

Designing Phase 2b studies for optimal Phase 3 dosing/regimen selection using end-to-end D-E-TE-R modelling

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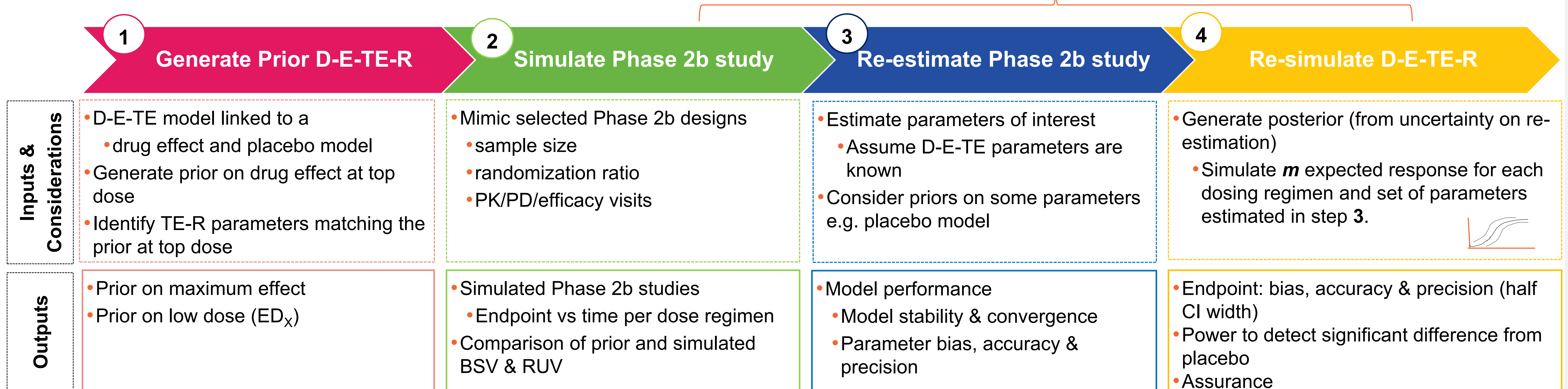
Objectives

- Getting the dose right in Phase 3 is an important requisite for the successful registration of new medicines highlighting the need for high quality fit-for-purpose Phase 2b programs.
- Traditional methods for dose selection in Phase 2b studies, such as pairwise comparison and empirical regression methods (e.g., direct Dose-Response models) face limitations in accounting for longitudinal changes in PK and PD, comparing multiple regimens, and incorporating prior data [1].
- The objective is to demonstrate the potential of full end-to-end pharmacometric Dose-Exposure-Target Engagement-Response (D-E-TE-R) based analyses methodology in designing Phase 2b studies to optimise Phase 3 dose selection.

Methods

The proposed methodology builds on the simulation re-estimation approach of Kowalski [2].

2-4: Repeat k times



Results – Case study

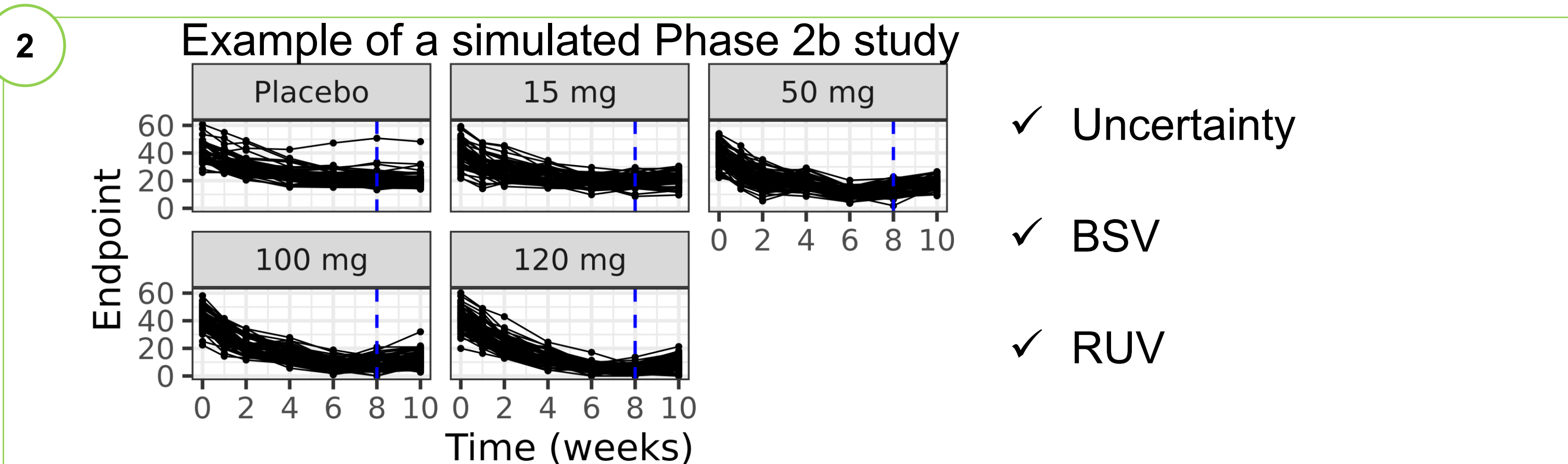
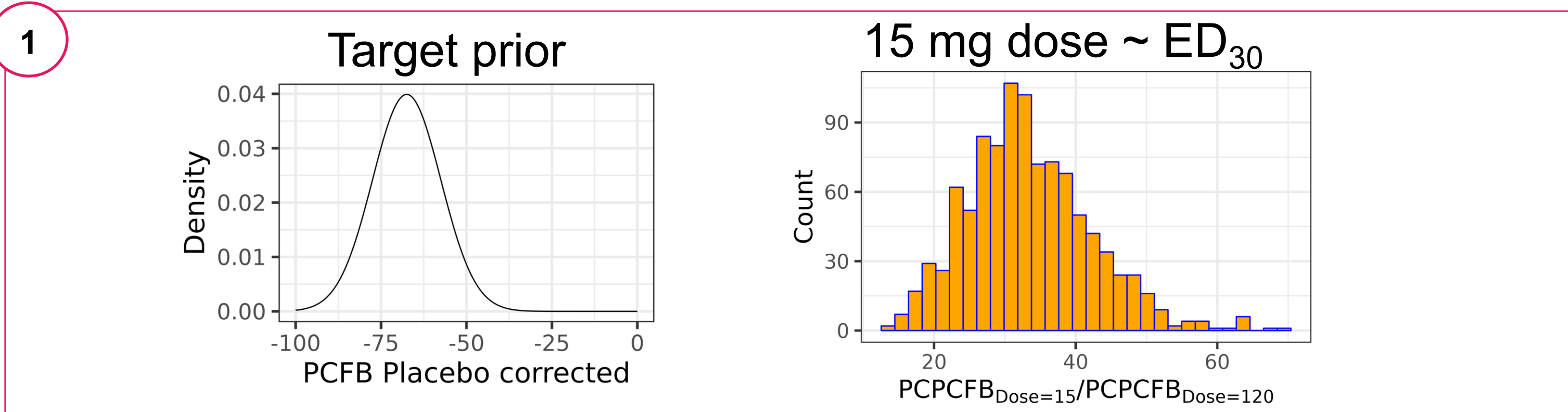
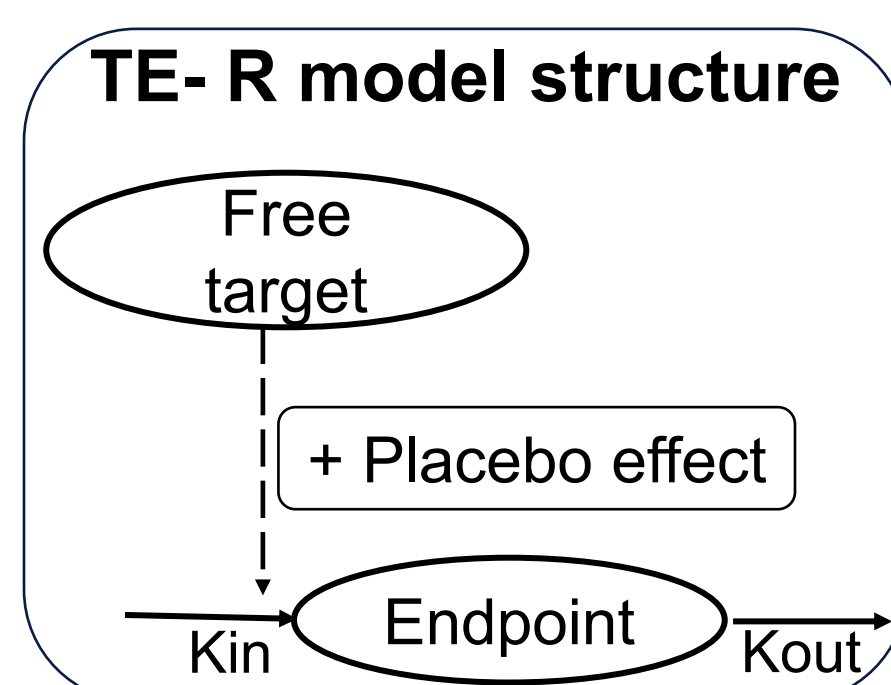
A hypothetical dose-ranging study with placebo and 4 (15 mg, 50 mg, 100 mg, 120 mg) active doses of a monoclonal antibody was used to demonstrate the approach.

Designs:

- D1:** 60 participants in each arm
- D2:** 60 participants (placebo & top dose), 30 participants (other dose levels)
- D3:** 60 participants (placebo & top dose), 15 participants (other dose levels)

Model structure:

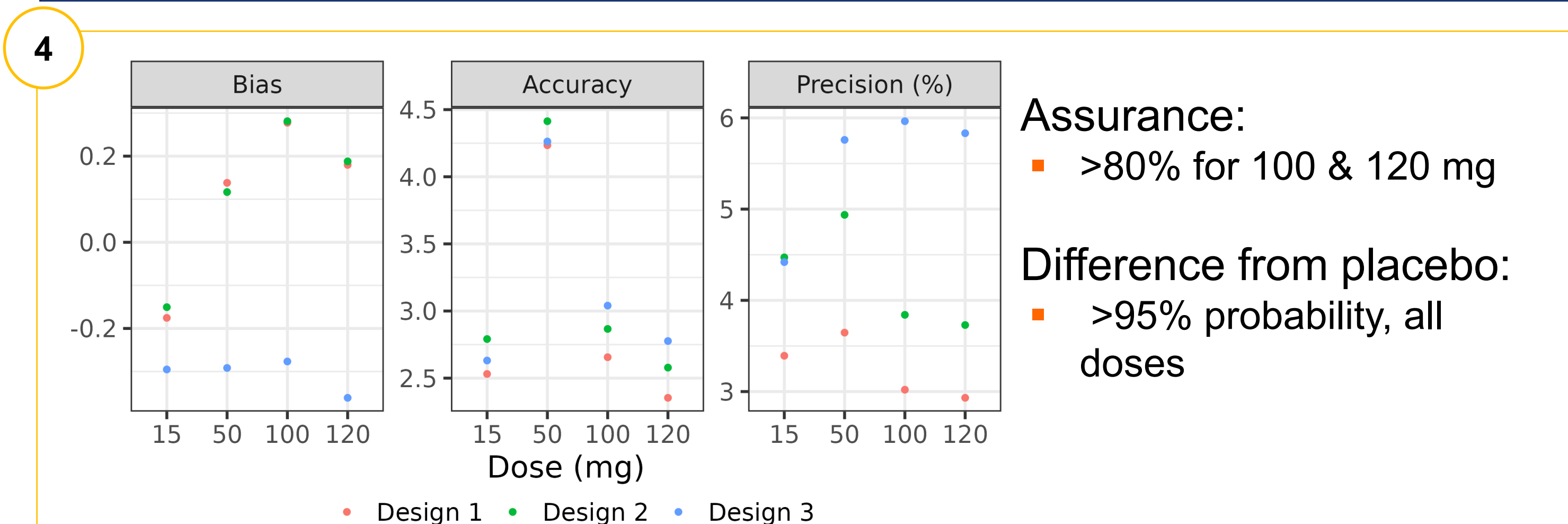
- PK: Two-compartment model[3]
- PD: QE approximation[4]
- TE-R: Power model - free target driving the response
 - $Kin_{placebo_effect} = Kout * SS_{placebo_effect}$
 - $Kin_{drug_effect} = Kout * SS_{drug_effect}$
 - $Effect_{placebo} = (Baseline\ free\ target)^{Hill}$
 - $Effect_{drug} = (Free\ target)^{Hill}$
 - $Kin = Kin_{drug_effect} + (Kin_{placebo_effect} - Kin_{drug_effect}) * (Effect_{drug} / Effect_{placebo})$



Parameter	Bias ⁱ		Accuracy ⁱ		Precision (%)	
	D1	D3	D1	D3	D1	D3
$Baseline_{endpoint}$	0.001	<0.001	0.013	0.019	6	8
SS_{drug_effect}	-0.001	-0.072	0.048	0.081	44	60
$SS_{placebo_effect}$	-0.026	-0.002	0.021	0.016	7	5
$Kout$	<0.001	<0.001	0.001	0.001	1	1
$Hill$	0.266	0.258	0.807	0.809	35	21

ⁱBias and accuracy are on the same scale as the parameter

- The proposed D-E-TE-R model is numerically stable with the proposed study designs.
- SS_{drug_effect} and $Hill$ parameters have poor precision, but this has minimal impact on the precision of Phase 2b response predictions.



Assurance:

- >80% for 100 & 120 mg

Difference from placebo:

- >95% probability, all doses

- Design 2 with 30% reduced sample size achieves comparable response predictions as design 1.

Bias: $E[mean(PCPCFB_{resimulated} - PCPCFB_{true})]$

Accuracy: $E[mean(abs(PCPCFB_{resimulated} - PCPCFB_{true}))]$

Precision: $E[0.5 * (quantile(PCPCFB_{resimulated}, 0.975) - quantile(PCPCFB_{resimulated}, 0.025))]$

Assurance: $p(quantile(PCPCFB_{resimulated}, 0.05) \leq -45 \& quantile(PCPCFB_{resimulated}, 0.8) \leq -25)$

Difference from placebo: $p(quantile(PCPCFB_{resimulated}, 0.975) < 0)$

Conclusion

The proposed methodological approach ensures

- optimization of phase 2b studies for robust characterization of granular D-R relationships
- accurate and precise selection of Phase 3 dose regimen(s)

References

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Abbreviations

D1 = Design 1; ME = Mean error; MAE = Mean absolute error; MRSE = Mean relative standard error; PCPCFB = Placebo corrected percentage change from baseline; SS = Steady-state

Disclosures

MC, TS, SZ, NBB are employees of, and shareholders in GSK