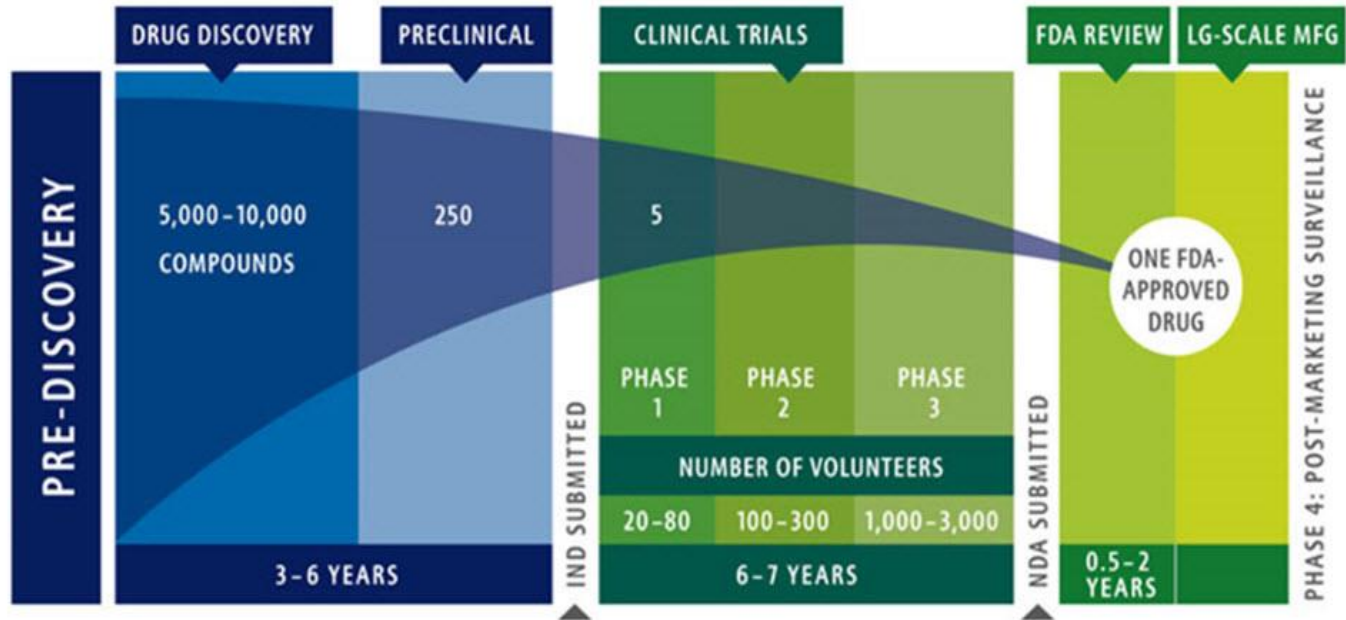Drug Discovery and Development: A LONG, RISKY ROAD

Source: Pharmaceutical Research and Manufacturers of America

Probability of success: a viable concept to inform the early development of a topical drug?

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BAYES2019, Lyon

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In a nutshell...

Full Development:

PoS : chance of observing sucessful phase III studies and getting approval with the target product profile, given phase II data

Relative PoS is key to support project prioritization, across portfolio

Early Development:

PoS : chance of observing sucessful phase II studies (statistically significant and clinically relevant), given phase I data

PoS is key to support early decision making for a specific project

PoS application in an early phase project in Atopic Dermatitis (AD)

- **AD**: high unmet need in particular for pediatric patients

- **Itching (Pruritus)** causes
  - Sleep loss
  - Superinfections
  - Impact on family life
  - Decreased work productivity

- **Large patient population,**
  - ~55M people in the G7
  - ~8% of adults, ~14% of children

- **Limited treatment options**
  - Biologics for moderate-severe AD in adults
  - Only topicals are approved for use in children (modest efficacy, short term use):
    - Crisaborole
    - Corticosteroids
    - Calcineurin inhibitors (black box warning)

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Ph1 study design and objectives

(Under discussion)

- Topical drug
  - No SAD / MAD in healthy volunteers
  - No historical data on vehicle

- Ph 1 objectives:
  - Primary: Safety and tolerability
  - Secondary: PK
  - Exploratory: efficacy at week 4
    - Investigator's Global Assessment (IGA) responder: clear or almost clear + at least 2 grades improvement
      (IGA score: clear - almost clear – mild – moderate – severe)
    - EASI score: Eczema Area Severity Index
    - Itching score

- Design:
  - Randomized double blind trial in adult patients with mild to moderate AD
  - Active cream or vehicle (2:1), b.i.d. topical application for 4 weeks
  - 24 patients (16:8)

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Ph2 study design and objectives

(Under discussion)

- Primary objective: Efficacy (IGA responders at week 4)

- Design:
  - Randomized double blind trial in adults and adolescents patients with mild to moderate AD
  - Active cream or vehicle, b.i.d. topical application for 4 weeks
  - 100 patients (50:50)

- What is the probability of success of Phase 2 study given the data observed in phase 1 ?

- Success is defined as:
  - Statisticially significant difference from vehicle on IGA rate
  - Estimated treatment effect on IGA rate ≥ 40% (Target Profile)

PoS : a Bayesian concept

- Accounts for uncertainties: about size of treatment effects, relevance of Phase 1 data, change in populations,...

- Incorporates available information such as industry benchmark, expert opinion,...

- 4-steps approach

1. Prior distribution for treatment effect in Ph1
2. Bayesian analysis of Ph1 data
3. Accommodate differences between Ph1 and Ph2 trials
4. Estimate the probability of succeeding in Ph2 by simulations

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Step 1: Prior distribution treatment effect in Ph1

- Two-component mixture prior for the average treatment effect in phase 1, μ_{Ph1}
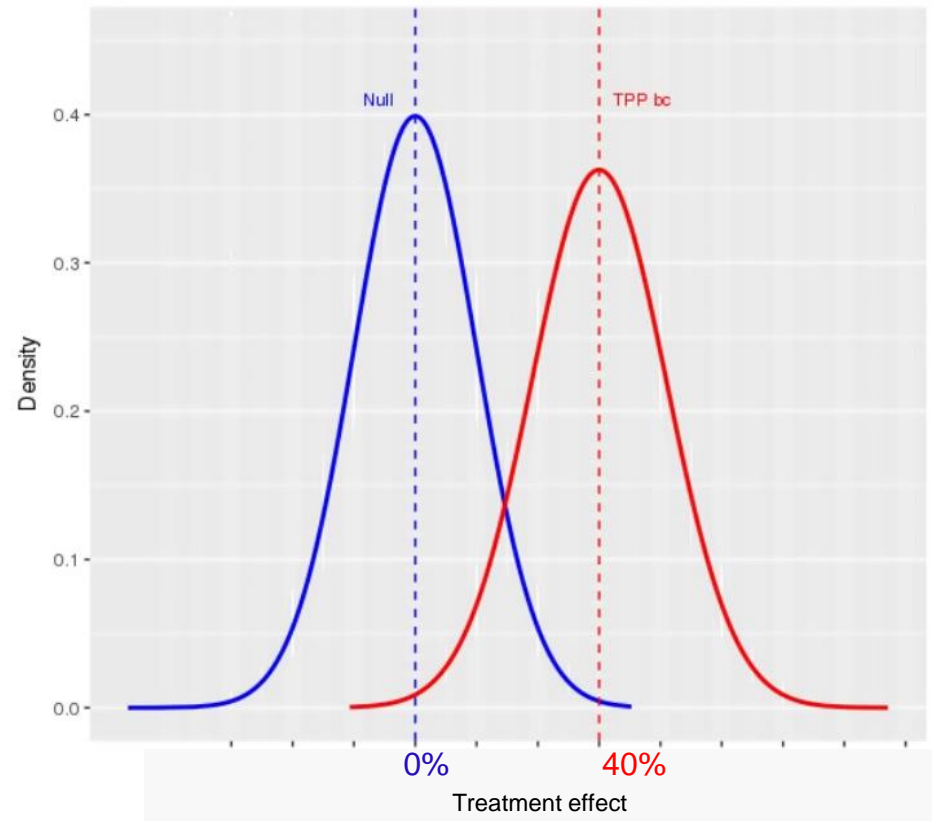
'Pessimistic component' (PC): normal distribution with
- Mode is set at null treatment effect
- Variance such that

    P(μ_{Ph1} > Target Profile| PC) = 0.01

'Optimistic component' (OC): normal distribution with
- Mode is set at Target Profile
- Variance such that

    P(μ_{Ph1} < null | OC) = 0.01

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Step 1: Prior distribution treatment effect in Ph1

How to select the weights for the mixture prior ?

- Calibrate weights such that, unconditional probability of a standard program achieving statistical significance in Ph1 and Ph2 trial (calculated by averaging the power function across the Ph1 prior distribution) is equal to the benchmark success rate in Ph1 and Ph2

- Choose ω   (ω*N(μ_0, σ_0^2) + (1- ω)* N(μ_T, σ_T^2)) to solve:

$\int_\Theta P(\text{Reject } H_0 \text{ in Ph2}|\theta)P(\text{Reject } H_0 \text{ in Ph1}|\theta)\pi_0(\theta) \, d\theta$ = benchmark success rate

Benchmark success rate:
- Database from thousands of historical trials
- Proportion of failures because of efficacy / safety / other by phase and by therapeutic area

Wong et al., Biostatistics, 2018
Hay et al, Nature Biotechnology, 2014

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Step 2: Bayesian analysis of Ph1 data

- Bayesian hierarchical model:

$$\theta_{11}, \cdots, \theta_{1N1} | \mu_{Ph1}, \tau_{Ph1} \sim N(\mu_{Ph1}, \tau_1^2)$$
$$\mu_{Ph1} \sim Mixture\ prior$$
$$\tau_1 \sim HN(z^2)$$

- $\theta_{11}, \cdots, \theta_{1N1}$: Ph1-study-specific treatment effects

- τ_1^2 : between phase I studies heterogeneity

- z is selected given the expected degree of heterogeneity*

*Neuenschwander B, Schmidli H (2019), "Use of historical data".

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Step 3: Accommodate differences between Ph1 and Ph2 trials

- Ph2-study-specific treatment effects are independent draws from the random effects distribution:

$$\theta_{21}, \cdots, \theta_{2N_2} | \mu_{Ph2}, \tau_2 \sim N(\mu_{Ph2}, \tau_2^2)$$

$$\tau_2 \sim HN(z^2)$$

- $\theta_{21}, \cdots, \theta_{2N2}$: Ph2-study-specific treatment effects

- τ_2^2 : between phase 2 studies heterogeneity

- If no difference between phase 1 and phase 2:

$$\theta_{21}, \cdots, \theta_{2N_2} | \mu_{Ph1}, \tau_2 \sim N(\mu_{Ph1}, \tau_2^2)$$

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Step 3: Accommodate differences between Ph1 and Ph2 trials

- Differences between the design of the Ph1 and Ph2 trials:

    – Endpoints (different outcomes; different timepoints)

    – Patient populations

    – Dosing regimen (dose or schedule)

    – Drug formulation

- Prior elicitation protocol being developed to understand our knowledge on the relationship between ph1 and 2 treatment effects

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Step 3: Accommodate differences between Ph1 and Ph2 trials

- Best guess : Treatment effect is the same in adults and adolescents

- Additional source of variability

$$\theta_{21}, \cdots, \theta_{2N2} | \mu_{Ph2}, \tau_{Ph2} \sim N(\mu_{Ph2}, \tau_2^2)$$
$$\mu_{Ph2} = \mu_{Ph1} + \delta$$
$$\delta \sim N(\mu_\delta = 0, \sigma_\delta^2)$$
$$\tau_2 \sim HN(z^2)$$

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Step 4: Estimate the probability of succeeding in Ph2 by simulations

Monte Carlo samples are used to estimate PoS

- $\theta_2^{(i)}$ contains the i*th* Monte Carlo sample for the Ph2-trial-specific treatment effects.

- Sample the standardized test statistics from :

$$Z^{(i)}|\theta_2^{(i)} \sim N\left(\left(\theta_2^{(i)}\sqrt{\text{I}}\right), 1\right)$$

  - I represents Fisher's information for the trial-specific treatment effects
    - Depend on the design of the Ph2 trial
    - Depend on 'nuisance' parameters (response rate on control)

- Averaging across the outcomes gives an estimate of the unconditional probability of succeeding for efficacy in Ph2.

Ph1 simulations

- Ph1 trial simulations under different true treatment effects
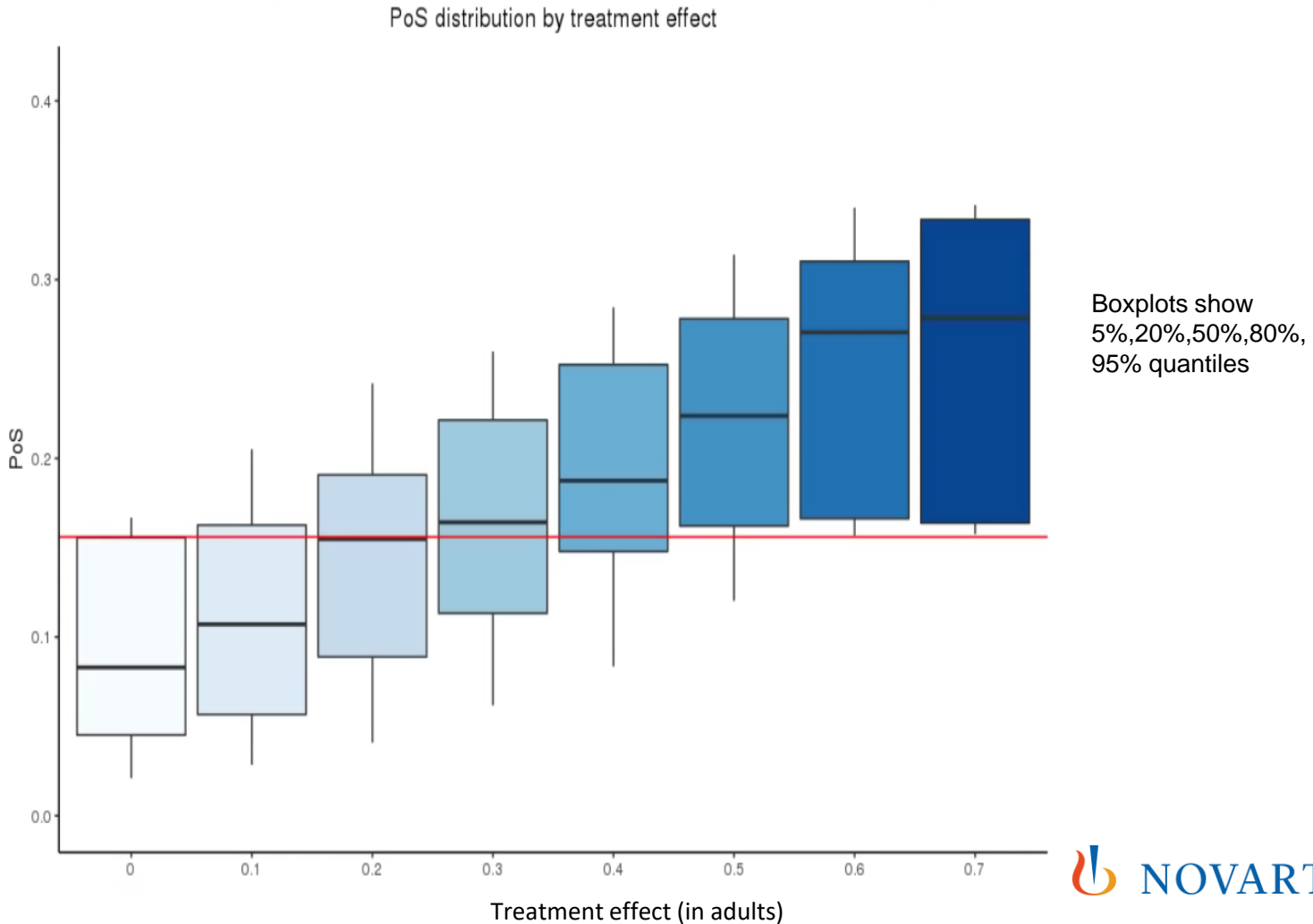
PoS distribution by treatment effect

Boxplots show
5%,20%,50%,80%,95%
quantiles

PoS
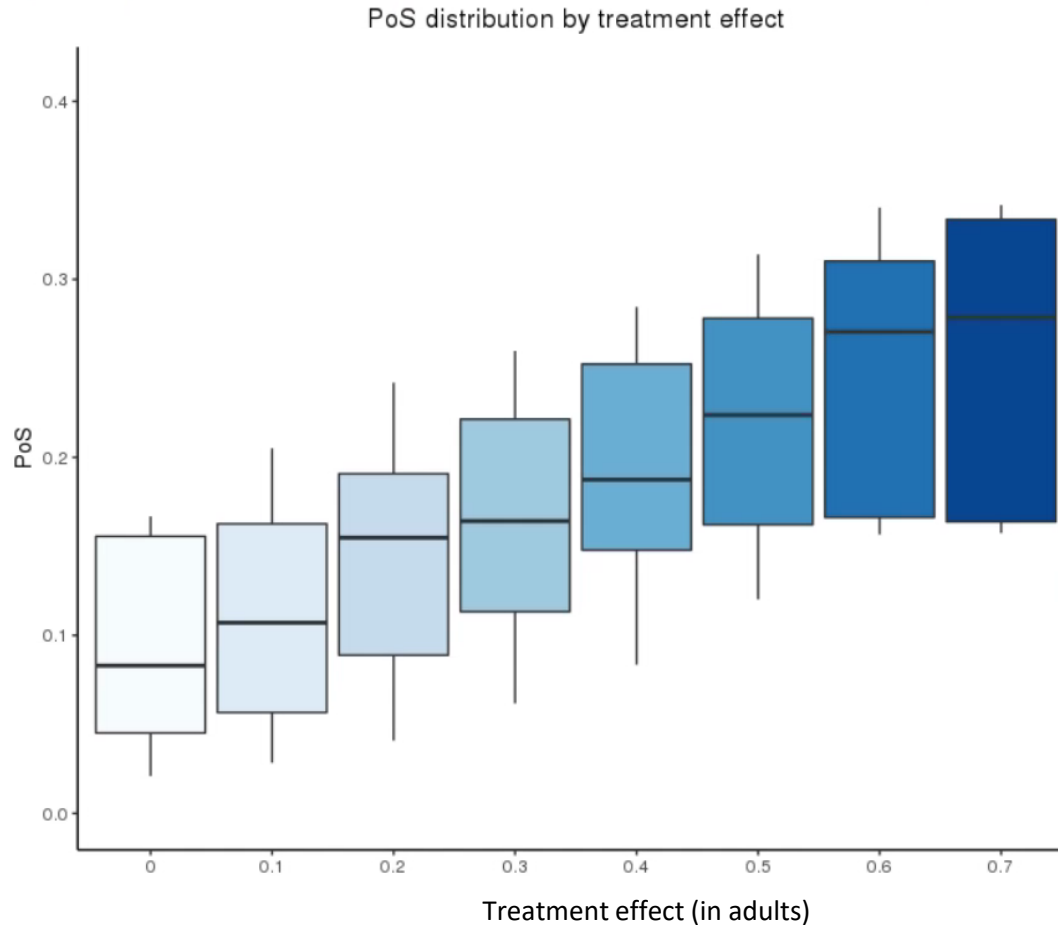
Treatment effect (in adults)

- Simulations help calibrating what a good PoS is

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Ph1 simulations

- Threshold put such that 20% chance of a «go» decision under the null

PoS distribution by treatment effect

Boxplots show
5%,20%,50%,80%,
95% quantiles

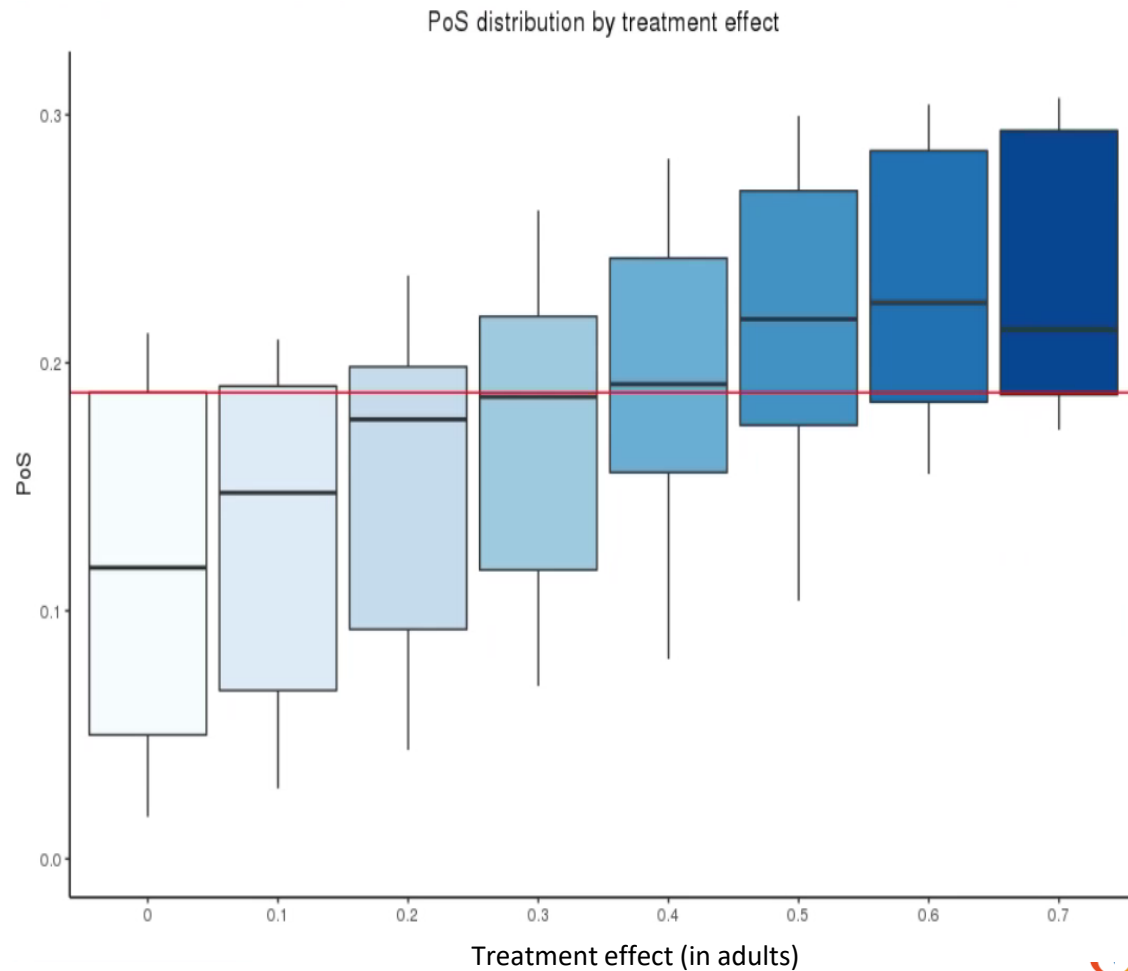Treatment effect (in adults)

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Design the phase I to allow the most informed decision

- Phase I endpoint

- Observation timepoint

- Sample size

- Use historical data

- Leverage expert's opinion

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Ph1 simulations with a different design

- Change from 24 patients to 18 patients (12:6)

PoS distribution by treatment effect

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Conclusions

- PoS approach allows for higher transparency, more objectivity, more consistency

- PoS to support early decision making
  - Reflects uncertainty in early development

- Enhance the communication with clinical teams
  - Simpler concept

- Helps the design of phase I / II studies

- Avoid running non-informative phase I studies

- Accept the risk associated to the decision

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Credits

- Cross-functional PoS team
  - Steffen Ballerstedt
  - Giovanni Della Cioppa
  - Lisa Hampson
  - Wolfgang Kothny
  - Kelvin Stott

- Quantitative PoS team
  - Bjoern Bornkamp
  - Mustapha Larbaoui
  - Lisa Hampson
  - Bjoern Holzhauer
  - Joseph Kahn
  - Markus Lange
  - WenLin Luo

- PoS team sponsors
  - Amit Agrawal
  - Stephen Cho
  - Florian Bieber
  - Pascale Burtin
  - Daniel Daetwyler
  - Eric Gibson

- Feedback & support
  - Markus Boehm
  - Kasper Dryer
  - Christine Strohmeier
  - Michael Wittpoth
  - Achim Guettner
  - Christian Loesche
  - Damien Picard

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Questions

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Back-up

PoS of Ph2 given Ph1 data

- Success is defined as:
  - Statisticially significant difference from vehicle on IGA rate
  - Estimated treatment effect ≥ 40%

P(Target Profile)

P(Statistical Significance)

Estimated Ph1 treatment effect (in adults)

Estimated Ph1 treatment effect (in adults)