A model for evaluation of novel on-demand treatment of bleeding events in haemophilia subjects

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Introduction

- Rare diseases suffer from small sample sizes which may negatively impact power to detect drug effects. Model-based analysis may improve power to detect drug effects in these settings[1-3].
- Subcutaneous (SC) marzeptacog alfa (MarzAA) is a recombinant variant FVIIa. Administered prophylactically, MarzAA lowered the annual bleeding rate by 90% in a phase-2 trial[4] and has demonstrated excellent safety[4-6]. Using a potency bridging strategy with population pharmacokinetic modeling[7] a phase-3 cross-over trial was launched to evaluate SC MarzAA for on-demand treatment[5] compared to current intravenous standard of care (SoC).
- The clinical data indicated that SC MarzAA was both efficacious and safe in subjects with hemophilia with inhibitors and was used to develop the evaluation models presented here.

Objectives

This work aimed to use a model-based analysis to detect drug effects during novel on-demand treatments of bleeding events in hemophilia A or B, by analyzing repeated categorical outcome data. Using the model, difference in drug effect were tested for between SC MarzAA and IV SoC.

Methods

Efficacy data from a randomized global cross-over phase-3 trial were used[5]. Subjects received either SC MarzAA (60 µg/kg) or IV SoC for 5 consecutive bleeds or vice versa before crossing over. SC MarzAA or IV SoC was administered on-demand one, two, or three times or as indicated by its label in three-hourly intervals following a bleeding event. Treatment responses were measured using a four-point clinical scale (poor, fair, good or excellent control) at different time-points.

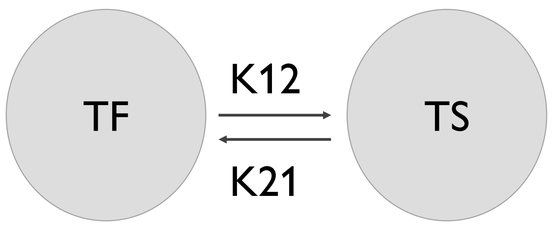

Figure 1. Illustration of the two-state continuous-time Markov model. TF; treatment failure, TS; treatment success K12; transfer from TF to TS, K21; transfer from TS to TF.

Two continuous-time Markov models[8] were developed in which the probability of the score was dependent on the previous score and the time since last score[8,9]. Initially, outcome data was binarized (Fig. 1) into treatment failure (poor/fair [TF]) and treatment success (good/excellent hemostatic control [TS]). Subsequently, the data was also analyzed using the full four-point scale (Fig. 2). Probability of each score was modeled using differential equations describing transition between the two scores. In the two-state model, the system was reset for each bleeding event and the patients were initialized with TF. For the four-state model, each patient was assumed to start in the poor state. In the four state models, shared transfers were tested for (e.g. K12-23, meaning that K12 and K23 are described by the same parameter).

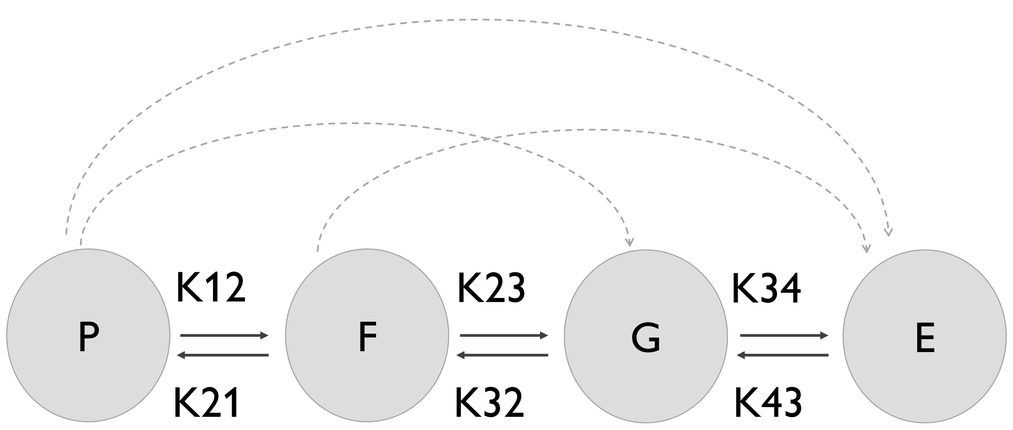

Figure 2. Illustration of the four-state continuous-time Markov model. P: poor, F: fair, G: good, E: excellent improvement, K12; transfer from P to F, K21; transfer from F to P, K23; transfer from F to G, K32; transfer from G to F, K34; transfer from G to E, K43; transfer from E to G. The dashed transfers illustrate direct transfers that were tested during model development bypassing the need to go through intermediate states.

Inter-individual variability (IIV) and inter-bleeding-variability (IBV) were tested additively on the logit scale on all transfer rates. Baseline age, bodyweight (BW), height, race, diastolic/systolic blood pressure (DBP/SBP), heart rate (HR), location and severity of bleed (BLOC and SBL) were tested as covariates on the transfer rates using stepwise-covariate modeling (SCM). Continuous covariates were implemented with linear or piece-wise functions and categorical covariates (including testing for difference in transfer rates between MarzAA and SoC) were tested additively on the logit scale with the most common category used as reference. Modeling was performed in NONMEM 7.5[10] and diagnostics were done in R using xpose4[11] and was guided by objective function value (OFV), parameter uncertainty and simulation properties.

References

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Results

The total number of evaluable bleeds were 71. Each subject (n=15) experienced 5 bleeds on average (90% inter-percentile range; 1-8 bleeds). The number of efficacy evaluations were 222 and 265 for MarzAA and SoC, respectively. The modelling work and covariate search were performed using ADVAN6 (differential equation solver) as it increased numerical stability. Both of the final models indicated good fits (Figs. 3-4) with parameter values estimated with acceptable uncertainty given the sample size (Table 1). The transfer rates indicated efficacy of both MarzAA and SoC.

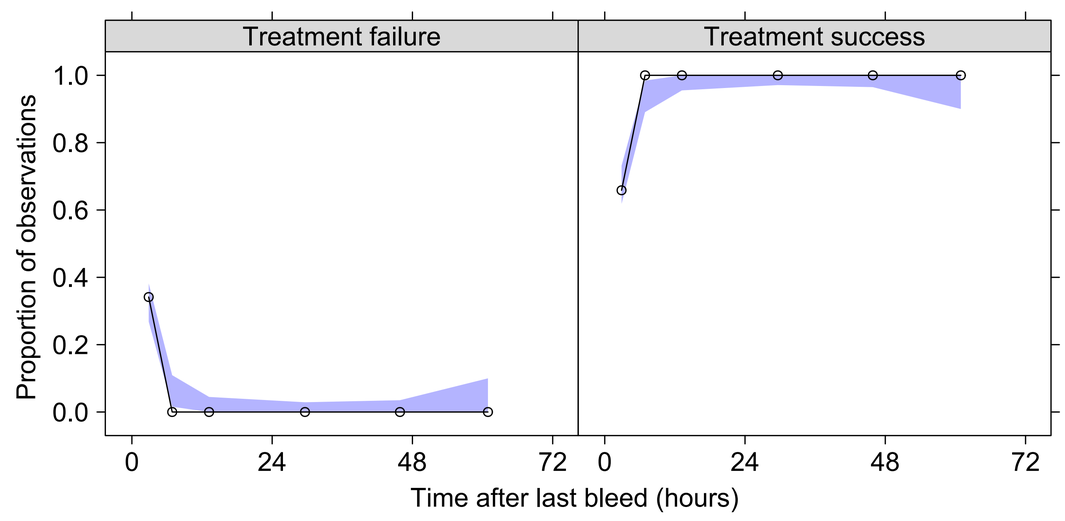

Figure 3. Prediction-corrected visual predictive check (pcVPC) of the proportion of observations in the TF or TS states versus time after last bleed. The circles are prediction corrected proportions over time and the blue shaded area is the 95% prediction interval based on 500 virtual clinical trials.

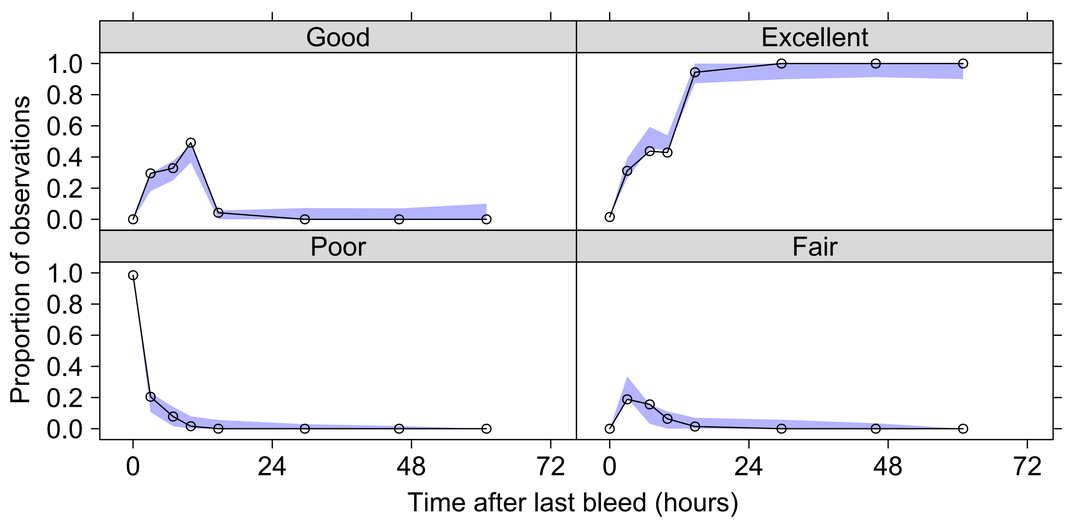

Figure 4. pcVPC of the proportion of observations in the G, E, P and F treatment response states versus time after last bleed. The circles are prediction corrected proportions over time and the blue shaded area is the 95% prediction interval based on 500 virtual clinical trials.

No statistically significant difference in the transition rates were identified between SC MarzAA and IV SoC using either a two-state or a four-state model, strongly indicating comparable efficacy between the treatments. Given the small sample size, the clinical impact of the identified covariate effects should be interpreted with caution and needs confirmation in larger trials.

Table 1. Parameter estimates and RSE% on logit scale. The arrows indicate if the covariate effect increased or decrease the transfer rate. DBP on K12 in the two state model was described by a piece-wise model with opposite effects dependent on the cutoff (increase of the rate for DBP<80 and decrease of the rate for DBP>80).

Two state

Parameter	K12 (day^{-1})	K21 (day^{-1})	DBP on K12	BW on K12
Typical (RSE% [IIV CV%] {IIV RSE%})	13.6 (14 [-])	0.1 (43 [-])	↑↓	↑

Four state

Parameter	K43-32-21 (day^{-1})	K12-23 (day^{-1})	K34 (day^{-1})	Age on K12-23	BLOC on K12-23	DBP on K34
Typical (RSE% [IIV CV%] {IIV RSE%})	0.24 (32 [-])	4.1 (48 [76] {67})	4.7 (50 [134] {23})	↑	↑	↓

Conclusion

Using either a binarized or full-scale endpoint, no statistically significant difference was found in the transfer rates between SC MarzAA and IV SoC which strongly indicates similar drug effects.

Next steps

The models can be used for characterization of exposure-response relationships of SC MarzAA and other novel on-demand treatments aiding future clinical trial designs and in the registrational process for treatments for haemophilia.

Acknowledgments

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