MODEL-BASED DRUG DEVELOPMENT

8 June 2011

EFSPI Statistical Leaders Meeting

Introduction

- As set out in the 1-pager, Sheiner, Senn, Lalonde and colleagues have highlighted an apparent slowness by statisticians to engage with model-based approaches to drug development

- Questions
  - do we agree with this negative verdict on our discipline?
  - is it true, as it seems, that the kineticists have stolen a march on us?
  - where is the leadership within our own profession to challenge this view?
  - What, if anything, can EFSPI do here?

Models exemplified

- To motivate discussion I will highlight examples from different areas of our business
  - 1. Modelling clinical data
    - (i) Predicting relative efficacy in a new indication
    - (ii) Modelling competitor data
    - (iii) More efficient trial design
  - 2. Pre-clinical PK-PD modelling
  - 3. Biological systems modelling

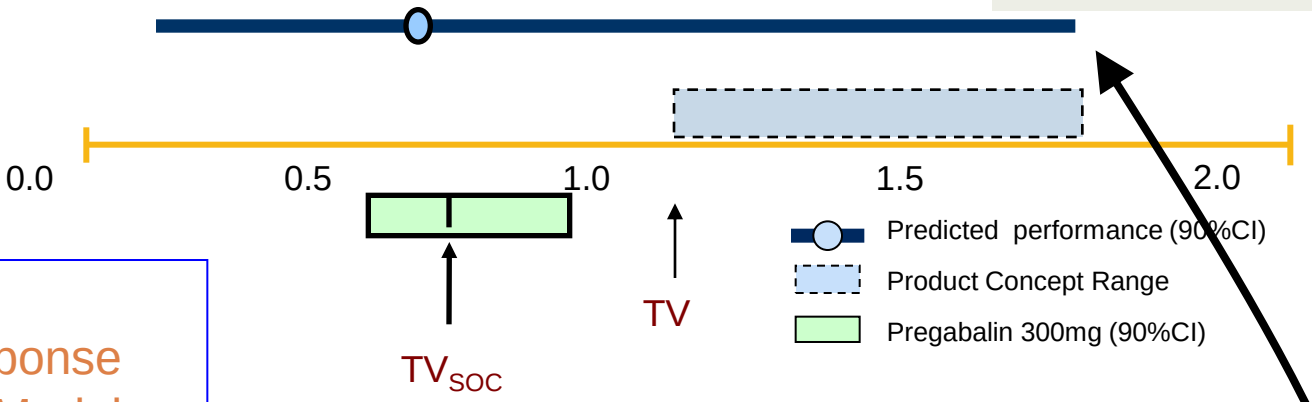
1. Modelling clinical data

(i) Predicting relative efficacy in a new indication

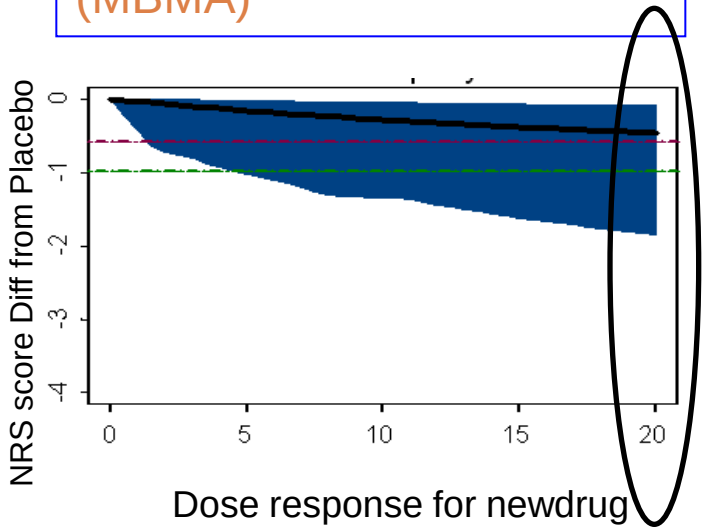
Efficacy

Placebo corrected improvement in NRS pain score
(scale 0-10)

Predicted performance and 90%CI for newdrug



A prediction of the expected dose-response for *newdrug* using Model Based Meta-Analysis (MBMA)

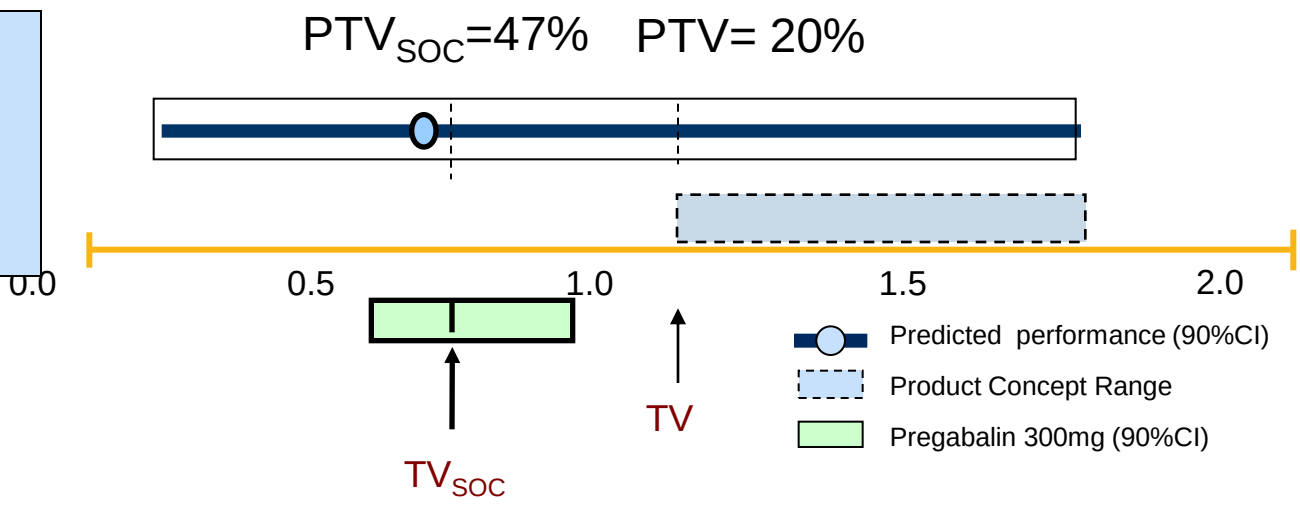


- We have date on *newdrug in PHN*
- We wish to predict efficacy in DPN
- We have competitor data in both indications

1. Modelling clinical data
(i) Predicting relative efficacy in a new indication

Efficacy

Placebo corrected improvement in NRS pain score
(scale 0-10)



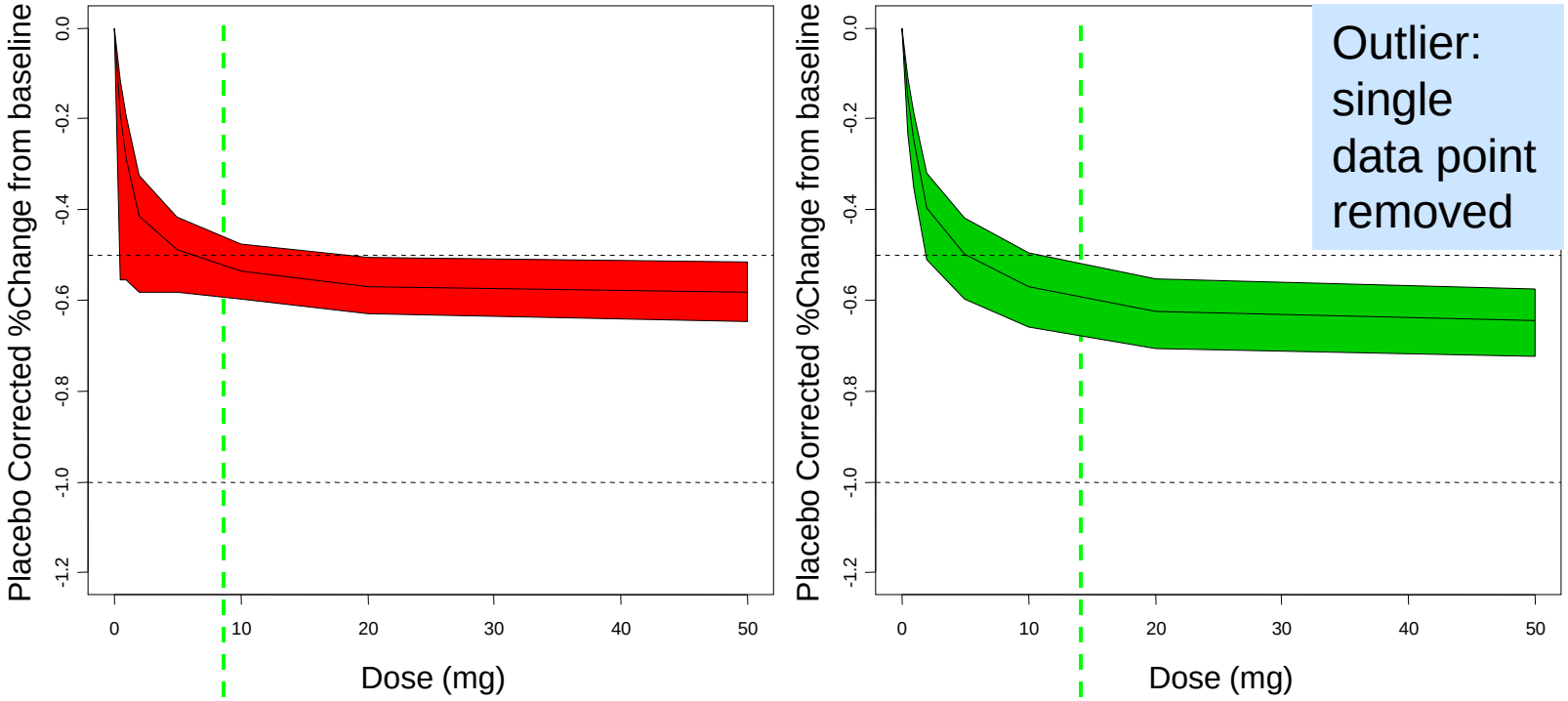
We can calculate the probability of achieving a Target Value (PTV) for newdrug in the new indication

1. Modelling clinical data
(ii) Modelling competitor data

Product Concept	**Diabetes agent providing weight loss and/or cardiovascular benefits**
Mechanism of Action	**X**
Strategy	**Accelerated development to be in the first wave for this MOA**
Competitive Landscape	***Company* is behind several competitors**
Key Gaps in Knowledge	**How to differentiate from the leading competitor?**

1. Modelling clinical data
(ii) Modelling competitor data

The leading competitor: dose-response for HbA1c%

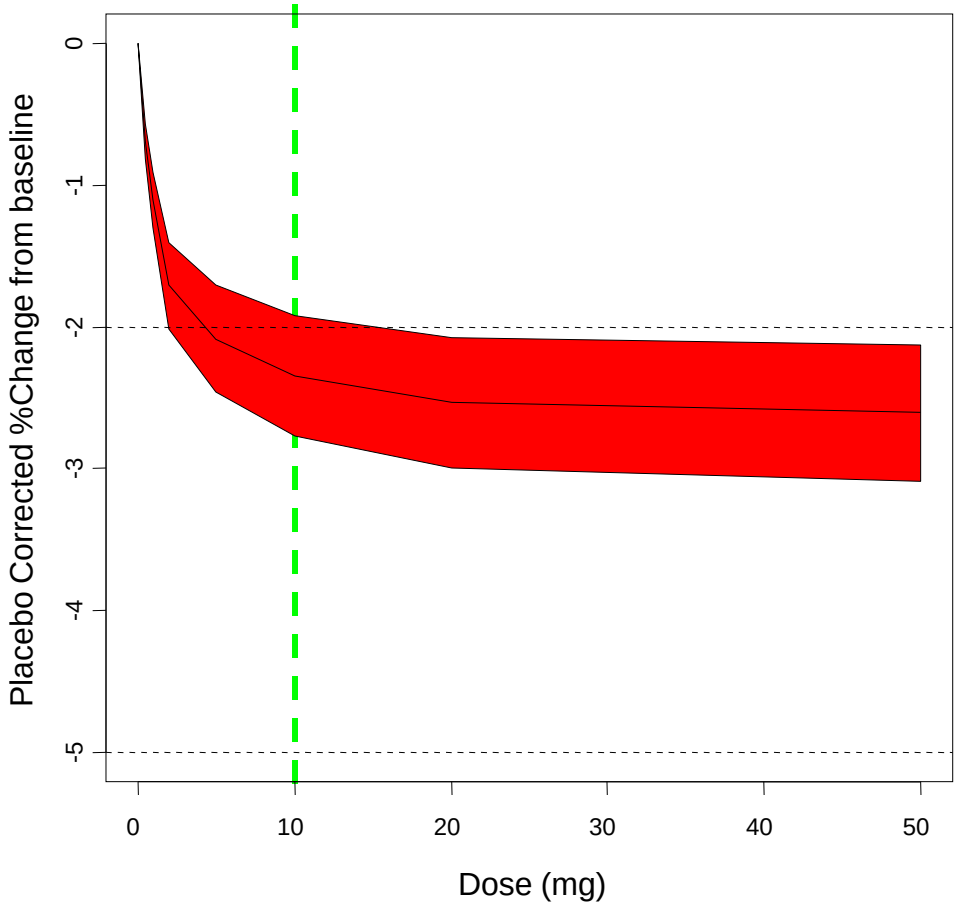


- Estimated E_{max}= 0.59 ± 0.1% with an ED_{50} of 1.05 ± 0.8 mg for HbA1c effect

- Potential outlier at 20 mg dose in diabetic naive study (-0.55% HbA1c) if removed yields
  - E_{max} = 0.67 ± 0.04, ED_{50} 1.7 ± 0.3 mg
  - variability significantly reduced, especially on ED_{50}

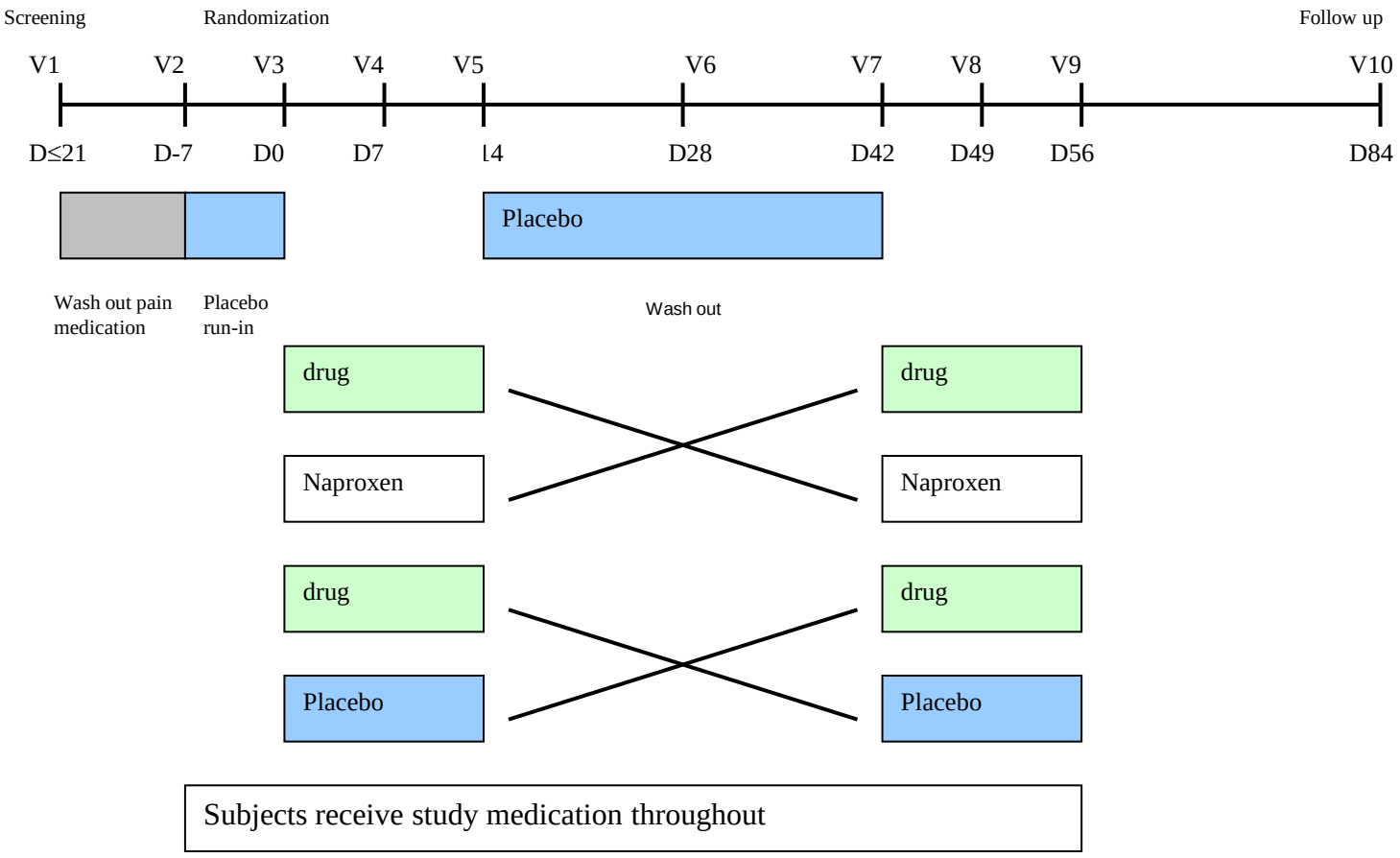
1. Modelling clinical data
(ii) Modelling competitor data

The leading competitor: dose-response for % weight loss



1. Modelling clinical data
(iii) More efficient trial design

Trial to investigate pain relief following two weeks treatment with *drug* in patients with knee OA



Bayesian Study Design

- Use informative prior for naproxen vs. placebo

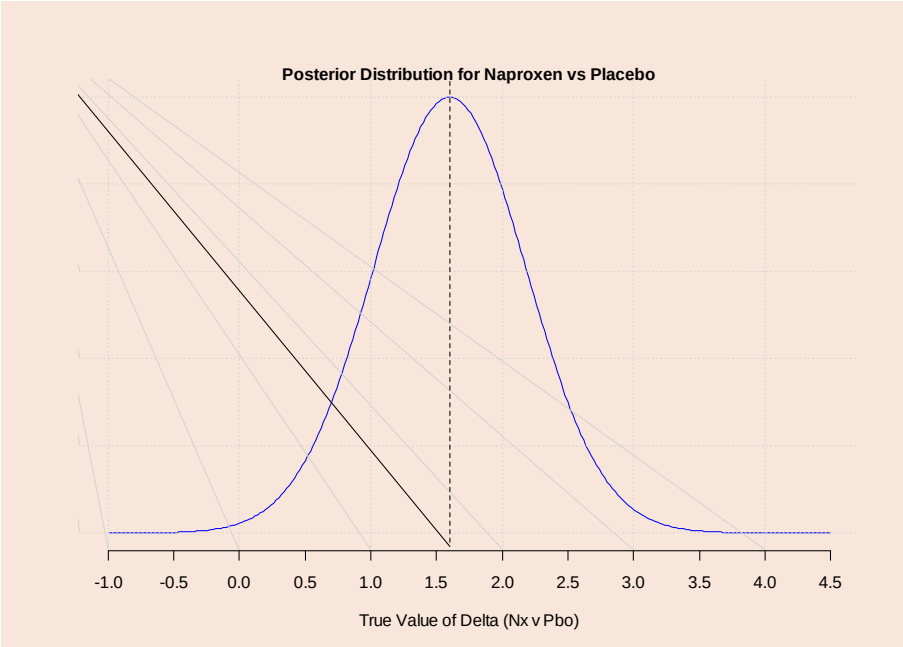
- Use elicited priors for:
  - drug vs. placebo
  - drug vs. naproxen

1. Modelling clinical data
(iii) More efficient trial design

- Prior for the effect of Naproxen vs. Placebo

$$\Delta \approx N(1.6, 0.58^2)$$

Study_Ref	Diff	SED	Variance
AAAAAAAAAA	2.0	0.33	0.11
BBBBBBBBBB	1.6	0.30	0.09
CCCCCC	2.0	0.66	0.44
DDDDDDDDD	2.1	0.83	0.68
EEEEEEEEEE	1.1	0.35	0.12
FFFFFFFF	1.1	0.51	0.26

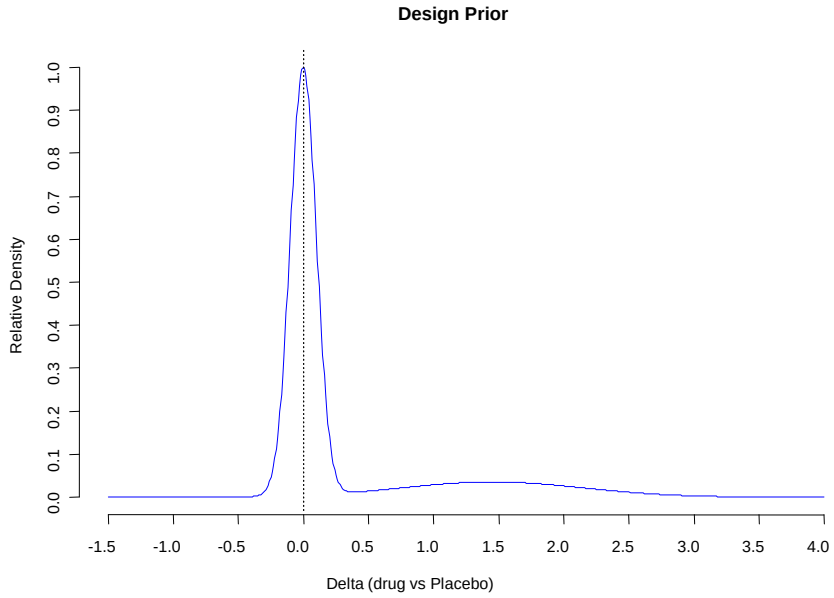


- Using this prior is equivalent to N = 54 subjects on naproxen – placebo → significant efficiency

1. Modelling clinical data
(iii) More efficient trial design

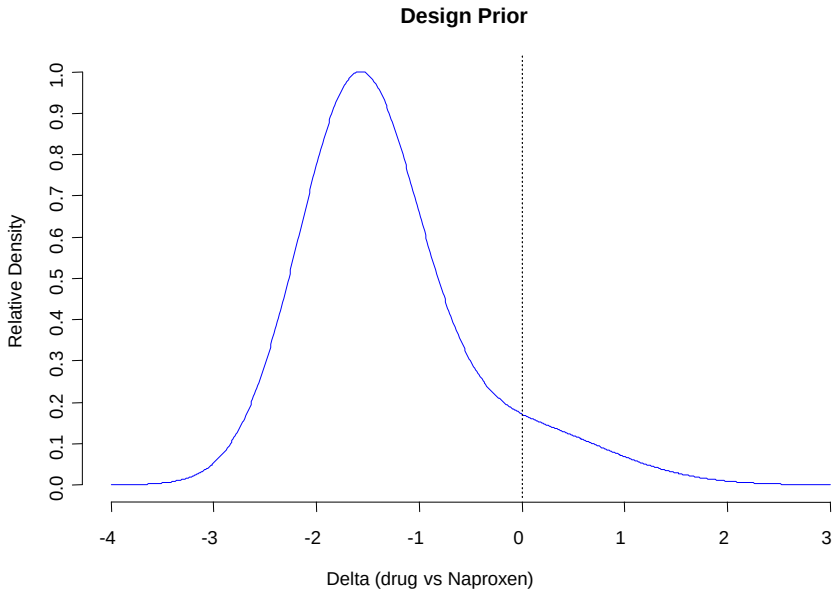
Elicited Prior Belief for drug vs. Placebo Effect

drug vs. Placebo



$0.8*N(0, 0.1^2) + 0.2*N(1.45, 0.7^2)$

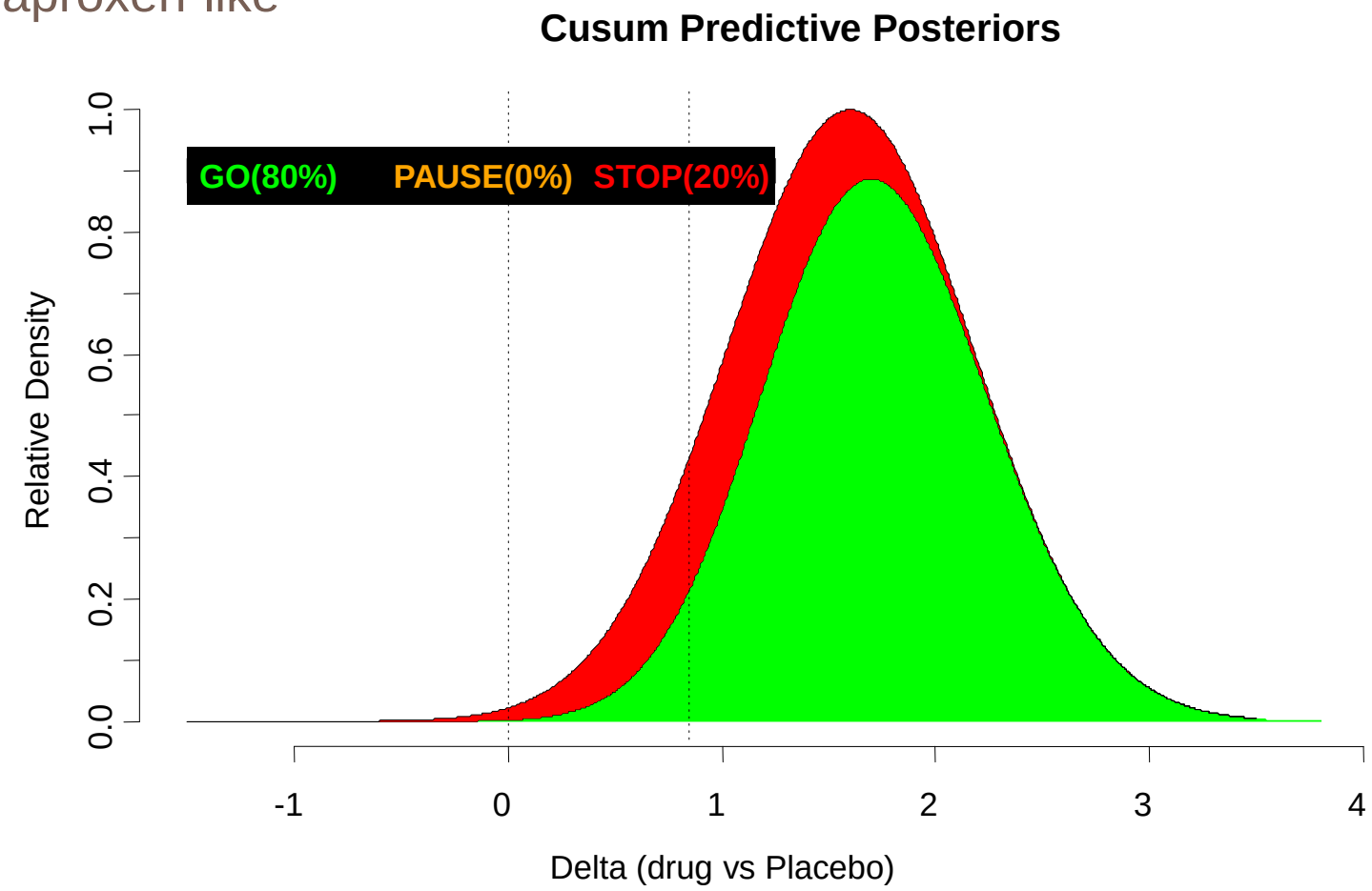
drug vs. Naproxen



$0.8*N(-1.6, 0.58^2) + 0.2*N(-0.15, (0.7^2+0.58^2))$

1. Modelling clinical data
(iii) More efficient trial design

Cumulative Predictive Posteriors for superiority to placebo when drug is Naproxen-like



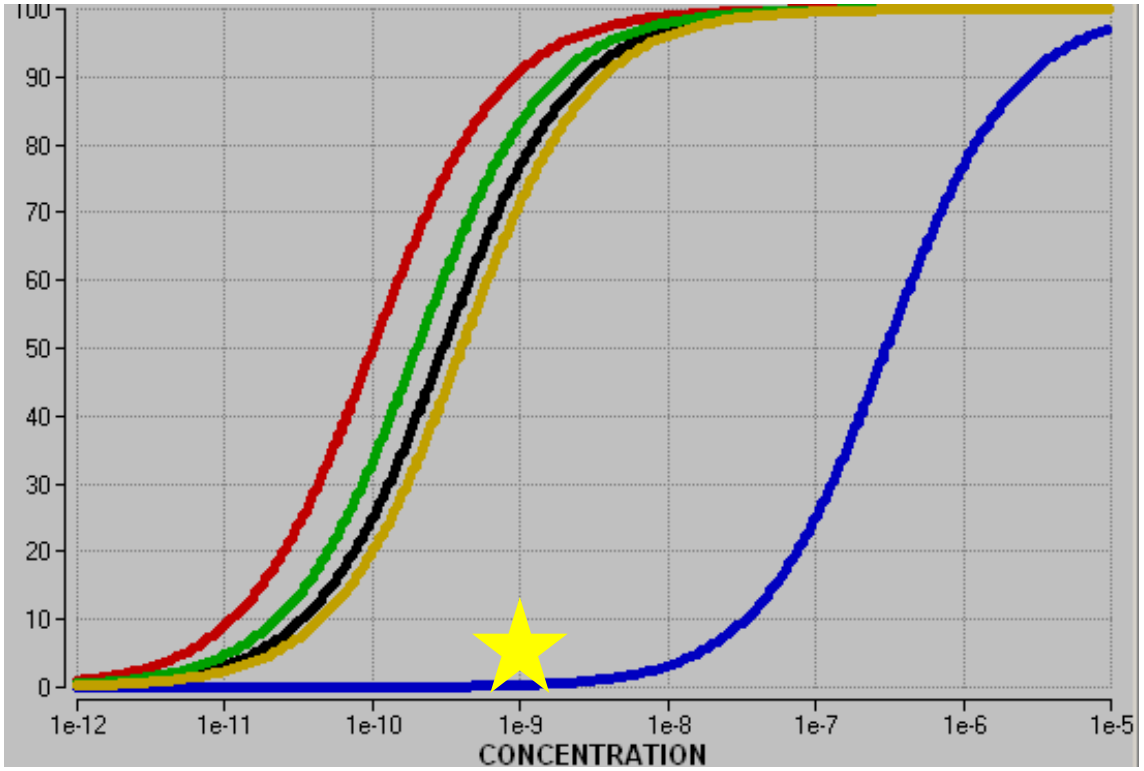
2. Pre-clinical PK-PD modelling

- Pre-clinical modelling is used to inform the expected dose or exposure needed to demonstrate efficacy in humans
- Defining and achieving ‘efficacious exposure’ (C_{eff}) is essential to create confidence that we have tested the mechanism and can walk away from a negative result in man
- Surprisingly, there is little agreement on how to define C_{eff}
- What it is not: the lowest drug concentration to yield a statistically significant difference from negative control (vehicle)

2. Pre-clinical PK-PD modelling

Human in vitro
rat in vivo binding to target
Rat in vivo down-stream pharmacology
Dog in vivo efficacy

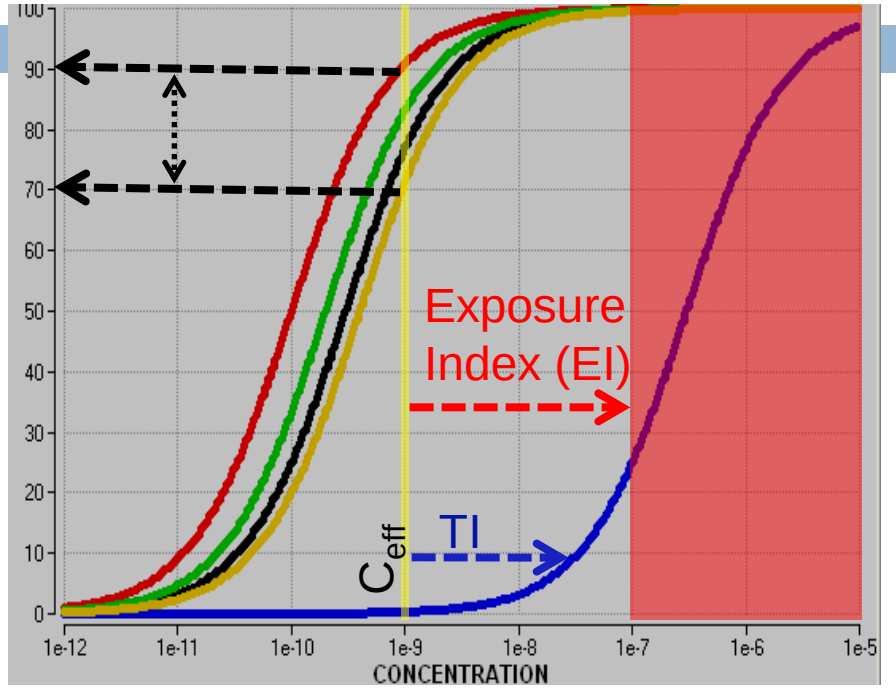
TK limit, most sensitive non-human species



Consistent pharmacology across species/models
PK-PD well characterised
Large TI
C_{eff} will test the mechanism

2. Pre-clinical PK-PD modelling

- in vitro and in vivo experiments provide estimates of IC_{50} / EC_{50} / K_i
- These are used to construct the E_{max} curves shown
- However, these estimates may not be completely robust



- How to estimate binding affinity (K_i) for a receptor antagonist in vitro?
  - Pooling across different salt forms of drug
  - Pooling of data from different labs
  - Inclusion / exclusion of data points from assay

2. Pre-clinical PK-PD modelling

Salt form	Lab 1	Lab 2
1	3.30 nM (1.98-5.49 n=5)	3.39 nM
2		1.48 nM (0.796-2.77 n=8)
3	3.81 nM (3.04-4.78 n=28)	0.969 nM (0.614-1.53 n=5)
4		>11.1 nM (3.21E-7-3.86E8 n=2)

Efficacious dose predicted at 20mg: no TI

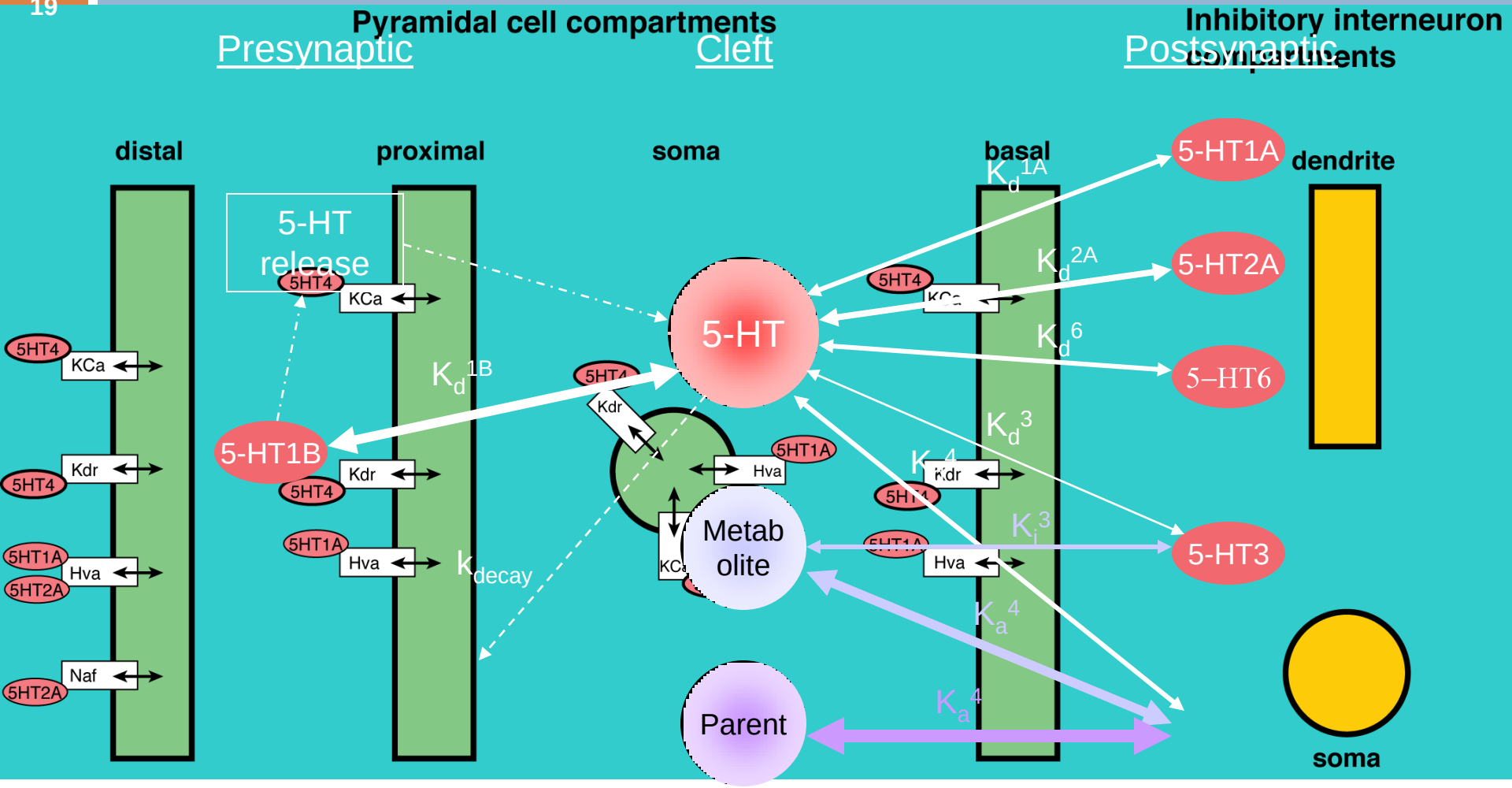
Efficacious dose predicted at 5mg: TI=2

- What is an appropriate estimator for Ki?
- What is a 'no-regrets' dose? 10 x Ki

3. Biological systems modelling

- Everything starts with target selection (human biological drug target)
- We are not biologists
  - Biologists and others are building complex models to describe basic human biology
  - Hypothesised cascade / pathway linking known biological processes
  - Suggests where to intervene to achieve desired pharmacology and avoid unwanted pharmacology
  - Rely on strong assumptions and typically take data from a variety of sources
  - Statisticians should be able to scrutinize these models
- The whole field of systems biology / pharmacology needs greater statistical scrutiny

3. Biological systems modelling



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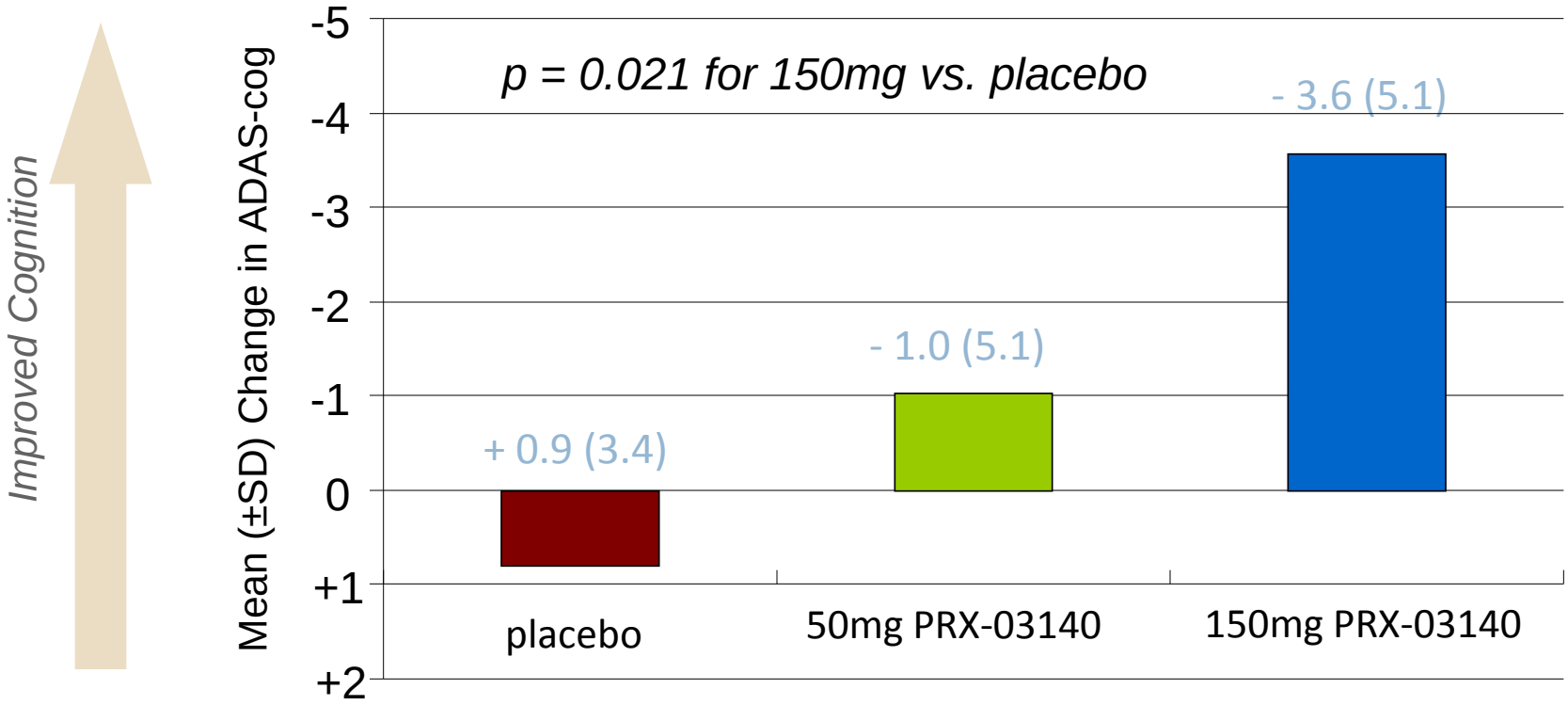

- After two weeks of dosing, mean ADAS-cog change for monotherapy (150mg) was 3.6 points
  - *Approved Alzheimer's drugs typically show 3-4 point improvement after 12-24 weeks*
- Statistically significant dose-response for 150mg vs. 50mg vs. placebo (p=0.026)

Model-based drug development: Questions

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