Looking for Clinical Activity in a First-in-Human Study

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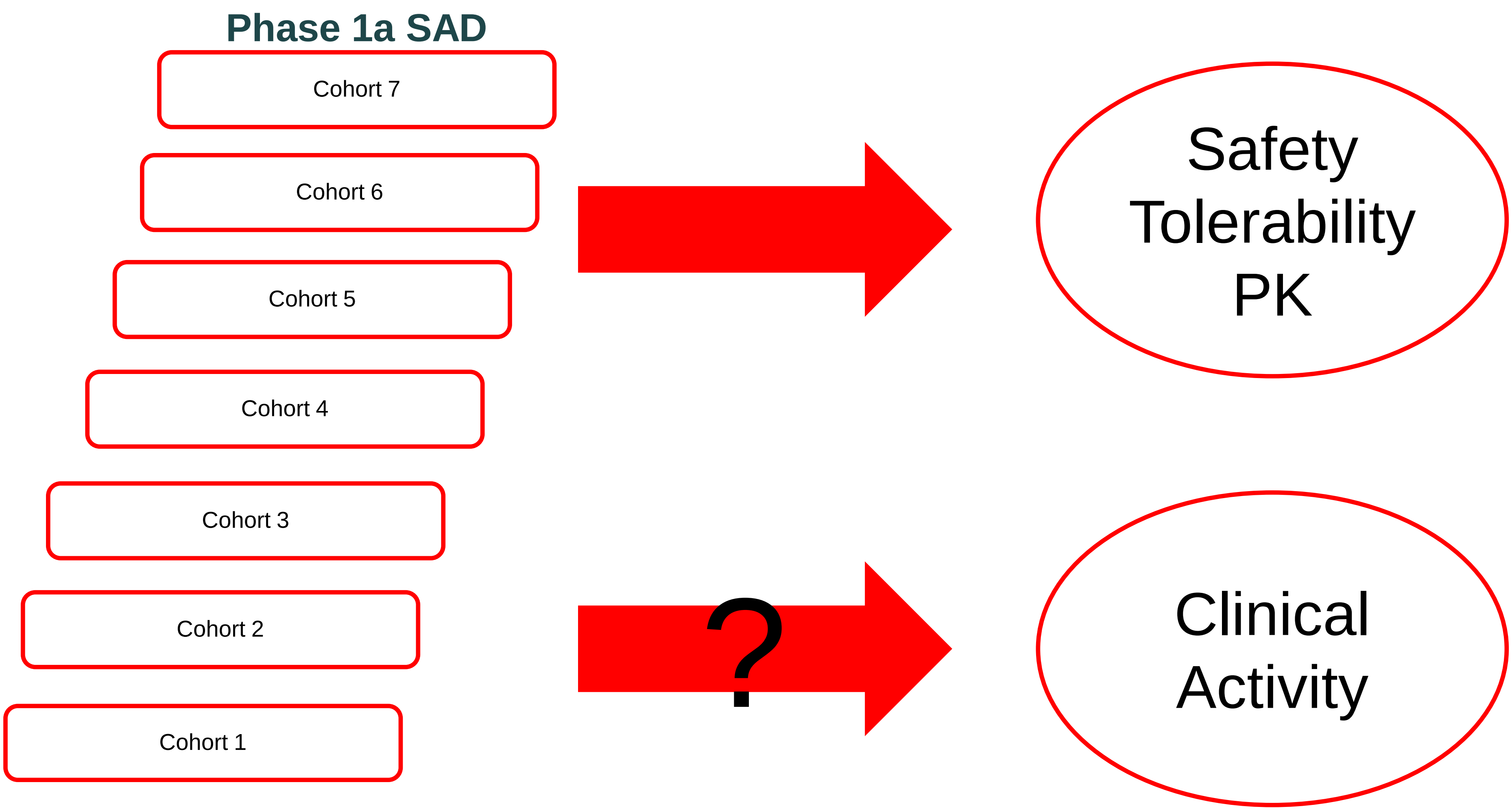
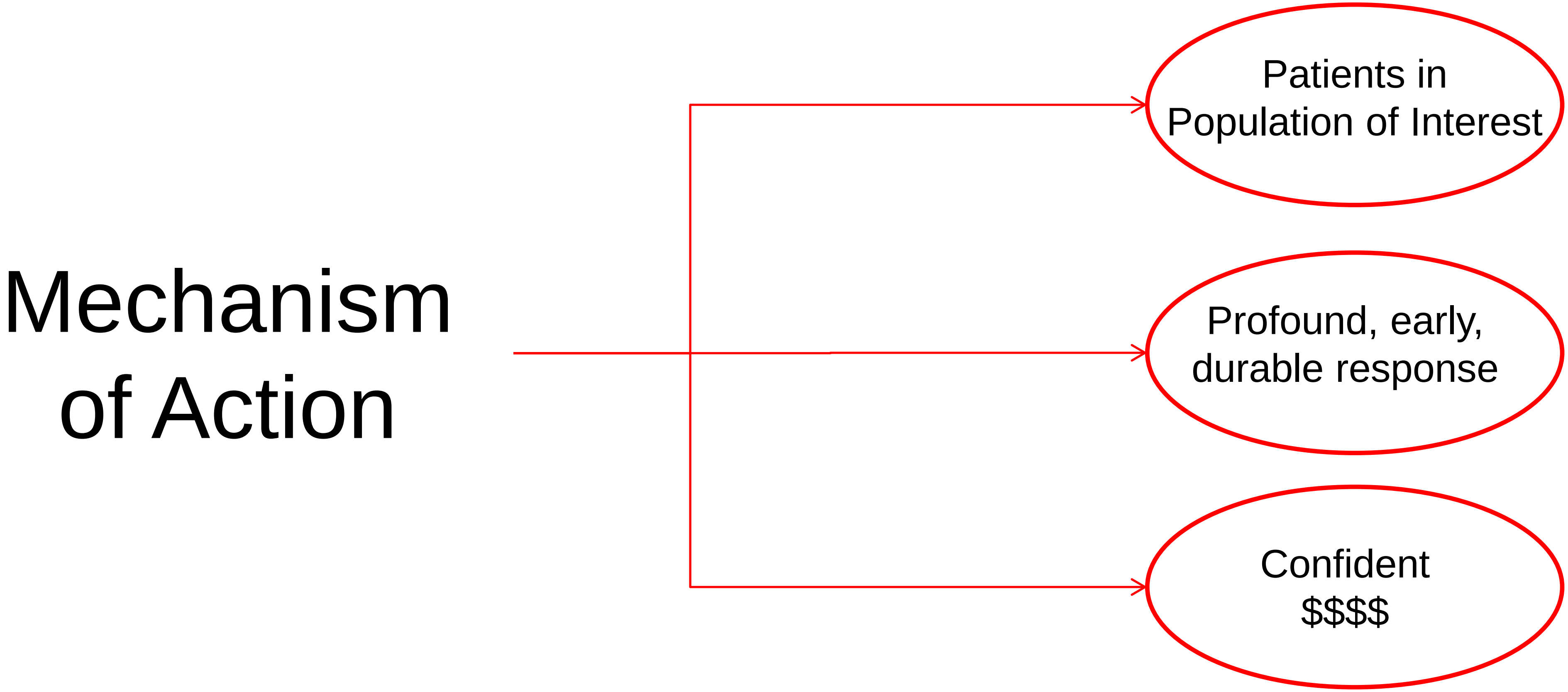
Company Confidential

Answers That Matter.

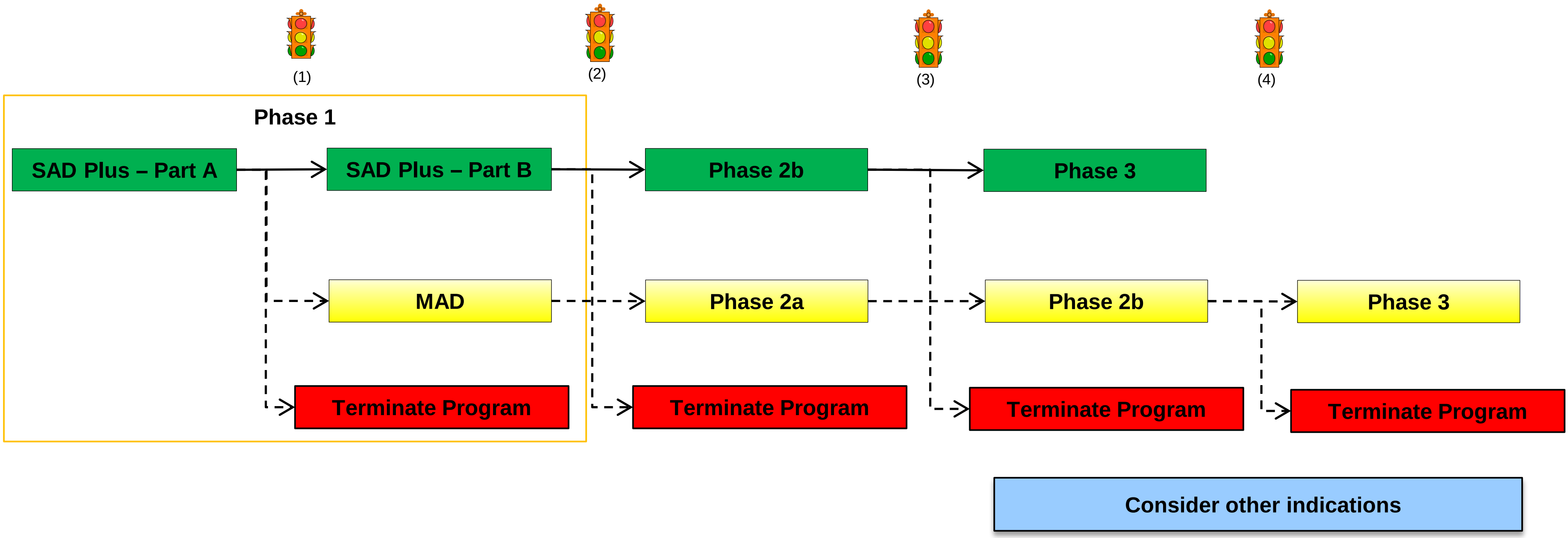
Introduction



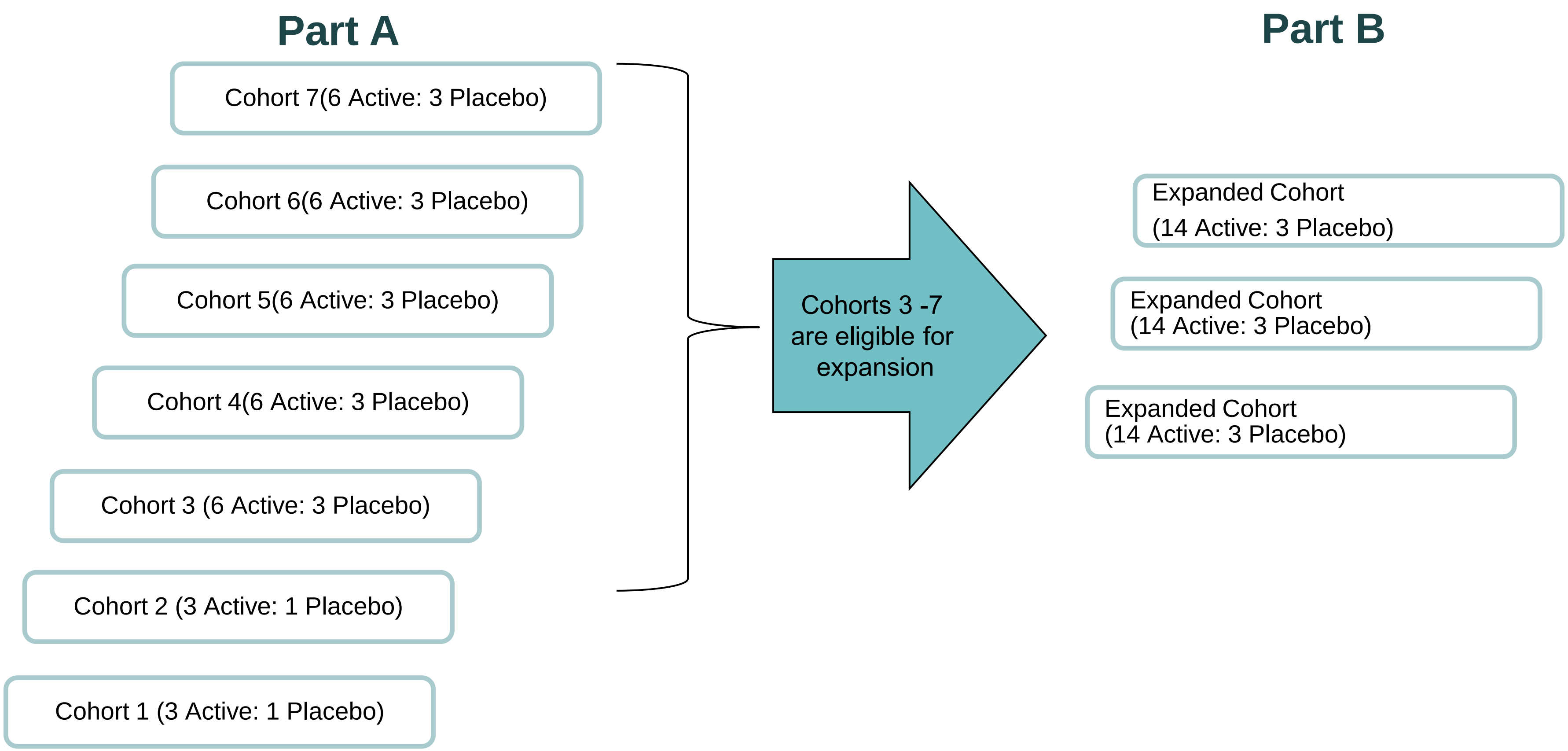
Background Information



Adaptive Development Plan



Phase 1: SAD Plus Design



Cohort Expansion Criteria

Endpoints	Target Threshold	
Endpoint 1 (Disease Activity)	≥ 0.6 Reduction (Continuous)	2 of 3 target thresholds must be met by at least 3 of 6 patients on active treatment at any timepoint during 4 weeks of treatment (data collected at weeks 1, 2, and 4)
Endpoint 2 (Disease Activity)	≥ 20% Reduction (Continuous)	
Endpoint 3 (PD Marker)	Within normal range (Binomial)	

Continuous Longitudinal Model (1)

Longitudinal improvement was modeled as a fraction of the final improvement.

$$y_{i,t} \sim N\left(f_t\left(\mu_j + \delta_i\right), {\varphi_t}^2 {\sigma_j}^2\right) = N\left(f_t \mu_j, {\varphi_t}^2 {\sigma_j}^2 + {f_t}^2 \tau^2\right)$$

$$\delta_i \sim N(0, \tau^2)$$

$$y_{i,T} \sim N\left(\mu_j, {\sigma_j}^2 + \tau^2\right)$$

$y_{i,T}$ is the final primary outcome for patient *i*

${\sigma_j}^2 + \tau^2$ is the variance for the final outcome

μ_j is the mean of the final outcome

${\varphi_t}^2$is the variance at visit *t* in terms of the fraction of the final variance (0 ≤${\varphi_t}^2$≤1)

f_t is the mean at visit *t* in terms of the fraction of the final mean (0 ≤f_t≤1)

Continuous Longitudinal Model (2)

i^{th} Patient	Visit 1	Visit 2	Visit 3	Final Visit
1	y_{11}	y_{12}	y_{13}	Y_1
2	y_{21}	y_{22}	y_{23}	Y_2
3	y_{31}	y_{32}	y_{33}	Y_3
4	y_{41}	y_{42}	y_{43}	Y_4
5	y_{51}	y_{52}	y_{53}	Y_5
6	y_{61}	y_{62}	y_{63}	Y_6

Based on desired fraction of final response, simulate values for visits 1-3

Simulate value for final visit

Binomial Longitudinal Model (1)

For the first visit:

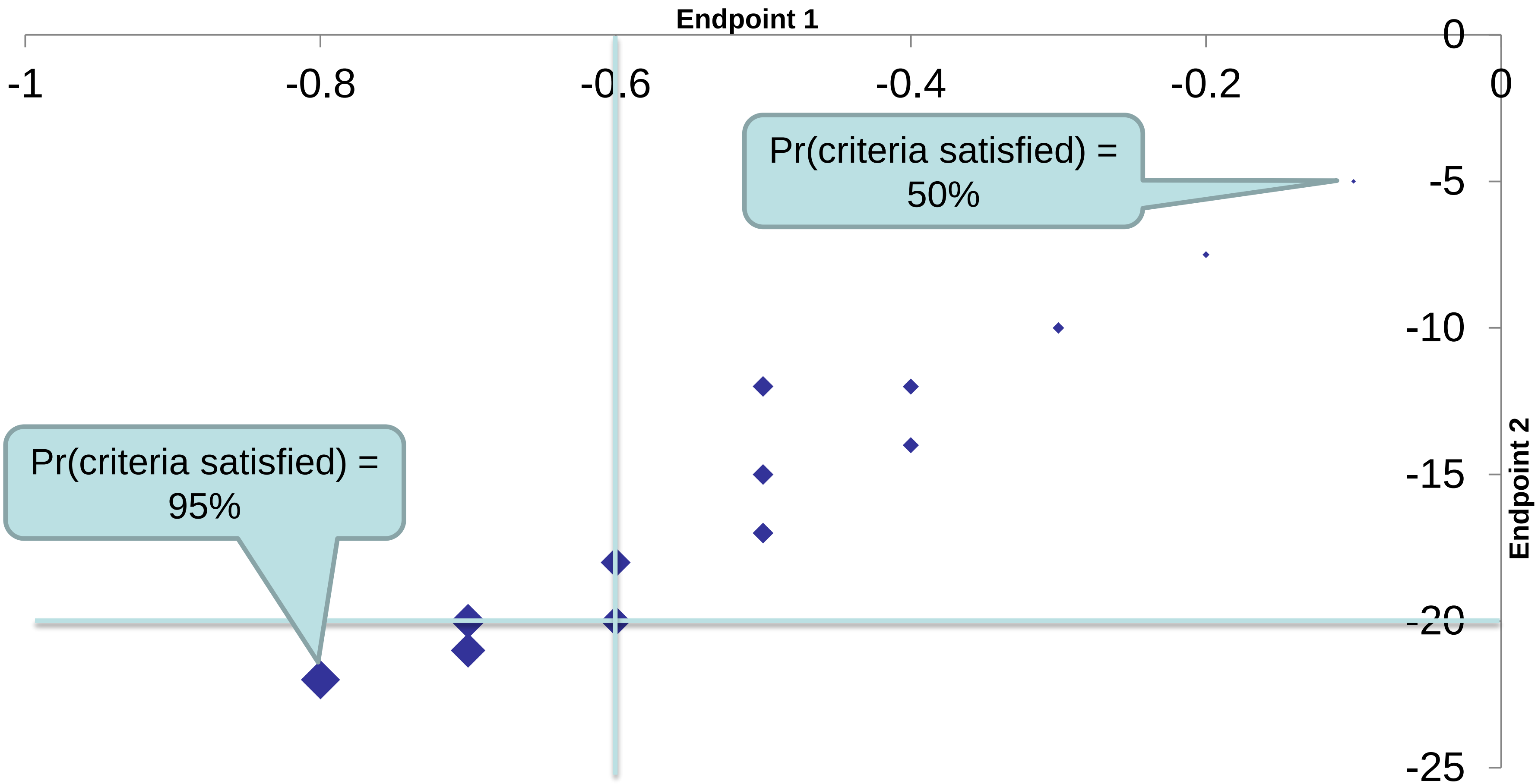
$$P(y_1 = 1) = Q_1$$

For subsequent visits:

$$P(y_t = 1 | y_{t-1} = 0) = Q_t$$
$$P(y_t = 1 | y_{t-1} = 1) = R_t$$

Where Q_t and R_t are matrices containing transition probabilities from 0 to 1 and from 1 to 1, respectively.

Simulated Values and Resulting Probabilities



Part B Success Criteria

- **Endpoint 1:** ≥ 1.2 absolute change from baseline
  If Pr(Therapy ≥ 1.2) ≥ 60% then success

- **Endpoint 2:** ≥ 30% decrease from baseline
  If Pr(Therapy - PBO ≥ 0.30) ≥ 60% then success

Part B success criteria evaluated based on data collected at weeks 1, 2, 4, and 8.

Part B Dose Modeling

- Let R_i be the change from the baseline period to the endpoint in the response. Let θ_d be the mean response for R_i when $d_i = d$. It was assumed that

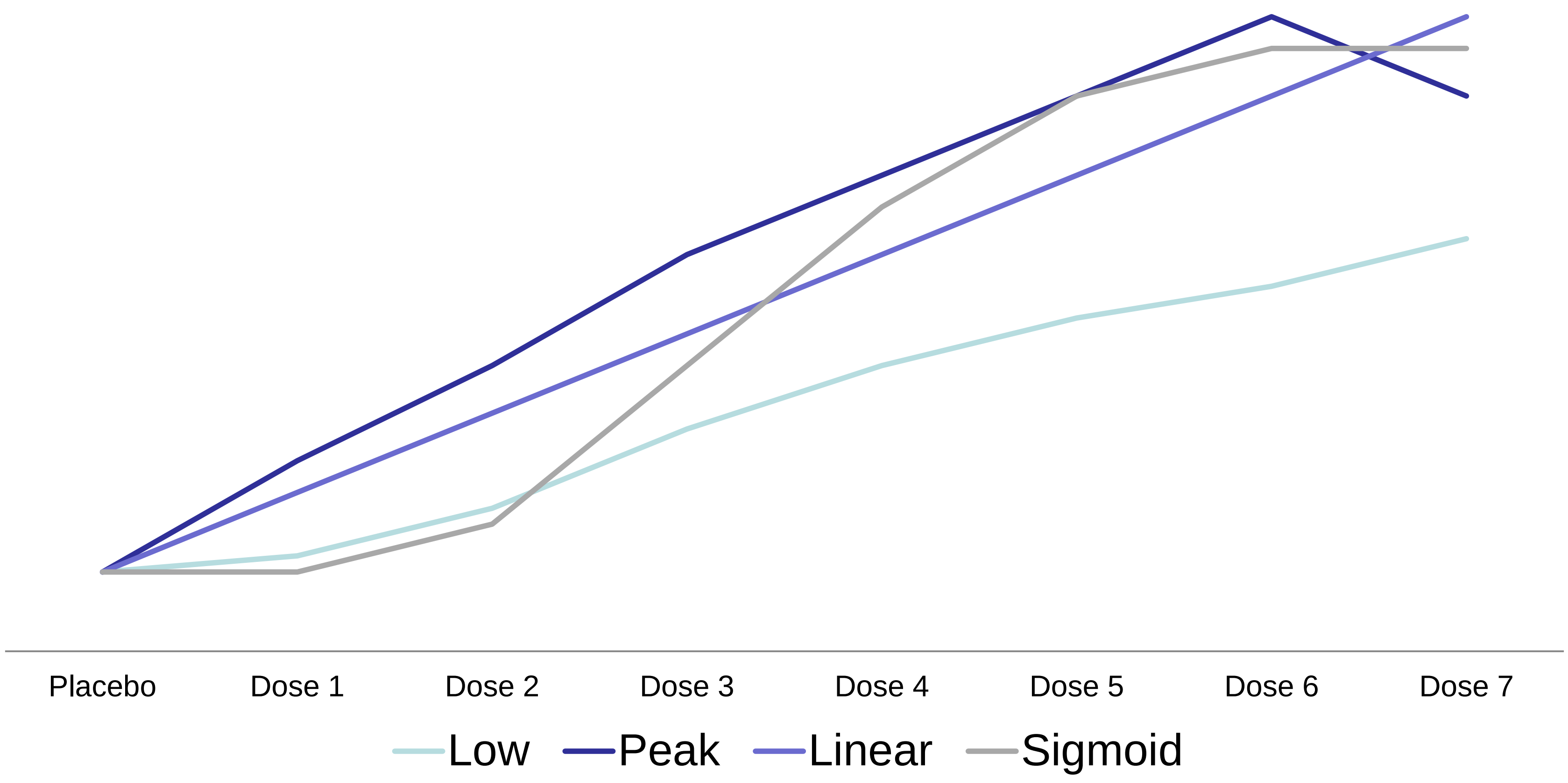
$$R_i \sim \theta_{d_i} + N(0, \sigma^2)$$

- Doses were modeled assuming $\theta_d \sim N(\mu_d, {v_d}^2)$ and

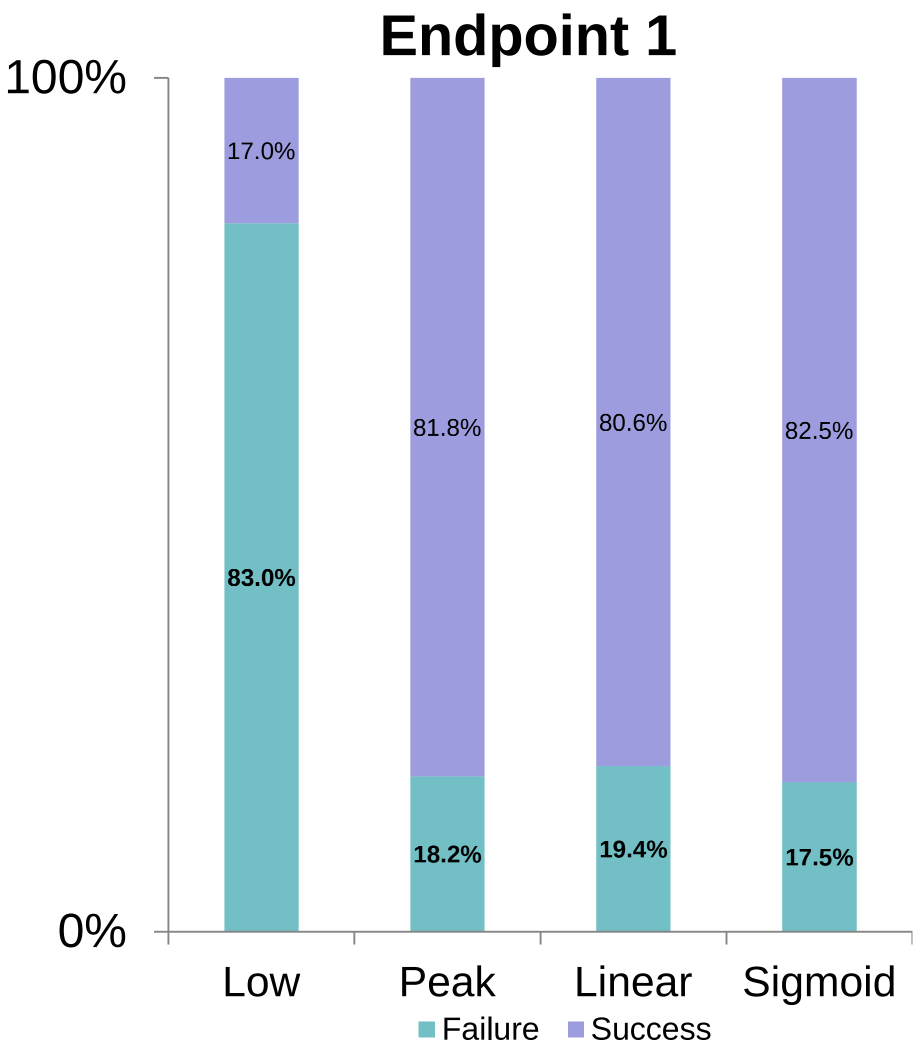
$$\sigma^2 = IG\left(\frac{\sigma_n}{2}, \frac{{\sigma_\mu}^2 \sigma_n}{2}\right)$$

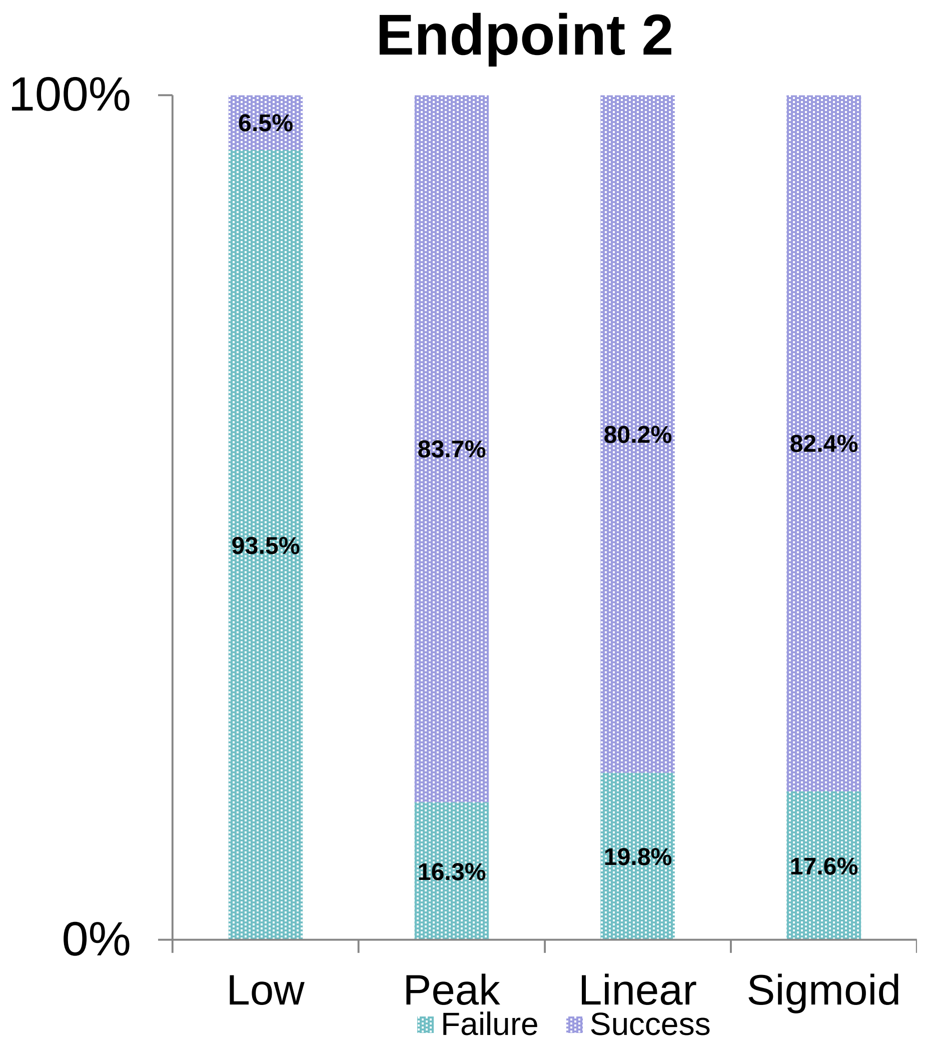
- Priors for endpoints 1 and 2 were diffuse with $\mu_d = 0$, $v_d = 100$, $\sigma_\mu = 12$, and $\sigma_n = 1$.

Dose Response Curves

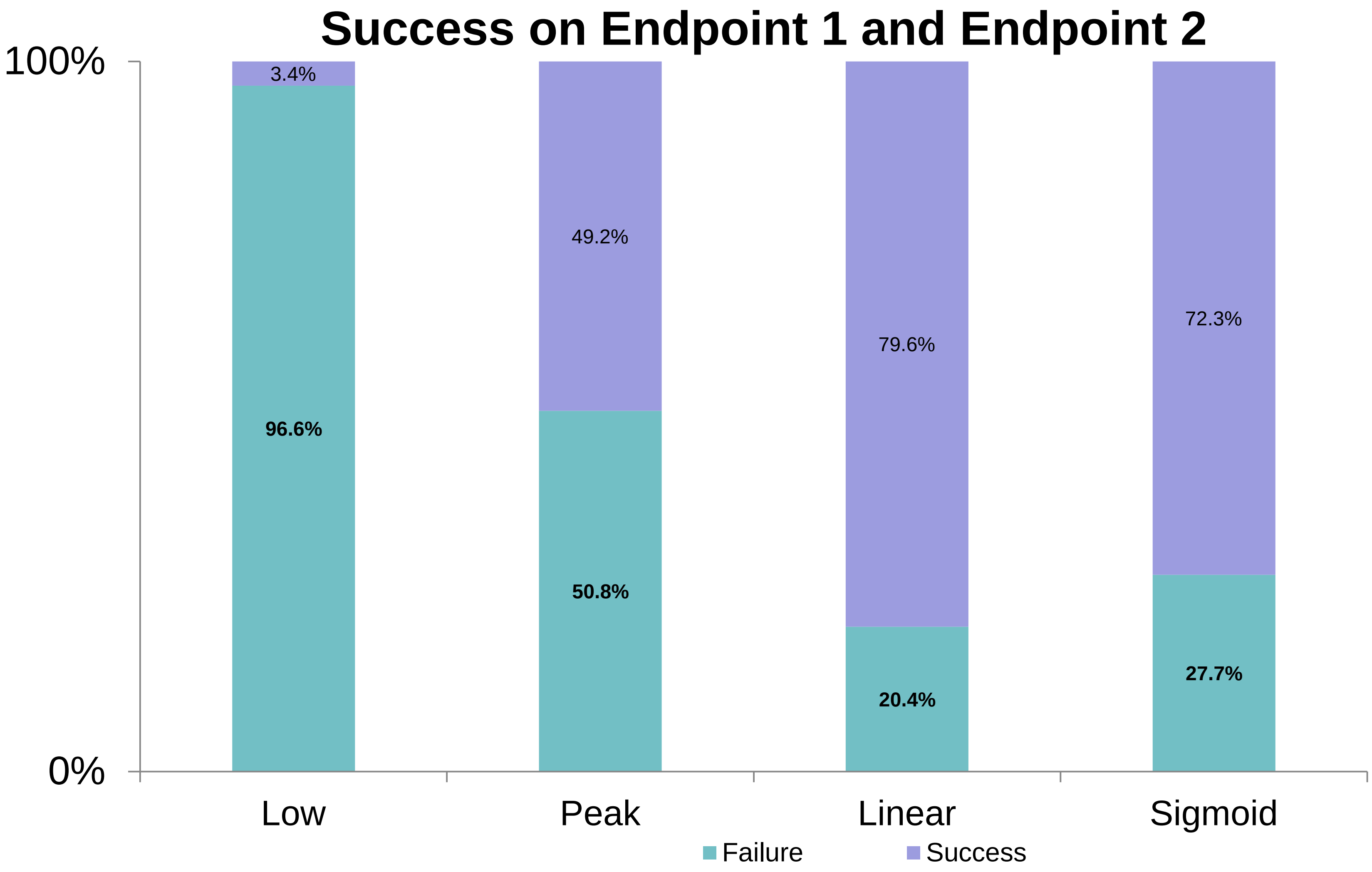


Probabilities of Success (1)





Probabilities of Success (2)



Concluding Remarks

If

Mechanism of Action

Patients in Population of Interest

Response with single administration

High confidence $$$$

Phase 1a SAD

Cohort 7

Cohort 6

Cohort 5

Cohort 4

Cohort 3

Cohort 2

Cohort 1

then

possibly

Detect Clinical Activity