

Uncovering Bias in Exposure-Response Relationships: Investigating the Impact of Exposure Calculation for Irregular Dosing Regimens

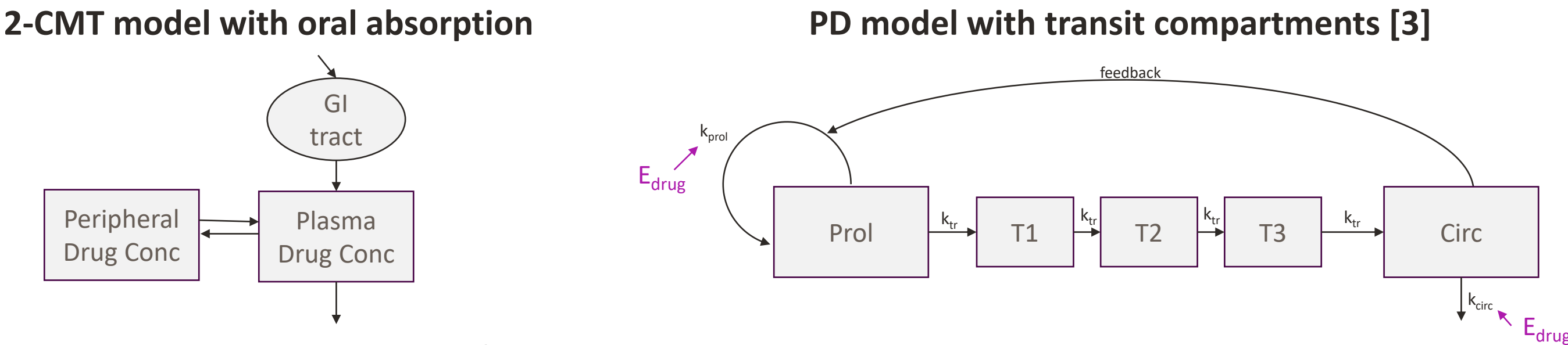
Corinna Maier¹, Sven Mensing¹, Insa Winzenborg¹
¹Clinical Pharmacology and Pharmacometrics, AbbVie Deutschland GmbH Co. KG, Ludwigshafen, Germany

Introduction and Objectives

- Understanding drug exposure and its link to clinical response is critical for informed decision-making in drug development
- Logistic regression models with one-point exposure summaries are commonly used due to ease of use but may introduce bias as shown previously [1,2]
- This simulation study explores the potential bias for the exposure metric average concentration up to the event (C_{avgTE}) in context of irregular dosing scenarios, including step-up designs, dosing holidays and dose reductions.

Methods

- Simulation framework for a hypothetical drug with effect on circulating cells:



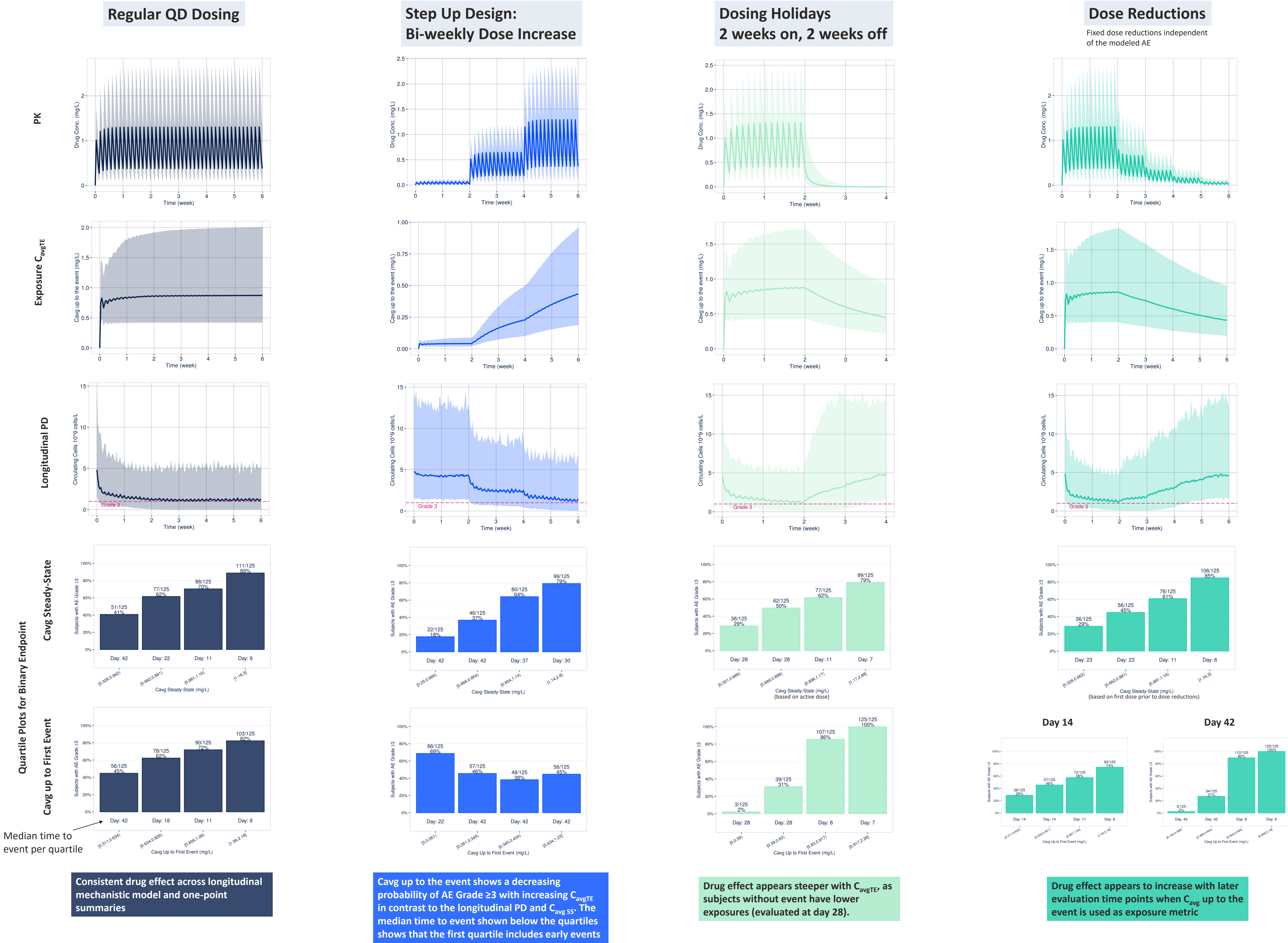
- The following parameter values were used for the simulation scenarios:

Parameter	Typical Value	IIV (standard deviation)
Absorption rate k_a (1/day)	3.5	--
Clearance CL (L/day)	450	0.4
Central Volume Vc (L)	120	0.5
Intercompartmental clearance Q (L/day)	100	--
Peripheral Volume Vp (L)	120	--
Baseline circulating cells $Circ_0$ (10^9 cells/L)	5	0.5
Exponent of feedback γ	0.15	--
Transit rate k_{tr} ($=k_{prol} = k_{circ}$) (1/day)	4/(120/24)	--
Linear Drug Effect on proliferation rate $E_{drug,prol}$	0.2	0.4
Linear drug effect on circulating cells $E_{drug,circ}$	1.7	0.7
Proportional Error (standard deviation)	0.2	--

Table 1. PK-PD Model Parameter Values Used for Simulations
Please note that these values are hypothetical values

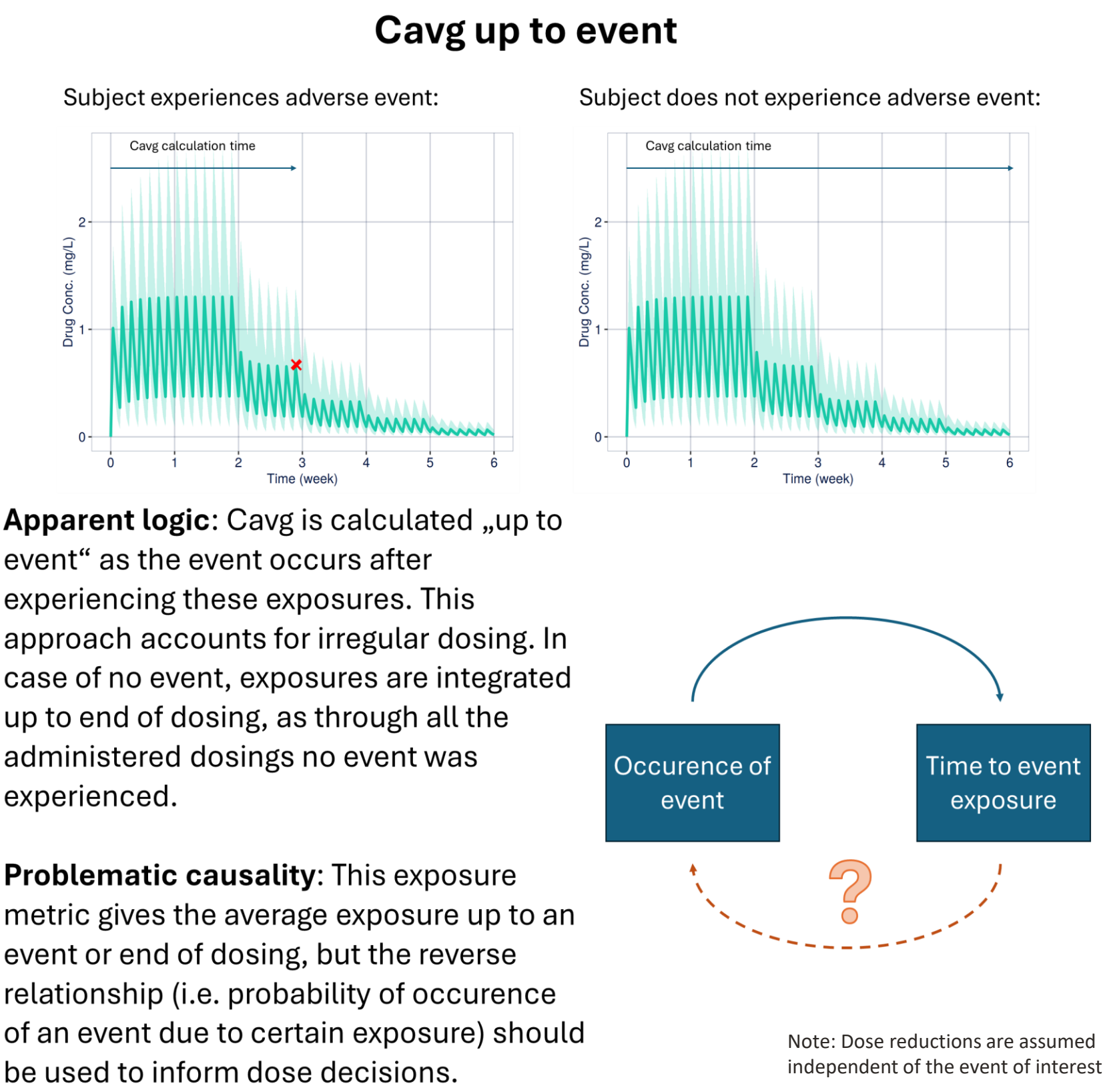
- Daily sampling was assumed for evaluation of the binary AE endpoint according to a chosen threshold.
- Exposure metric calculation:
Cavg Steady-State: $C_{avgSS} = \text{Dose}/CL$
Cavg up to First Event: $C_{avgTE,i} = \int_0^{t_i} C_i(t) dt / t_i$ where t_i denotes the time of the first event of subject i .

Results



Conclusions

- The simulation study confirms previous finding that average concentration up to event as the exposure metric can introduce bias in exposure-response models
- Steady-state C_{avg} is consistent across the considered dosing scenarios and correctly shows the increasing drug effect with decreasing clearance, however, it is not suitable to characterize the effect of dosing holidays or dose reductions to mitigate the risk of AEs.
- This simulation study highlights the value of longitudinal mechanistic models or longitudinal Markov models (not shown) to correctly characterize exposure-response relationships for irregular dosing scenarios.
- A-priori simulations using appropriate (semi-) mechanistic models can help identify potential biases and select appropriate exposure metrics for the question at hand.
- Carefully selecting exposure metrics and conducting a-priori simulations is found to be key for meaningful exposure-response analyses to inform dose selection and confirmation throughout drug development stages.



References

- Wiens MR, French JL, Rogers JA. (2023). *Confounded exposure metrics*. CPT Pharmacometrics Syst Pharmacol; 00: 1-5. doi:[10.1002/psp4.13074](https://doi.org/10.1002/psp4.13074)
- Largajolli A et al. (2023). *Considerations when deriving time-averaged exposure for censored subjects for logistic regression exposure-response analyses*. PAGE meeting url: <https://www.page-meeting.org/default.asp?abstract=10425>
- Friberg L et al. (2002). *Model of chemotherapy-induced myelosuppression with parameter consistency across drugs*. Journal of Clinical Oncology, 20(24), 4713–4721. doi: [10.1200/JCO.2002.02.140](https://doi.org/10.1200/JCO.2002.02.140)

Disclosure: AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

All authors are employees of AbbVie Inc. and may hold stock or options in the company.

©AbbVie Inc. 2024