

Interactive shiny application to support design of non-inferiority trials based on surrogate biomarkers

Martine Neyens¹, Juan Jose Perez Ruixo², Ruben Faelens¹

¹ Johnson & Johnson, Beerse, Belgium, ² Johnson & Johnson, Madrid, Spain

Introduction

- 1
- When transitioning to a new candidate dosing posology with variations in dose, dosing interval, administration route, or formulation, pharmacokinetic (PK) bio-equivalence may not be demonstrable.
- 2
- Repeating pivotal clinical trials to demonstrate favorable benefit/risk profile using clinical endpoints may requires prohibitively large sample sizes.
- 3
- However, the availability of a pharmacodynamic (PD) biomarker offers an alternative by facilitating the establishment of non-inferior effects on the PD marker. This approach uses a non-inferiority margin on PD biomarker that correlates with a minimal (non-regrettable) loss of clinical endpoint efficacy.
- 4
- Establishing NI on a PD biomarker is feasible with lower sample sizes.

Model and Parameters

Parameter	Theta	IIV
Vc (L)	5	20%
CL (L/h)	3	20%
Vp (L)	4	
Q (L/h)	2	
KA (/h)	0.3	10%
F1	10	10%
BSL Biomarker (mg/L)	10	5%
KOUT (/h)	0.1	10%
EC50 for PD biomarker (mg/L)	50	10%
EMax for PD biomarker	1	
Hill coefficient PD	0.8	
Base response probability	35%	
OR per 10% of biomarker CFB	1.15	

Pivotal Phase 3 completed

IV 50mg/kg QW vs Placebo. N=100 / arm

Results:

IV 50mg/kg QW 56% response rate

Placebo 35% response rate

Difference (Drug Effect) 21%; 95%CI [8.3%; 35.7%]

How to demonstrate efficacy for an oral dosing formulation?

1 IV reference and Oral test dose

Transitioning to a new candidate dosing posology

IV 50mg/kg QW is the reference dose, with predicted response rate of 56%



To achieve the same response rate, an oral dose of 300mg QD is selected.

2 Pivotal trial for Oral dose

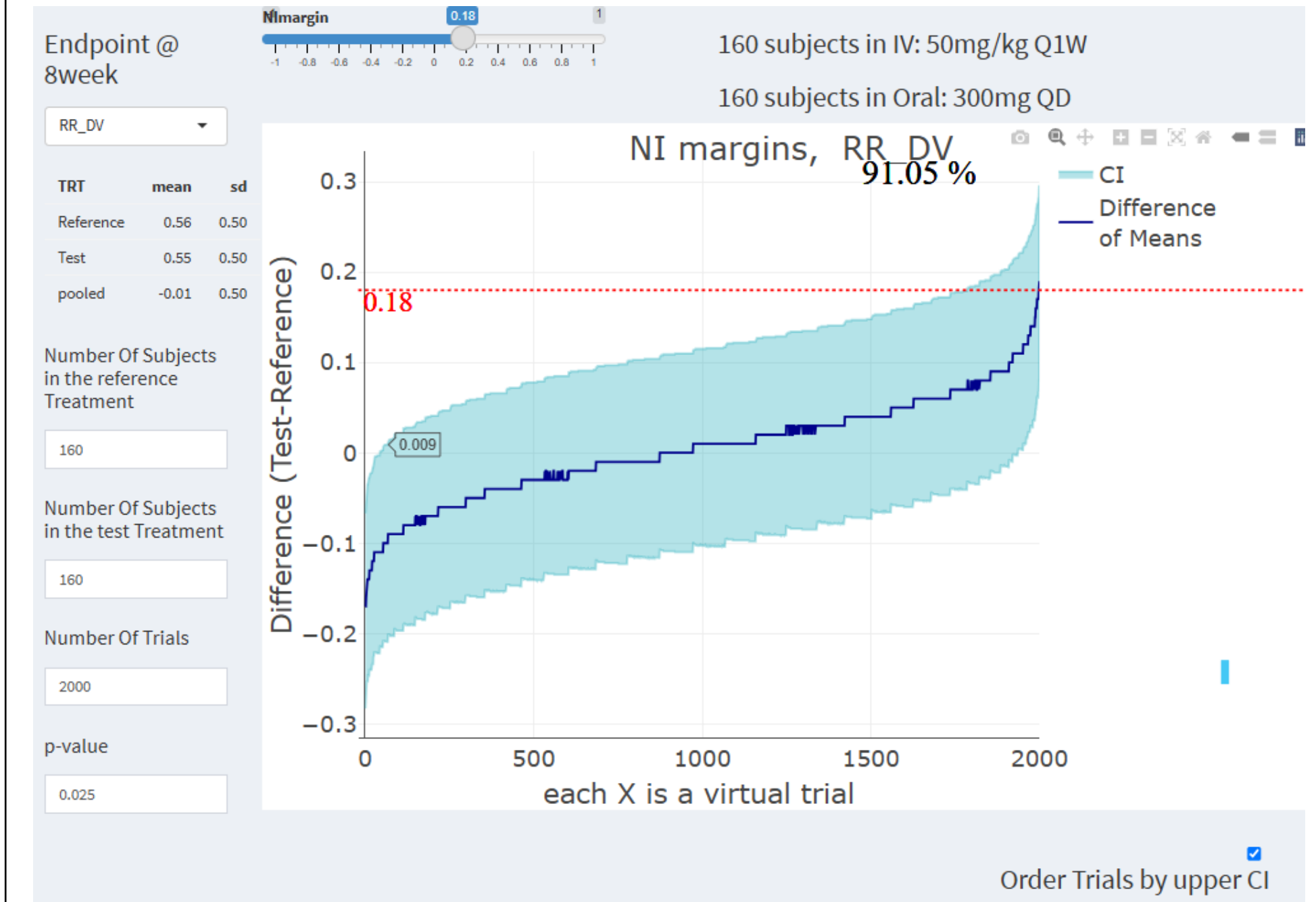
Clinical endpoints require prohibitively large sample sizes

Oral 300mg QD non-inferior to IV 50mg/kg

How many participants do we need for a study showing non-inferiority on the response rate of the oral test regimen to the IV reference?

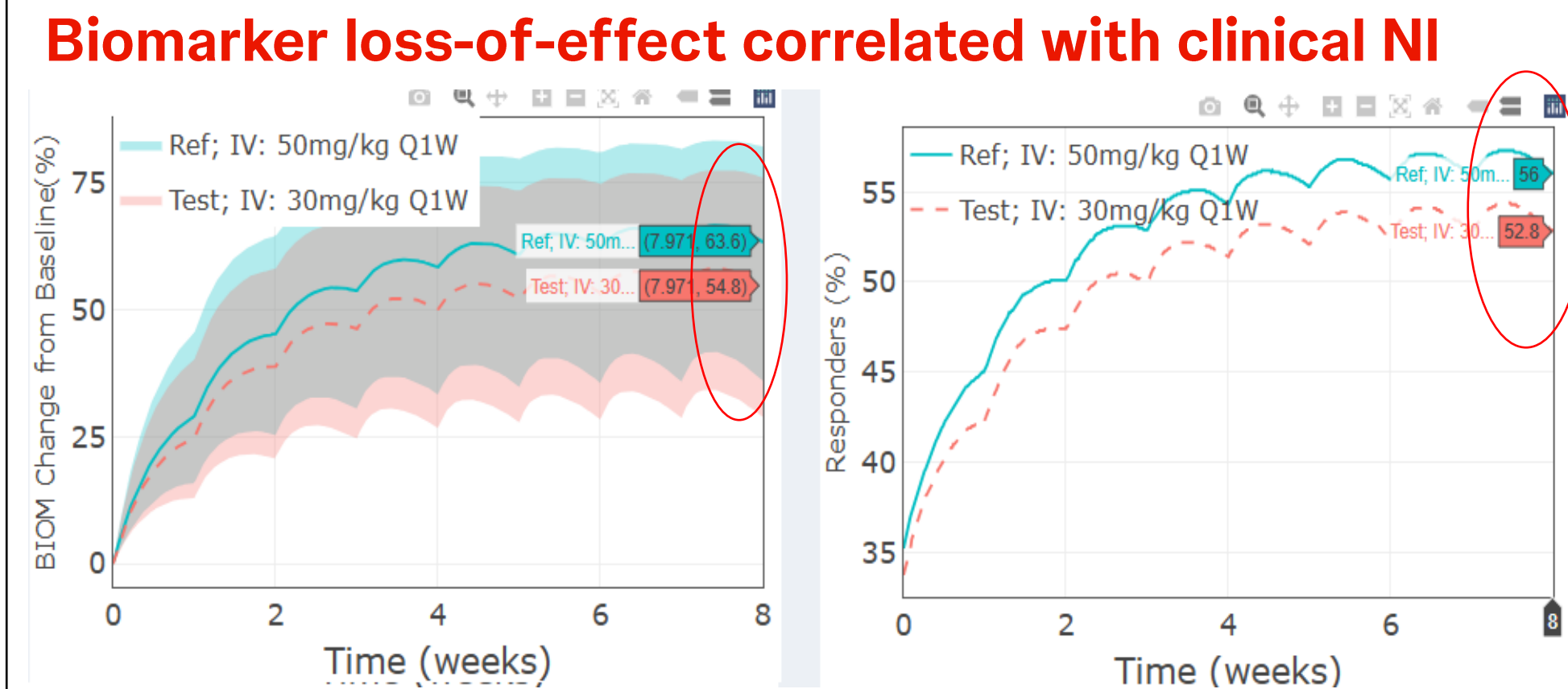
M1 is the worst-case drug effect (8.3%)

M2 is the maximum we are willing to lose: 1/3rd of drug effect i.e. 3% loss in response rate



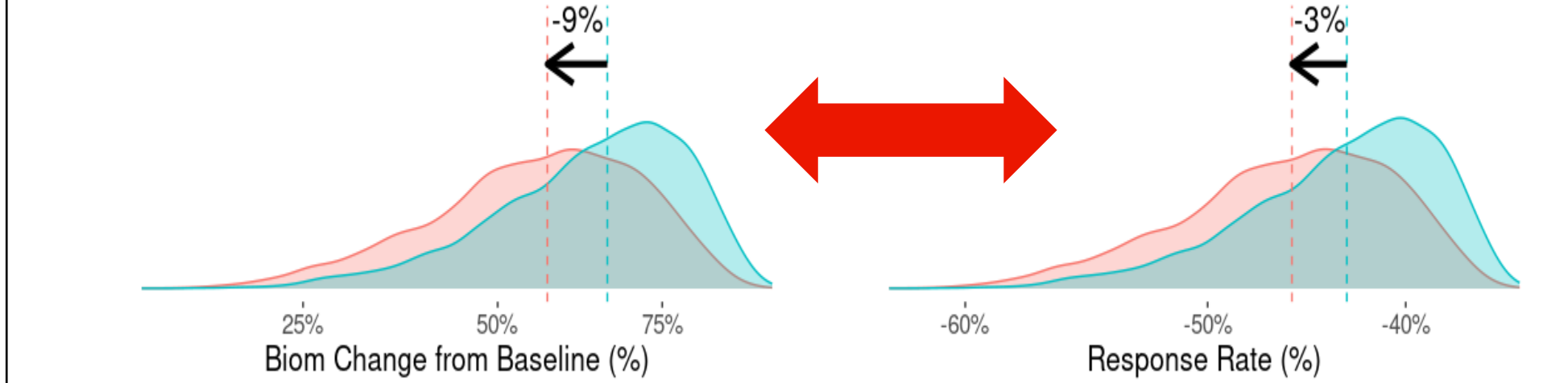
This requires impractically large sample size of 160/arm.

3 Biomarker NI margin



Instead of using Response Rate as endpoint, we will demonstrate NI on the biomarker change from baseline. The biomarker correlates with the endpoint and explains a large proportion of the treatment effect.

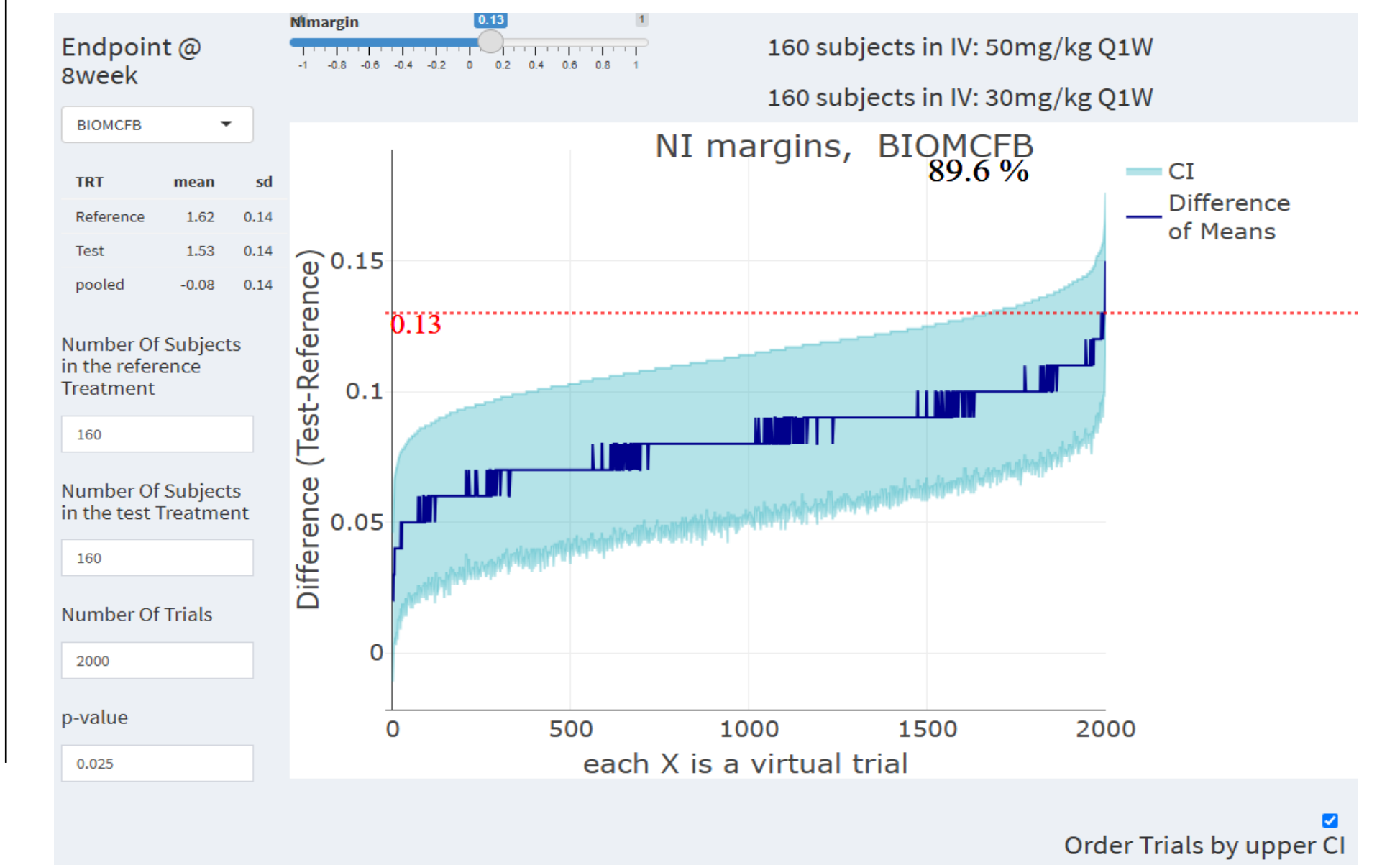
What IV dose and biomarker response is associated with 3% loss in response rate given the biomarker to endpoint correlation?



The difference reference vs test in biomarker CFB: 63.6 - 54.8 = 8.8% (obtained using a simulated dose of IV 30mg/kg QW).

Biomarker NI margin

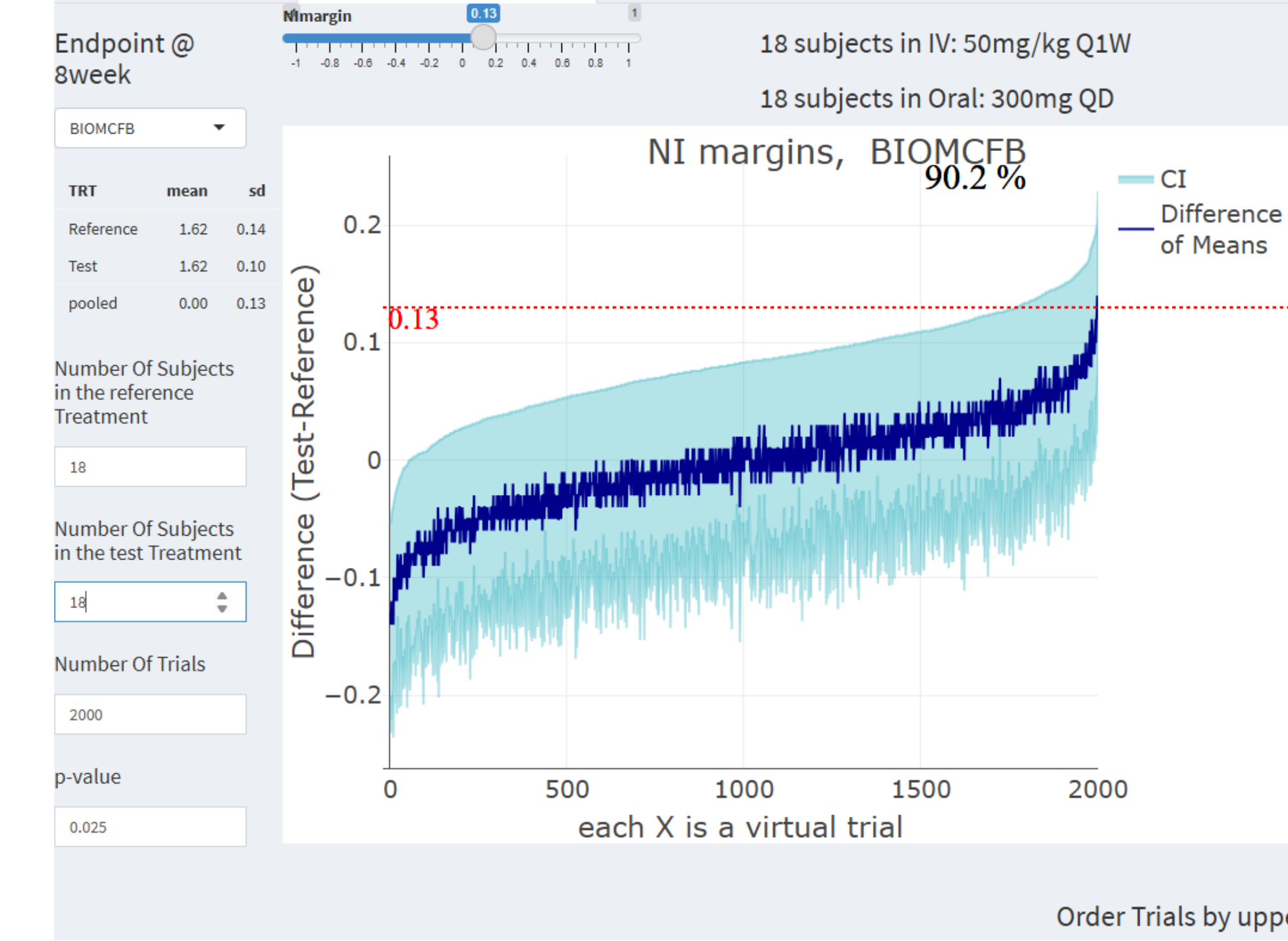
Allowing for some variability in a trial with large enough sample size (N=160 / arm), the NI margin is 13%, with a PoSS >90%.



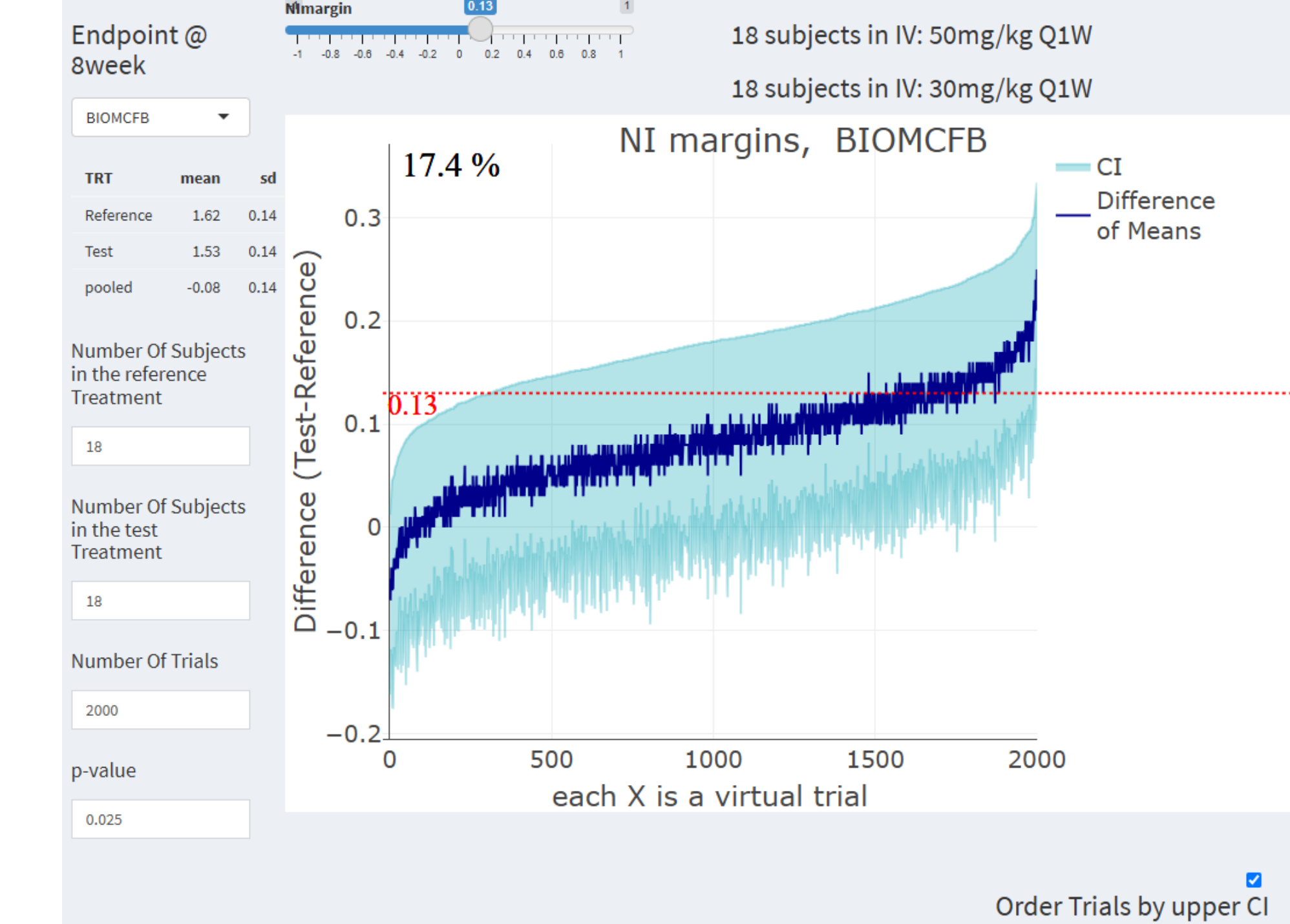
4 Sample Size for biomarker NI trial

How many subjects do we need to reliably demonstrate (PoSS > 90%) that the Oral 300mg QD dose is non-inferior to reference based on the biomarker?

Using a NI margin of 13%, we need 18 subjects per arm to have >90% PoSS.



Using the IV 30mg/kg test dose, 18 subjects per arm results in a PoSS of 17%, i.e. an acceptably low false positive rate.



The study design identified in this example reduces NI sample size from N=160/arm to N=18/arm, with low predicted false negative (10%) and false positive (17%) rates.

Conclusions

A shiny app to explore a non-inferiority margin for a biomarker can support clinical discussions on study design, bypassing the usual turnaround delay when performing clinical trial simulations.

References

- <https://cran.r-project.org/web/packages/shiny>
- <https://cran.r-project.org/web/packages/plotly>
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials>