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Trial Simulations to Support Proof-of-Concept Study Design: Application to Immunology

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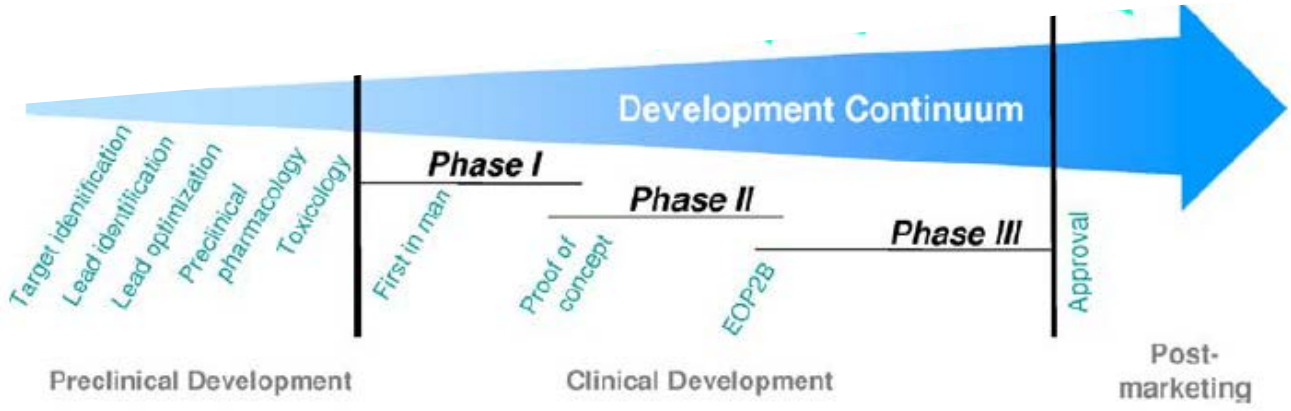
Disclosure: John Gibbs is an employee of AbbVie and may hold AbbVie stock or options.

Proof-of-Concept as a milestone in drug development

POC – earliest point in drug development at which the weight of evidence suggests that the drug candidate has key attributes for success

- Successful attributes encompass safety, efficacy, manufacturing and commercial
- Important role for quantitative sciences to assess the likelihood of success



ME Cartwright *et al*., CPT **87**: 278-285, 2010.
L Zhang *et al*. AAPS J **10**: 552-559, 2008.

Burden of “false negatives” in early development

- False positives
  - Appear to be promising new treatments
  - Fail to demonstrate adequate treatment benefit in larger studies
- False negatives
  - Wrongly eliminated from development
  - Very costly to R&D productivity

Project teams use appropriate trial designs and decision criteria to balance risk in identifying promising new drug candidates

Burt *et al*., Clin Trans Sci, 2017.

Model-based meta-analysis (MBMA)

- Combines summary level or aggregate data across trials
- Incorporates pharmacologically relevant models to control for dose and time.
- Characterize the impact of patient factors or trial designs on the outcome of interest.
- Understand the degree in trial-to-trial variability in response.

Selected examples of the application of MBMA Across Therapeutic Areas

Disease	Drug Class	Application	Reference
Hyperlipidemia	Statins	Dose-response relationships	Mandema et al., 2005
Alzheimer's Disease	AChe inhibitors	Disease progression	Ito et al., 2010
Pain	Mu opioids	Efficacy and adverse events	Mercier et al., 2014
Rheumatoid Arthritis	Biologics and methotrexate	Longitudinal analysis of efficacy	Demin et al., 2012
Oncology	Paclitaxel	Efficacy and neutropenia	Lu et al, 2014

Motivational example

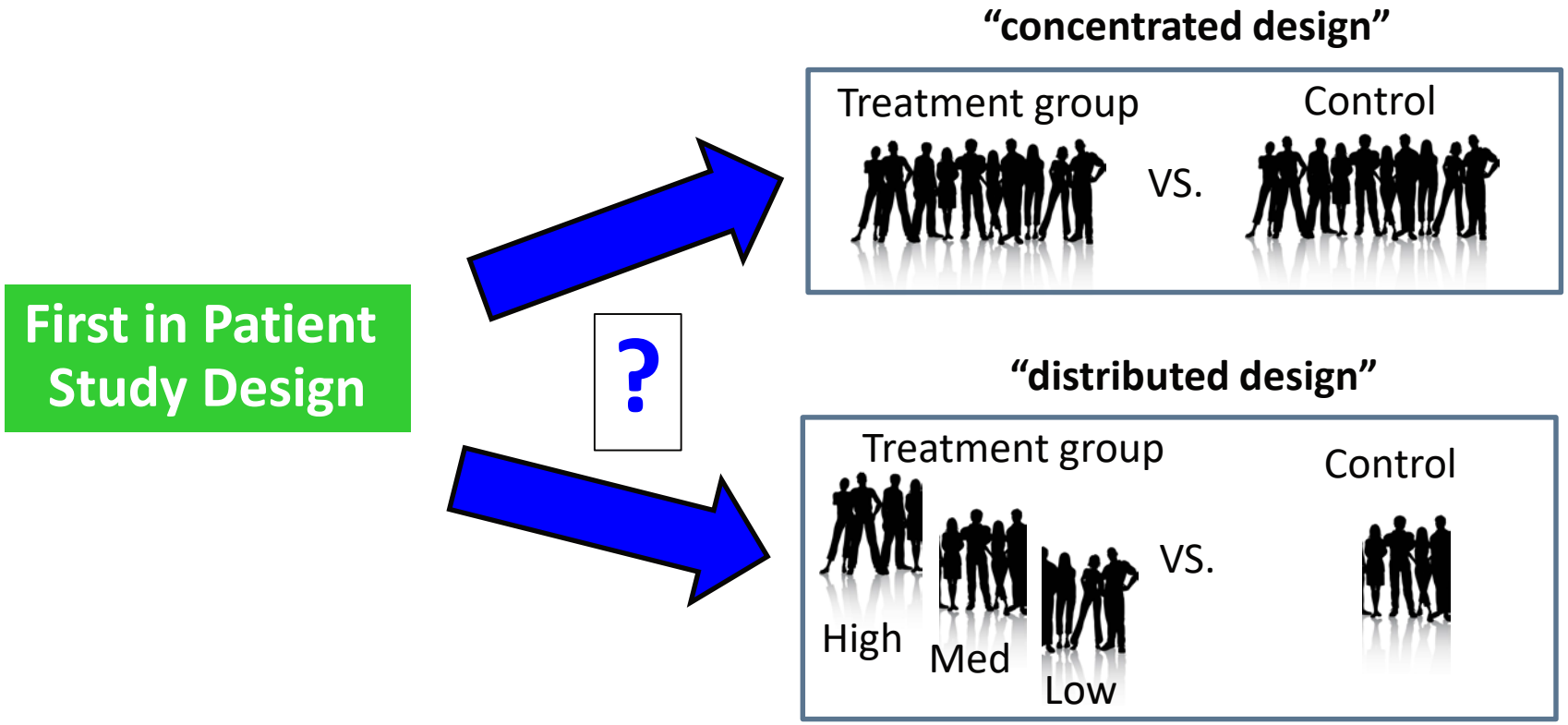
- Strong organizational preference for use of the highest tolerated dose
- Focus on all or none success
  - Further belief that this would derisk uncertainties about the mechanism – how much efficacy could be obtained
  - Provide absolute proof that the drug has merits

Counter points

- Need to guide the design for future experiments
- Drugs generally have predictable dose-response relationships

Comparison of concentrated vs distributed study designs in psoriasis

- Objectives
  - Examine the quality of Go / No-Go decisions
  - Determine the adequacy of estimated dose-response for concentrated vs distributed trial designs



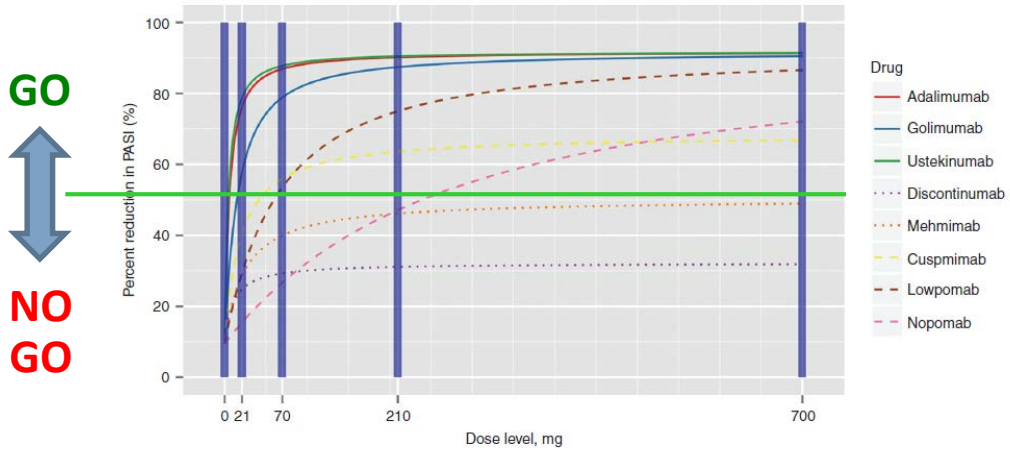
Comparison of concentrated vs distributed first-in-patient study designs in psoriasis

- Methods (continued)
  - MBMA of biologics used in the treatment of inflammation
  - Clinical trials were simulated in NONMEM (n = 9,999)
  - Sample size per trial = 16
  - Different allocations of treatment/control were assessed
    - 7 active:1 placebo; 3 active:1 placebo, 5 active:3 placebo; 1 active:1placebo
  - Go / No go decision criteria
    - Maximal drug effect >50% reduction in disease activity score
    - Estimation of the dose associated with half-maximal efficacy within 2-fold of the true value

Dodds et al., *CPT:PSP* 2: e58 (2013)

Test Cases- real drugs and hypothetical scenarios

- **MBMA guided selection of E_{max} and ED_{50} for existing psoriasis treatments.**
- **Hypothetical compounds with distinct potency parameters were selected to represent a range of scenarios.**



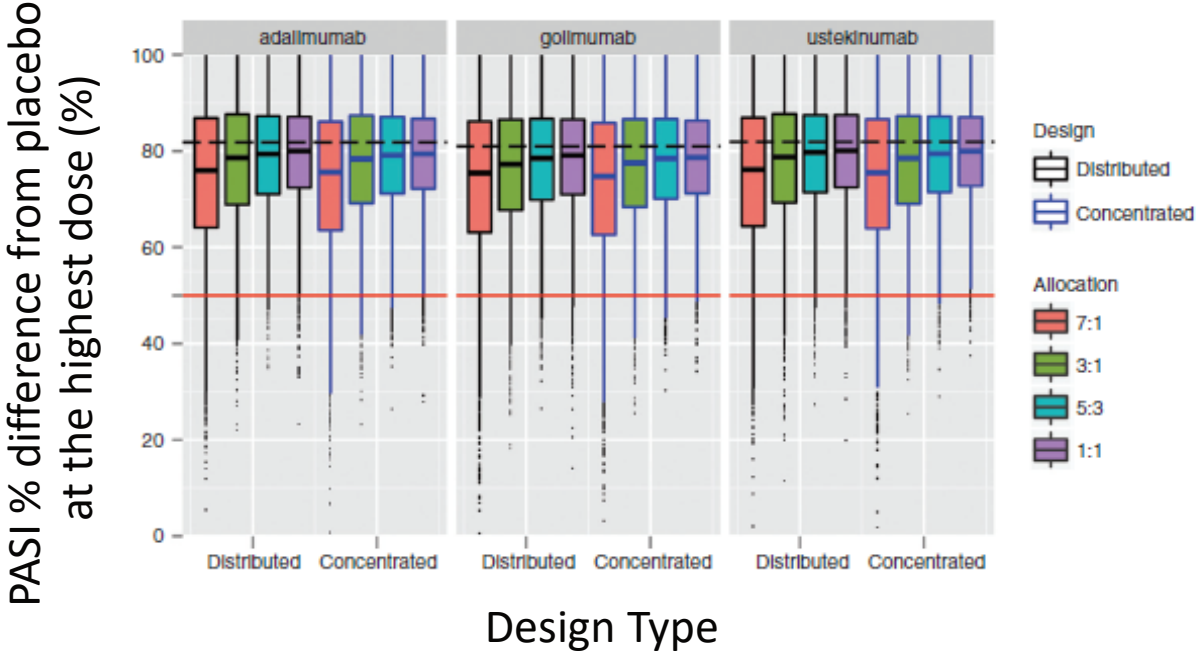
		Simulation parameters		Desired trial outcome	
Group	Compound	Maximal absolute difference from placebo PASI % change (%)	ED_{50} (mg)	Correct G/NG	Estimated ED_{50} within
Marketed examples	adalimumab	82.3	16.9	G	8.50–33.8
	golimumab	82.3	45.5	G	22.8–91.0
	ustekinumab	82.3	13.9	G	6.90–27.7
No-Go examples	discontinumab	22.6	11.8	NG	5.90–23.6
	mehmimab	40.7	32.1	NG	16.0–64.1
Go examples	cuspmimab	58.8	32.1	G	16.0–64.1
	lowpomab	82.3	182	G	91.0–364
	nopomab	82.3	728	G	364–1460

Placebo response (E_0) is 9.5% for all compounds.
ED_{50}, the dose providing half maximal drug response; G/NG, Go/No-Go; PASI, Psoriasis Area Severity Index.

Dodds et al., *CPT:PSP* 2: e58 (2013)

Design Performance for Go/No-Go Decision Making

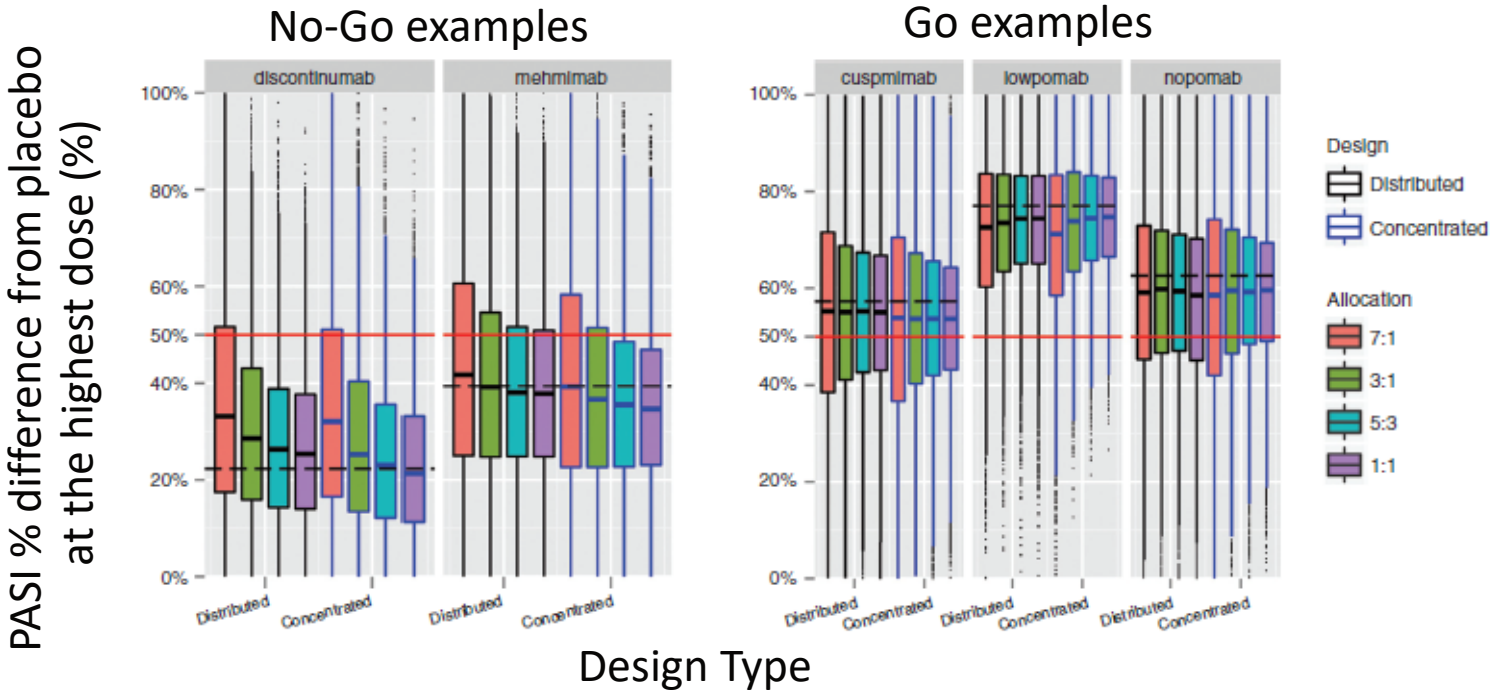
Marketed Drugs



- The correct Go decision was frequently identified (93-100%).
- The percentage of correct Go decisions was similar between designs for marketed drugs.

Design Performance for Go/No-Go Decision Making

Test Cases



- Correct decision was frequently identified (58-98%).
- Concentrated design performance slightly favored for No-go examples. (3-6% better)
- More balanced for the Go examples.

Percentage of simulated trials providing the correct development decision

		7 active:1 placebo		3 active:1 placebo		5 active:3 placebo		1 active:1 placebo	
Group	Drug	Distributed (%)	Concentrated (%)	Distributed (%)	Concentrated (%)	Distributed (%)	Concentrated (%)	Distributed (%)	Concentrated (%)
Marketed Examples	adalimumab	94	94	98	98	99	99	99	100
	golimumab	94	93	97	98	99	99	99	99
	ustekinumab	95	94	98	99	99	99	99	100
No-Go examples	discontinumab	78	81	87	90	91	94	92	95
	mehmimab	64	67	70	75	74	78	75	81
Go examples	cuspmimab	60	58	60	58	61	58	61	59
	lowpomab	90	88	94	95	95	97	94	98
	nopomab	68	66	69	69	70	72	66	73

- Balancing placebo and active subjects achieved the best design performance.

Percentage of simulated trials providing an ED50 within 2-fold of the true value

Group	Drug	7 active: 1 placebo (%)	3 active: 1 placebo (%)	5 active: 3 placebo (%)	1 active: 1 placebo (%)
Marketed examples	adalimumab	59	57	52	49
	golimumab	65	65	61	58
	ustekinumab	55	53	47	45
No-Go examples	discontinumab	18	17	14	14
	mehmimab	32	32	29	28
Go examples	cuspmimab	45	44	40	38
	lowpomab	52	53	51%	48
	nopomab	25	24	25	23

ED_{50}, the dose providing half maximal drug response.

- Distributed design frequently estimated the ED50 correctly (45-65%) for marketed drugs
- Less frequently estimated the ED50 correctly for the test cases (14-53%)

Other considerations / challenges

- Dose selection generally a function of multiple inputs
  - Safety signals
  - Formulation and manufacturability
- Shape of the dose-response relationship well defined
- Endpoint observed after a single dose

Summary

- Distributed designs supported accurate go / no go decisions and helped to guide future trial design decisions with information about the shape of dose-response curve.
- MBMA approaches combined with clinical trial simulations can be valuable to inform clinical development strategy
  - Does the drug have the intended therapeutic benefit
  - What dose(s) should we consider to study in the future
- Clinical trial simulation can increase the efficiency and quality of internal decision making by closely examining limitations and benefits of study designs.
  - anticipating the impact of design choices so that we can make the best decisions

Thank You!