

Population Pharmacokinetic/Pharmacodynamic Modelling of Cytokine Releasing Syndrome (CRS) Events during T cell Engager Therapy



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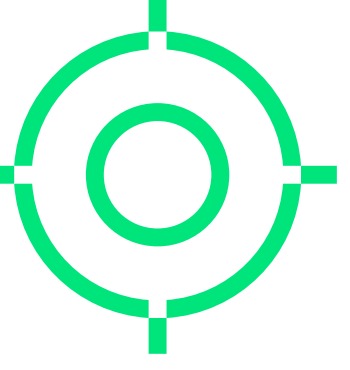
Introduction

- T cell engager (TcE) therapies can direct T cells to attack tumor cells, thereby creating an immunological synapse that results in the elimination of tumor cells (Figure 1).¹
- The downstream signaling of the T cell receptor in these therapies triggers the release of pro-inflammatory cytokines, potentially causing Cytokine Release Syndrome (CRS).²
- The predictability and management of CRS incidence pose significant challenges associated with the on-target activity of TcE therapies.³



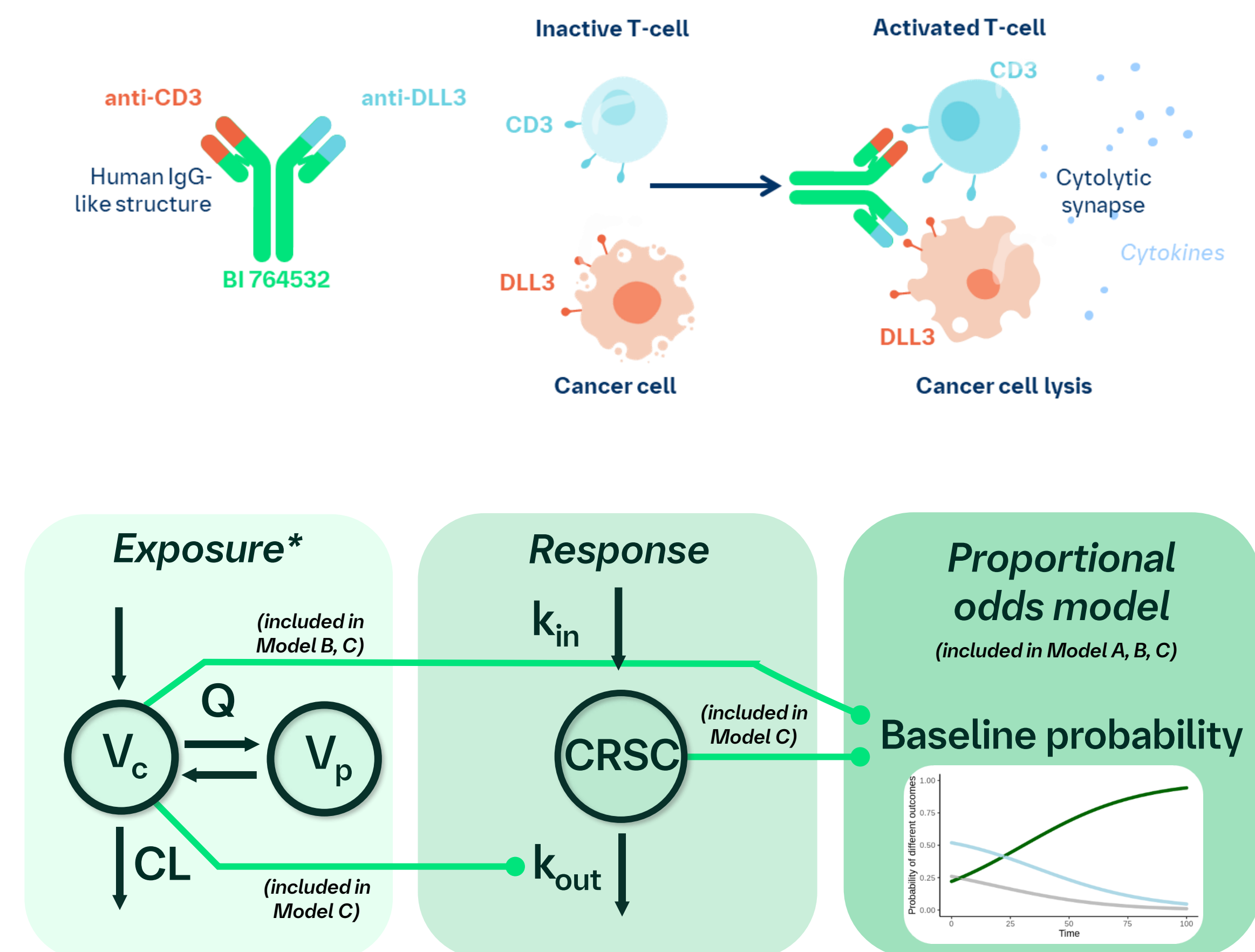
Objectives

- To gain a better understanding of CRS and to foster quantitative approaches and tools to optimize TcE therapies.
- To develop a population pharmacokinetic/pharmacodynamic (PK/PD) model for the TcE BI 764532 that can describe the incidence of different CRS event grades (according to Common Terminology Criteria for Adverse Events v5.0) over the time course of TcE treatment.
- To build a framework to enable investigation of predictors of CRS events and to simulate CRS event rates in different settings.



Methods

- The ordered categorical CRS event data used for model development originated from a Phase I dose escalation trial (NCT04429087) that investigates the anti-tumor efficacy of BI 764532 in patients with relapsed/refractory small-cell lung cancer or neuroendocrine carcinomas at different doses and dosing regimens (weekly, three-weekly, weekly with step-in dosing).⁴
- The data was investigated applying a proportional odds model ('Model A') for the probabilities of observing CRS grades '1', '2 or higher' and 'no CRS event' after repeated dosing using NONMEM® v7.4.3. The model estimated the cumulative probabilities of the different CRS event grades.
- The effect of the drug concentration in the central disposition compartment ('Model B') as well as the drug effect on a hypothetical CRS capacity (CRSC, 'Model C') were investigated to improve the prediction of CRS events.
- Goodness of fit and model selection were assessed based on the objective function value (OFV), Akaike information criterion (AIC) and visual predictive checks (VPCs).



Key findings and conclusions

- The integration of an exposure-response relationship improved the base proportional odds model and led to adequate description of the incidence of ordered categorical CRS event data from 107 patients.
- The model could be used to further investigate predictors of CRS events as well as to simulate CRS event rates in different settings.
- This model may help to support the clinical development program of BI 764532 and other TcEs.

Results

- CRS event data was available from 107 patients. Overall, 89 CRS events of grade 1 and 20 CRS events of grade 2 or higher were integrated for model development.
- Based on AIC and VPCs, Model C was able to best describe the decreasing risk of CRS events over time in the Phase I dose escalation trial setting (Figure 3).
- In Model C, the CRS event probabilities depended on the drug concentration in the central compartment (represented as maximum concentration within a dosing interval, C_{max}) and on the CRSC (Figure 2).
- From different evaluated models describing the direct drug effect on the probability of CRS events (e.g., linear, log-linear, E_{max}), the current best model (Model C) included a linear drug effect. The CRSC was implemented as a turnover model with a linear drug effect on k_{out} (Figure 2).
- In the current best model (Model C), k_{in} was fixed to 0.001 h^{-1} and the parameter describing the linear drug effect on k_{out} was estimated to be $0.013 \text{ mL ng}^{-1} \text{ h}^{-1}$ (relative standard error 46.9%).
- Random effects were implemented as additive distribution on baseline parameters and exponential distribution for drug effect-related parameters.

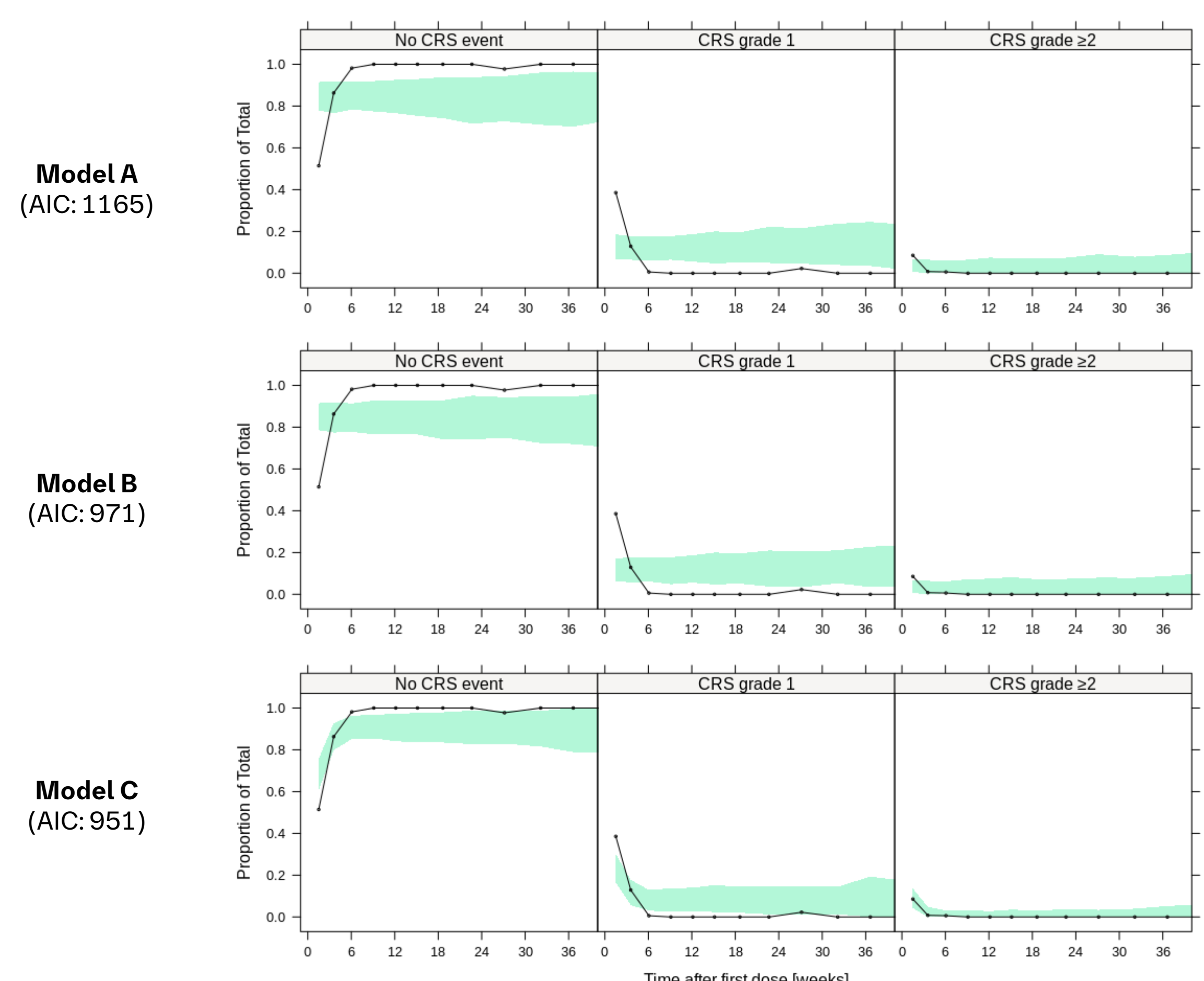
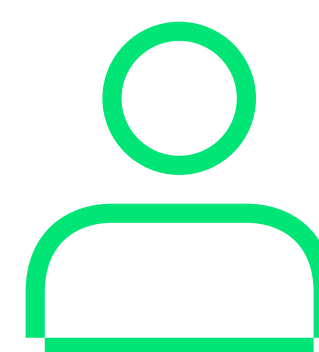


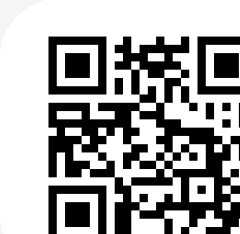
Figure 3. Categorical visual predictive checks for weekly target dosing with two step-in doses up to 40 weeks. Model A, Proportional odds model; Model B, Proportional odds model with drug effect; Model C, Proportional odds model with drug effect and cytokine release syndrome capacity (CRSC). 500 simulations were performed to create the visual predictive checks. Solid black lines and filled black dots represent the observed proportions of different CRS event grades; shaded green areas represent the 95% confidence intervals; AIC, Akaike information criterion; CRS, cytokine release syndrome.

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