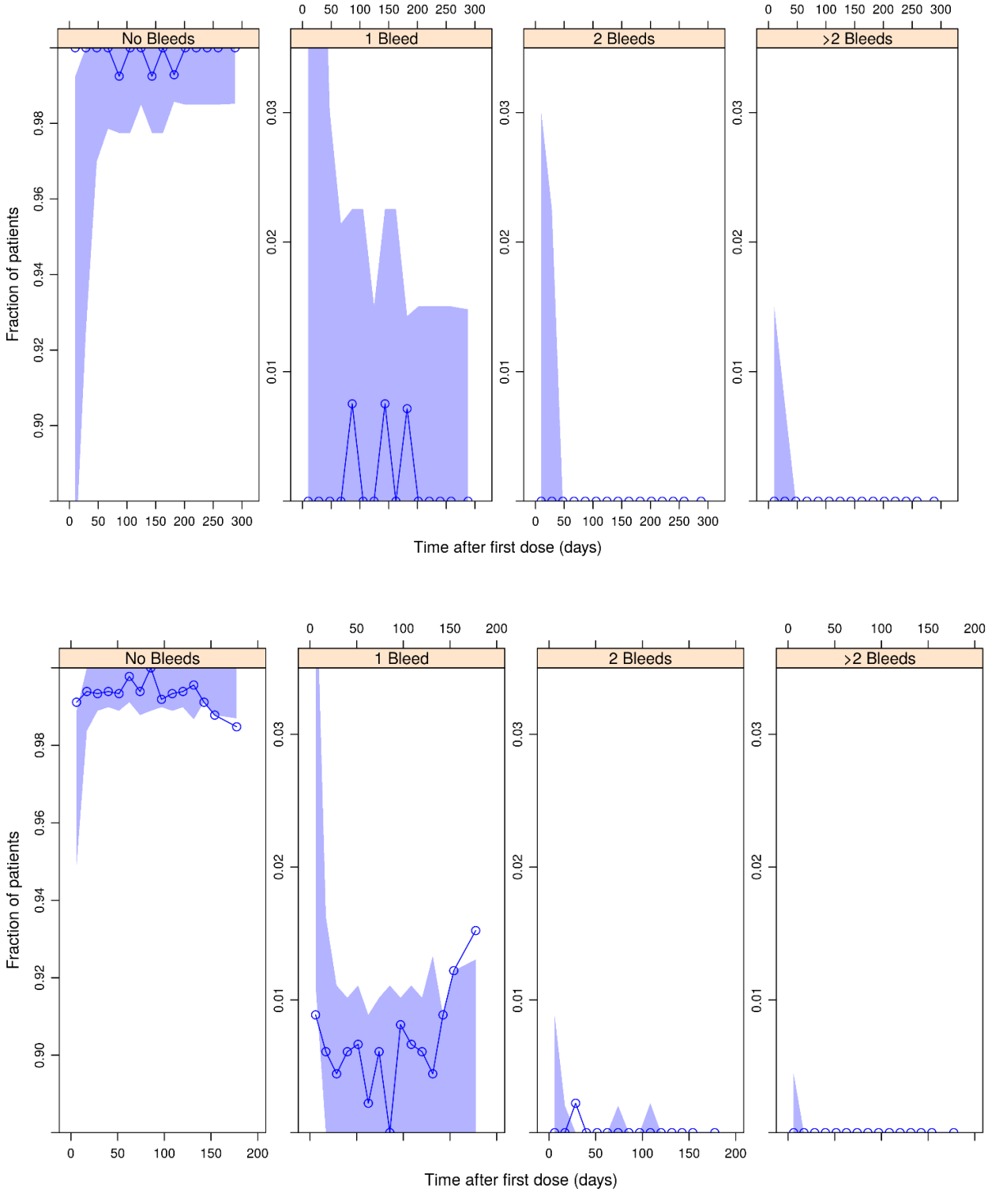


Fig. S9 Visual predictive check plots for the count data model - (**top**) Non-intervention study (**bottom**) HAVEN 2 (Pediatric Study). *Circles and solid blue lines* are the observed fractions of persons with hemophilia A in each category experiencing the respective number of daily bleeds in each period, *shaded areas* are the simulated 95% prediction intervals.

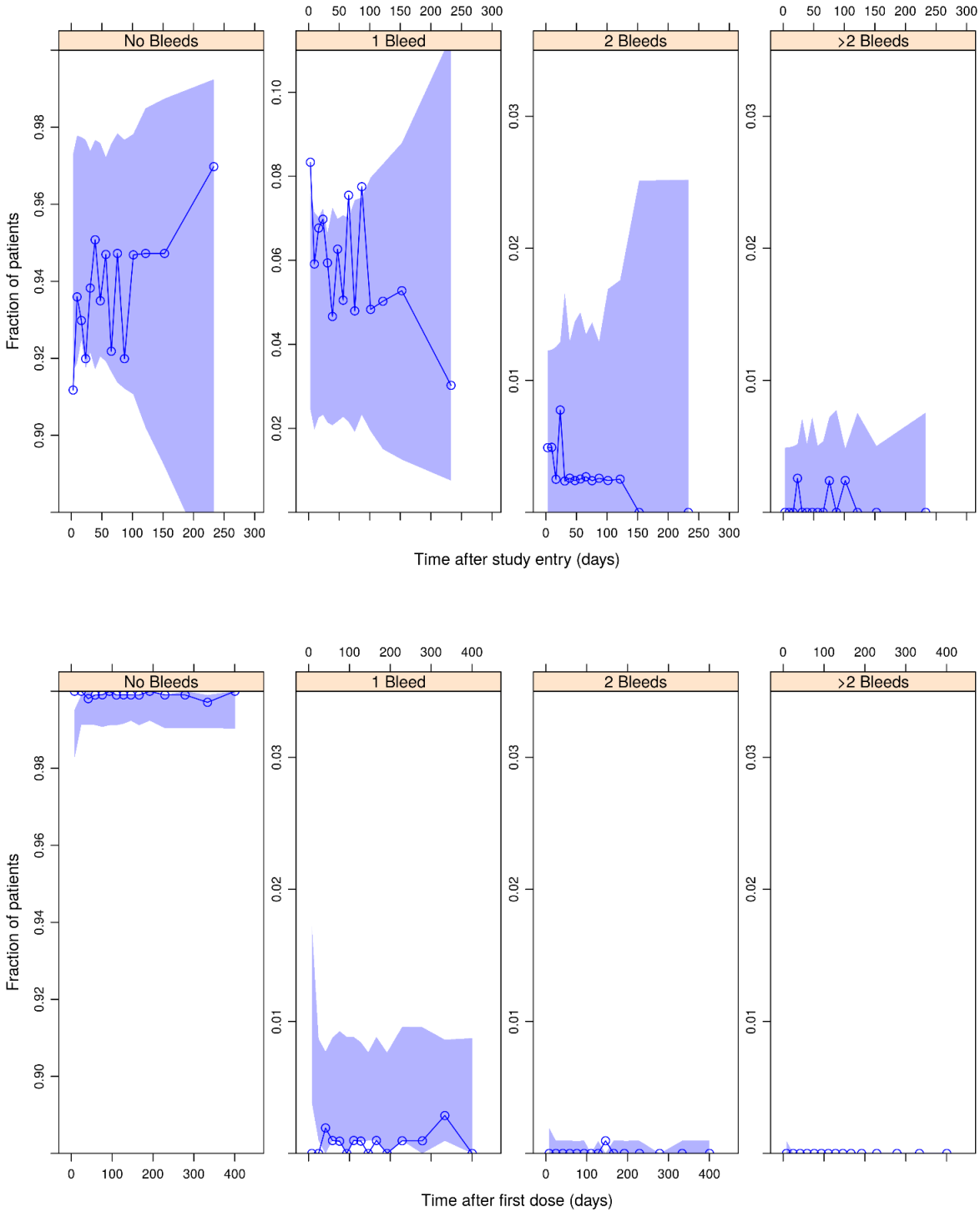
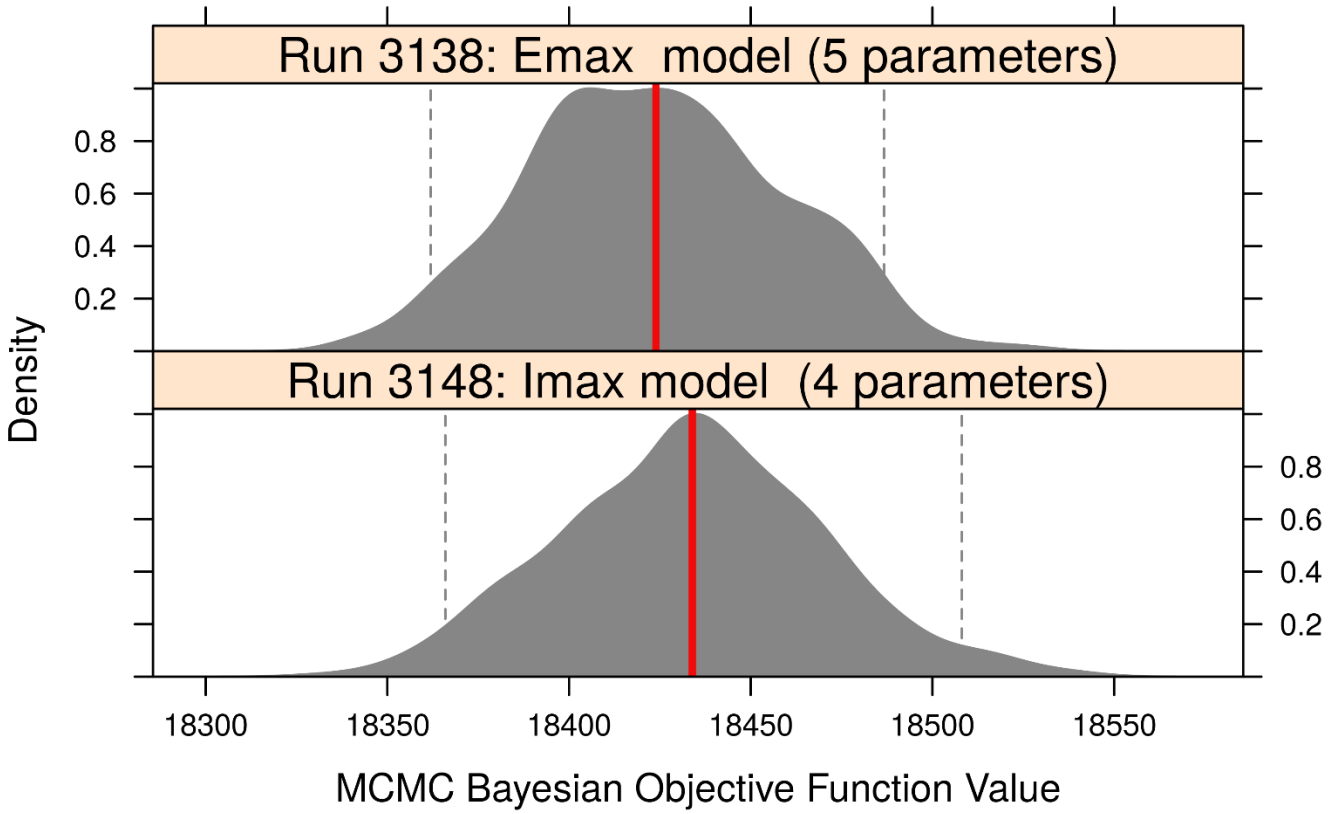


Fig. S10 Comparison of the posterior distribution of the objective functions of E_{max} and I_{max} models.



Supplementary References

S1. Lindbom L, Pihlgren P, and Jonsson, EN. PsN-Toolkit - a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005; 79: 241-57.

S2. Akaike, H. A new look at the statistical model identification, IEEE Transactions on Automatic Control. 1974;19 (6): 716-23.