

# Modelling Recurrent Safety Events in Drug Combinations using a Time-Varying Poisson Process

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## Background

Phase I oncology trials often declare a recommended Phase II dose (RPIID) at an early stage using few patients data. Reassessment of an optimal dose based on safety and efficacy data may be required once more patients data becomes available. Challenges often include

- Dose adjustments & treatment modifications
- Delayed drug combination effects
- Recurring adverse events (AE)
- Lacking ready pharmacokinetic (PK) data

## Objectives

The key objective is to evaluate optimal treatment dose utilizing exposure and predicted risk in reference to the determined RPIID. As an example, the current work presents evaluation of an optimal dose based on data generated in a phase Ib study [1] of orally administered Ruxolitinib (RUX) and Panobinostat (PAN) for the treatment of patients with Myelofibrosis. The analysis must

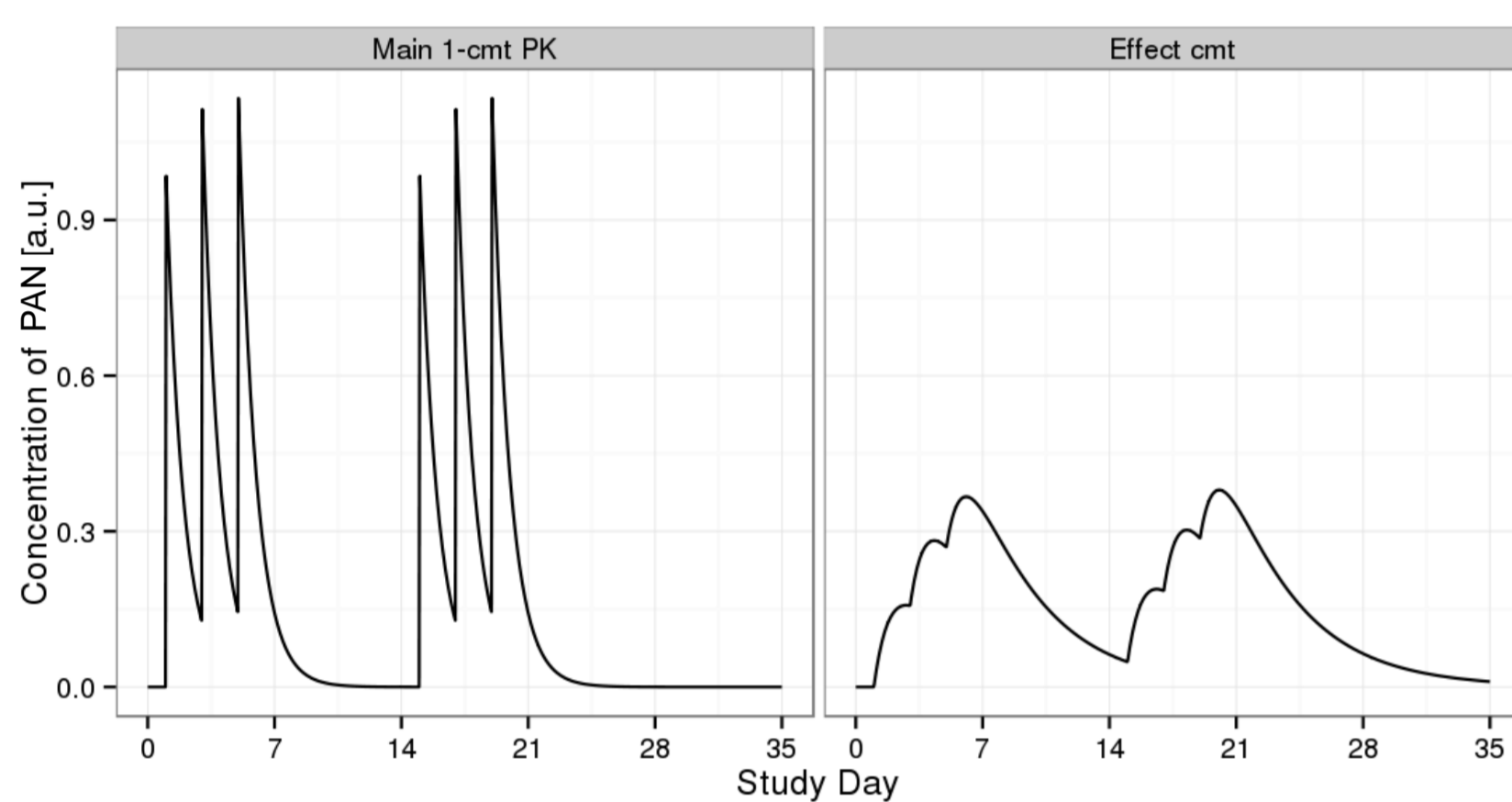
- Address the absence of PK data
- Evaluate association of drug exposure with AEs
- Predict future outcomes to support ongoing development

## Conclusion

- While true PK data is preferable, the use of patient's dosing history with a simplified PK model coupled with an effect compartment (cmt) adequately describes long-term treatment while accounting for dosing adjustments.
- Time-Varying Poisson Process with an additive hazard provides an appropriate description of the different processes of baseline and two drugs
- Model allows probabilistic predictions and can provide important metrics for further development of the compound(s)

## Methods

Exposure model: 1-cmt PK + effect cmt



### Exposure model

- Time-resolution of events only by day => only model steady-state changes as function of individual patient dosing history
- The exposure model uses the exact dosing history of each patient
- Individual differences in pharmacokinetic parameters are not considered and should be added at a later stage
- Previously fitted (multi) compartmental models for PAN and RUX where used to obtain the elimination half-life  $T_e$
- Simplified 1-cmt model used without absorption cmt
- Delays were modeled with an effect cmt.

$$E(t) = D \frac{k_e}{k_e - \frac{\log(2)}{T_e}} (\exp(-\log(2)/T_e t) - \exp(-k_e t))$$

The main purpose of the exposure model was to predict steady state in presence of dose adjustments

### Posterior Predictive Model Check

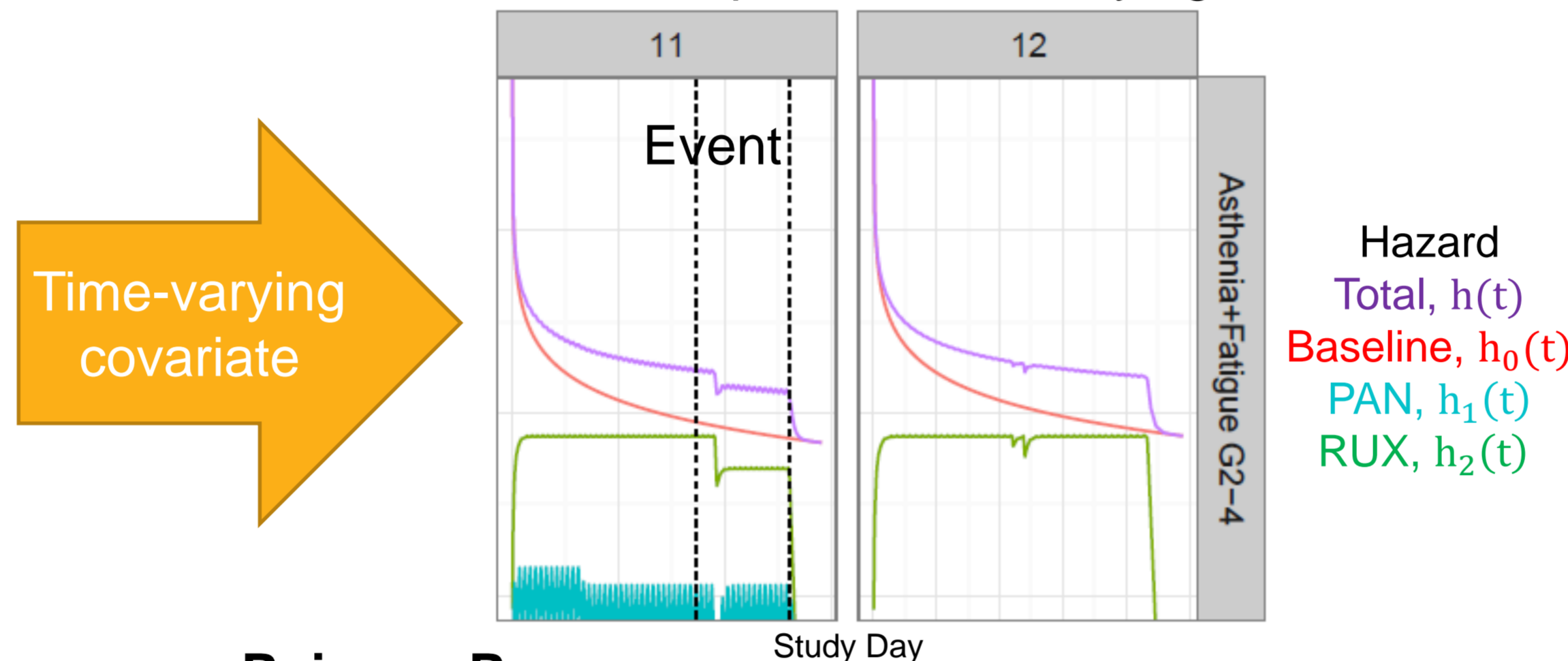
Simulation of the study design with parameter uncertainty of  $\theta = (\alpha_1, \alpha_2, \beta_1, \beta_2)$

1. Sample a parameter vector  $\theta$  from posterior
2. Simulate study design
3. Summarize simulated study by summaries of interest
4. Repeat many times (>100)

Summaries considered

- Free: patients without any event
- Max: maximal # of events of any patient
- Mean: Average # of events per patient
- First: Mean time of first event
- Inter: Mean time between successive events

Event model: Compound Time-Varying Poisson



### Poisson Process

- Independent events => memoryless process
- Predictable events => mean event rate at  $t=T$  must follow from the history  $t < T$

Fully defined by the hazard function  $h(t)$  [2]

- Hazard function,  $h(t) = \lim_{\delta t \rightarrow 0^+} \frac{P(t \leq T < t + \delta t | T \geq t)}{\delta t}$
- Probability density for an event at  $t$ ,  $f(t) = h(t) \exp[-\int_0^t h(s) ds] = h(t) \exp[-H(t)]$

Observed events are assumed to follow a compound Poisson Process

=> Defined by the sum of individual hazards  $h(t) = h_0(t) + h_1(t) + h_2(t)$ .

Independent Poisson Processes

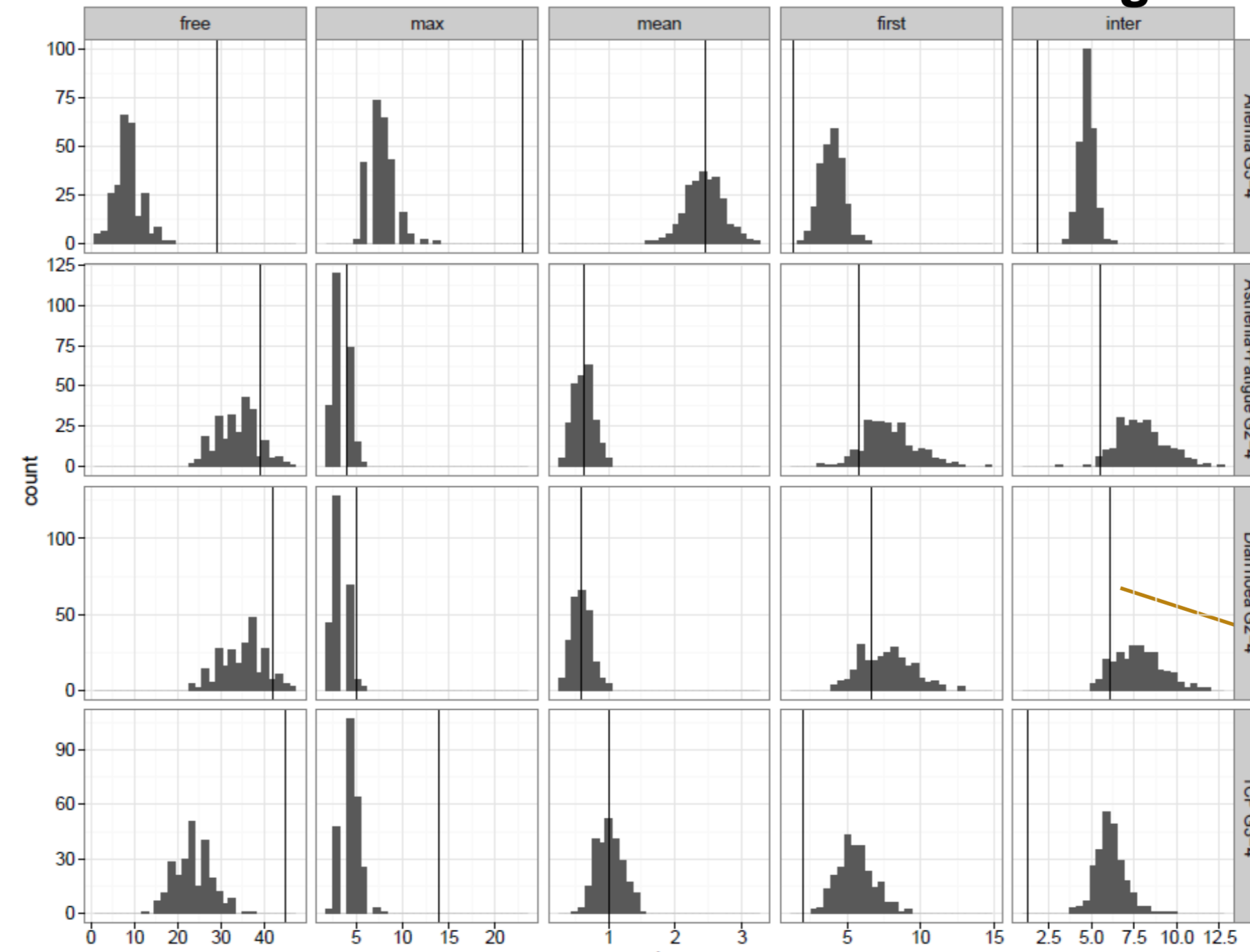
- Baseline Weibull,  $h_0(t) = \alpha_1 \alpha_2 (\alpha_1 t)^{\alpha_2 - 1}$
- Drug exposure RUX,  $h_1(t) = \beta_1 E_1(t)$
- Drug exposure PAN,  $h_2(t) = \beta_2 E_2(t)$

$E_1(t)$  and  $E_2(t)$  are the concentrations in the effect cmt for each drug.

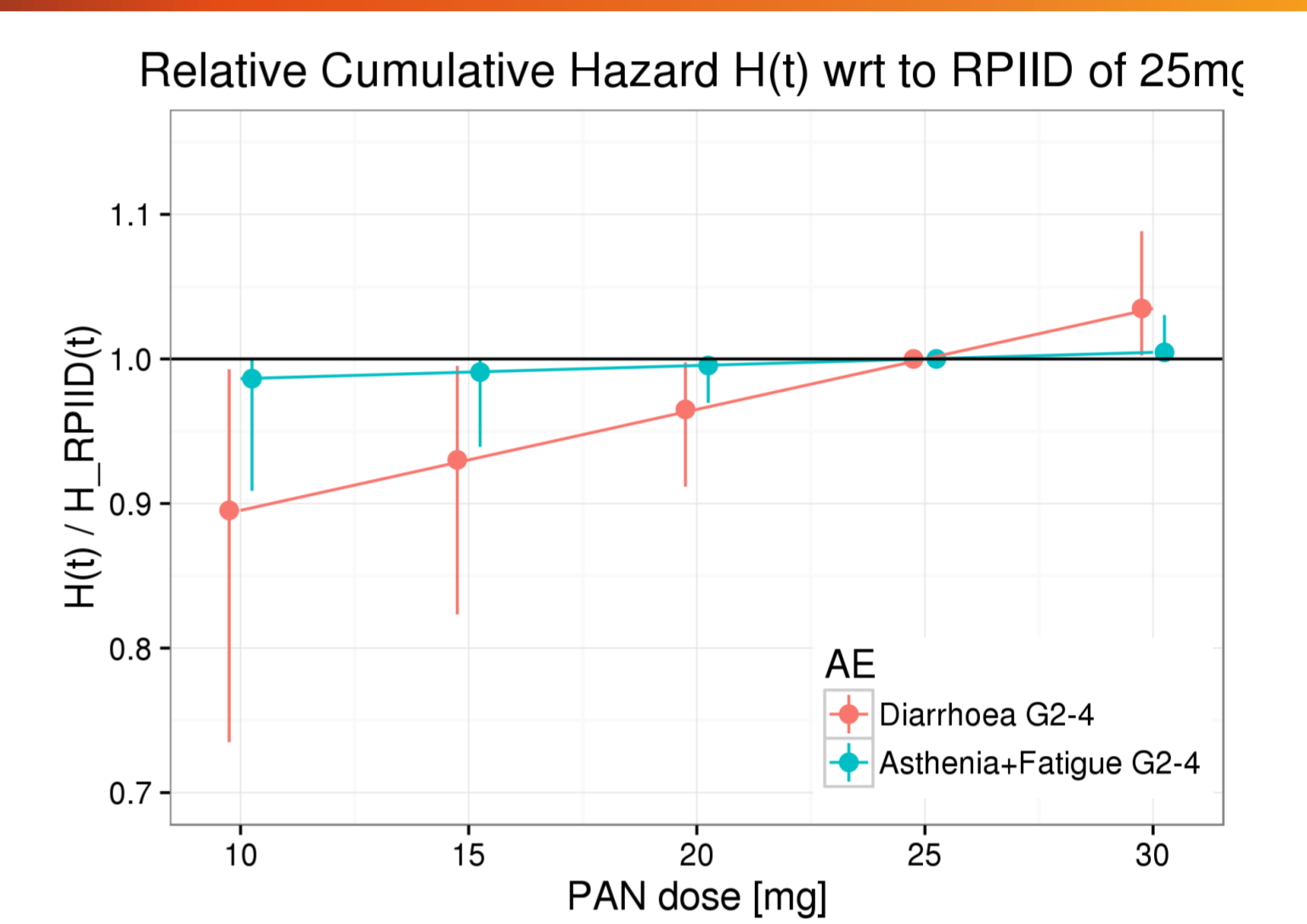
=>  $H(t)$  is given by the AUC for each drug

Model has been fit in a Bayesian approach [4] with weakly-informative priors  $\theta = (\alpha_1, \alpha_2, \beta_1, \beta_2)$

### Posterior Predictive Model Check Histograms



## Results



### Posterior Predictive Check Results

- Model can predict study data AEs
  - Diarrhoea grade 2-4
  - Asthenia+fatigue grade 2-4
- Model cannot predict study data AEs
  - Thrombocytopenia grade 3-4
  - Anemia grade 3-4

### Model Results

- Baseline contribution large wrt to drug effect
- Quantification of relative contribution of each drug to the overall event rate per AE
- Model predicts a reduction in cumulative hazard for diarrhoea grade 2-4 when reducing the PAN dose

## Discussion

### Time-Varying Poisson Process strengths

- Exact dosing history used
- Time to first & recurrent events
- Drug combinations

### Applications

- Across indication pooling
- Use of historical data (study-variation)
- Flexible dosing regimens
- Generative model allows probabilistic predictions for alternative dosing regimens
  - Expected # of events
  - Expected time between events
  - $P(\# \text{ AE} \geq 1/2/3)$  within a time-frame
  - Relative cumulative hazard

### Outlook

- Drug-drug interactions via exposure model
- Joint event modeling

## References:

1. Ribrag, V. et al., 55th ASH meeting, Dec. 7-10, 2013, <https://ash.confex.com/ash/2013/webprogram/Paper56214.html>
2. Kalbfleisch, J.D. and Prentice, R.L., 2002, The Statistical Analysis of Failure Time Data
3. Cox, Eugene H. et al., J. Pharmaco. and Biopharm., Dec 1999, Vol. 27, 6, pp 625-644
4. Stan Development Team (2016). Stan: A C++ library for probability and sampling.