

# OPTIMIZING ADAPTIVE DESIGN FOR PHASE 2 DOSE FINDING TRIALS INCORPORATING LONG-TERM SUCCESS AND FINANCIAL CONSIDERATIONS

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## Disclosure

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- **The design, study conduct, analysis, and financial support of the analysis were provided by AbbVie. AbbVie participated in the interpretation of data, writing, review, and approval of the content.**
- **Jingjing Gao is an employee of AbbVie, Inc.**
- **Narinder Nangia was an employee of AbbVie, Inc. when this research was conducted and was not compensated for the development of this presentation.**
- **Jim Bolognese, Jaydeep Bhattacharyya, and Nitin Patel are employees of Cytel, Inc. and were not compensated for the development of this presentation.**

# Outline

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- **Introduction**
- **Designing a Dosing-finding Phase 2 Trial with a Case Study**
- **Simulation Results**
- **Conclusion and Discussion**

# Introduction (1)

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## Objectives of Phase 2 Dose-finding Trials

– Select the optimal dose(s) to bring forward to Phase 3 trial(s) that is

- Efficacious
- Safe/Tolerable
- Profitable

## Introduction (2)

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### Dose Selection Approaches – Definition of Optimality

- Focused on **efficacy**
  - Optimal dose = Minimum Effective Dose (MED)
  - Safety is evaluated separately
- Focused on **safety**
  - Optimal dose = Maximum Nontoxic Dose (MND)
  - Efficacy is evaluated separately
- Focused on **tolerability**
  - Optimal dose = Maximum Tolerated Dose (MTD)
  - Efficacy is evaluated separately
- **Financial consideration** is not statisticians' responsibility, but commercial department's. And it is done independently.

## Introduction (3)

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### Changing the way to evaluate optimality

– Program-level optimization

### Designing a dose-finding Phase 2 trial taking into consideration

- Efficacy
- Safety
- **Cost-effectiveness!**

## Introduction (4)

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- *To incorporate evaluation of efficacy and safety*
  - ✓ **Clinically Significant Minimum Utility (CSMU) for Both Efficacy and Safety**
- *To incorporate economic factors*
  - ✓ **Net Revenue and Net Present Value (NPV)**

## Established Work

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**Patel and Ankolekar (2007)** introduced a Bayesian approach to incorporate economic factors in sample size determination and design for clinical trials and portfolio of drugs.

**Burman et al. (2007)** proposed a decision analytic approach to calculate the sample size from a perspective of maximizing company profits.

**Mehta and Patel (2006)** used net revenue and NPV for sample size re-estimation in confirmatory trials.

**Patel et al. (2012)**

- expanded the NPV concept to design a phase 2 trial choosing a dose selection method and planning future phase 3 trials;
- proposed **traditional fixed sample size design** to optimize expected net present value of the product.



## Fixed-arm Design vs. Adaptive Design

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### Types of Phase 2 Trials in terms of Allocation of Treatment

- **Fixed-arm design:**

- Doses are fixed throughout treatment period.
- Treatment arms are parallel.
- Randomization pre-specified and fixed.

- **Adaptive design:**

- Doses can be up or down titrated.
- Treatment arms could be dropped.
- Randomization ratios could be modified.

**Extending Patel et al.'s work by incorporating NPV with adaptive design.**

## Objective

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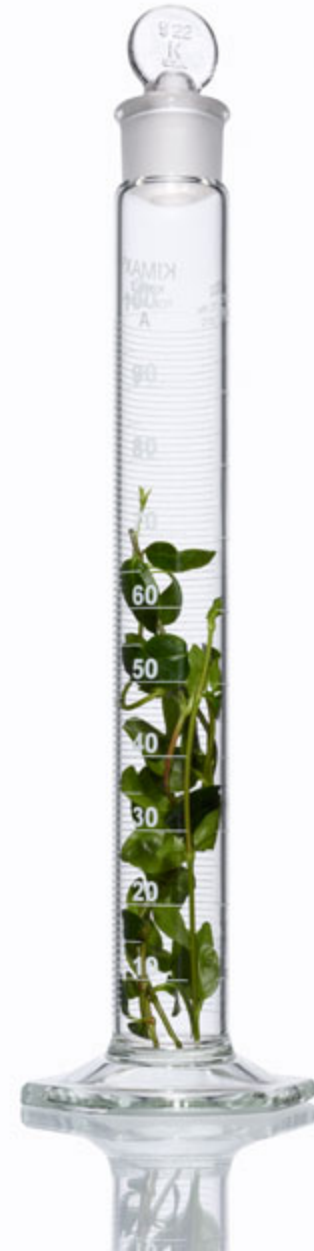
### Benefits of an Adaptive Design:

- Reduced time to NDA using totality of data in characterizing dose-response
- Smaller average sample size
- Improved estimate of probability of success in Phase 3 trials
- Increase in expected net present value (ENPV) ?

### Objective:

- ✓ Evaluate ENPV for adaptive design versus fixed-arm design in dose-response studies

DESIGNING A COST-  
EFFECTIVE DOSE-  
FINDING PHASE 2 TRIAL  
WITH ADAPTIVE  
DESIGN



# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design

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## Key Concepts of a Cost-effective Adaptive Design

### *Incorporating evaluation of efficacy and safety*

- Dose-Response Characterization for Efficacy
- Longitudinal Model to Predict yet to be Observed Efficacy Data
- Safety Evaluation
- Response-adaptive Randomization through Utility Function incorporating Efficacy and Safety/Tolerability
- Stopping for Futility and Success based on CSMU

### *Incorporating economic factors*

- ENPV

## Case Study – Design

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**Design:** Multicenter, double-blind, placebo and active controlled, fixed-arm or adaptive design

**Population:** Adult subjects with diabetic peripheral neuropathic pain

**Primary Efficacy Variable:** Weekly Mean of Average Pain Over 24 hours

**Duration:** 12 weeks

**Treatment Groups:**

- Placebo
- Active comparator
- ED 6mg, 9mg, 12mg, 15mg, 18mg

**Size:** Max. SS 400

**Minimal Clinically Significant Difference (CSD):** 0.8 (Relative to Placebo)

# Case Study — Adaptive Randomization and Monitoring

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- **Adaptive Randomization:**

- Fixed rate at 20% for Placebo and Active Comparator.
- Following the burn-in period, subjects will be allocated to the 5 doses of ED using **information sampling method** to maximize the reduction in variance expected from adding one more subject to the dose.

- **Interim Monitoring:**

- Trial can be stopped early for futility or success.
- Begin after 200 patients have been accrued.
- Adaptive randomization probabilities will be updated every two weeks and monitored by Data Monitoring Committee.

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – Dose-response Model for Efficacy

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## Dose-Response Model for Efficacy

- **Normal Dynamic Linear Model (NDLM)**
- **A flexible and robust model for capturing non-monotonic curves.**

## Longitudinal Model for Efficacy

- **Design the trial with multiple visits instead of a single visit.**
- **Enable final observations to be imputed for those subjects that only have intermediate responses.**
- **Simple linear regression model is used to accommodate the correlation between final observations and intermediate responses.**

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – Efficacy Response Scenarios (1)

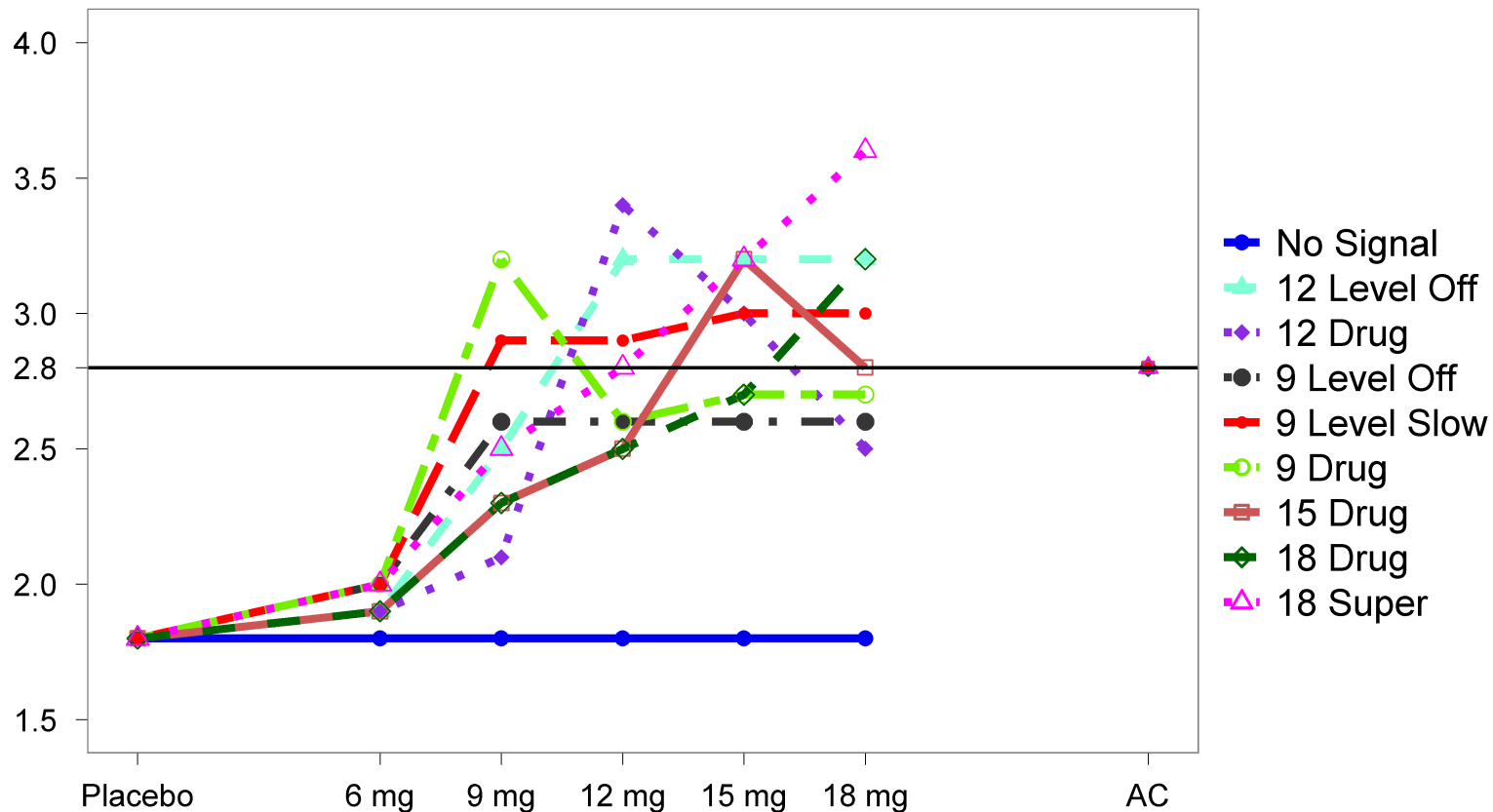
- To evaluate how the design performs, we consider different efficacy response scenarios.

Efficacy Response	Pbo	6 mg	9 mg	12 mg	15 mg	18 mg	Active
No Signal	1.8	1.8	1.8	1.8	1.8	1.8	2.8
12 Level Off	1.8	1.9	2.5	3.2	3.2	3.2	2.8
12 Drug	1.8	1.9	2.1	3.4	3	2.5	2.8
9 Level Off	1.8	2	2.6	2.6	2.6	2.6	2.8
9 Level Slow	1.8	2	2.9	2.9	3	3	2.8
9 Drug	1.8	2	3.2	2.6	2.7	2.7	2.8
15 Drug	1.8	1.9	2.3	2.5	3.2	2.8	2.8
18 Drug	1.8	1.9	2.3	2.5	2.7	3.2	2.8
18 Super	1.8	2	2.5	2.8	3.2	3.6	2.8

## Efficacy Response Scenarios



# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – Efficacy Response Scenarios (2)



## Efficacy Response Scenarios

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – Safety Evaluation

## Safety Evaluation

- Quantified and expressed as overall dropout rates.
- Dropout rates commonly increase as the dose is up-titrated.
- Dropout rates should be approximated based on historical data or reliable sources such as notable publications or agencies' guidance.
- We assume the following overall moderate dropout scenario

Dropout Scenario	Pbo	6 mg	9 mg	12 mg	15 mg	18 mg	Active
Moderate	17%	30%	30%	30%	35%	35%	24%

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – CSMU (1)

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## Clinically Significant Minimum Utility (CSMU) for Both Efficacy and Safety

1. Employ utility functions that quantitatively describe efficacy and safety as one 1-dimensional component utility function separately first
  - Component utility function for efficacy  $e$  as  $U_E(e)$
  - Component utility function for safety  $s$  as  $U_S(s)$
2. Balance them by combining both component utility functions into one 2-dimensional bivariate function.
  - Multiplicatively, i.e.,  $U_{E,S}(e,s) = U_E(e) U_S(s)$ .
3. Each component utility function is piece-wise continuous function over a set of intervals. Within each interval  $i$ , the function takes flexible parametric form:

$$U_i(x) = \alpha x^2 + \beta x + \gamma + \delta \exp(\epsilon x) + \phi \log(x)$$

- Utility functions are feasible and reasonable because of their arbitrary origin and scale (Keeney and Raiffa (1976)).

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – CSMU (2)

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## Clinically Significant Minimum Utility (CSMU) for Both Efficacy and Safety (cont'd)

Each segment of the utility function within an interval along with the knots are pre-specified based on historical data or prior knowledge.

Combined utility function is then used for allocation and evaluation of the trial's both interim and final success and futility.

Clinically Significant Minimum Utility (CSMU) value is the **lower bound of acceptable utility function** values.

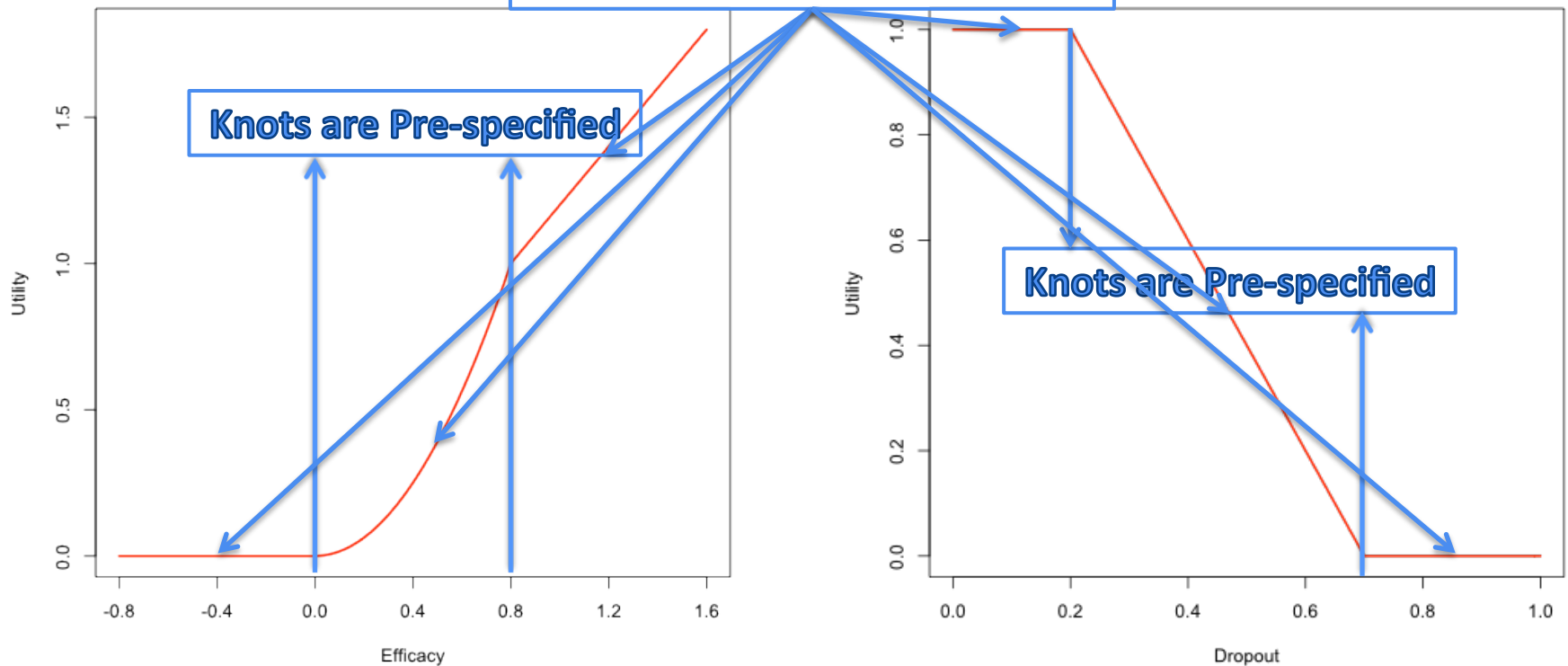
Dose with the highest utility value, i.e., maximizing  $U_{E,S}(e,s)$ , is called the **maximum effective utility dose**, denoted as  $d_{U_{\max}}$ .

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – CSMU (3)

$$U_x(x) = \begin{cases} 0 & \text{if } -\infty < x \leq 0 \\ 1.5625x^2 & \text{if } 0 < x \leq 0.8 \\ x + 0.2 & \text{if } 0.8 < x < \infty \end{cases}$$

$$U_y(y) = \begin{cases} 1 & \text{if } 0 \leq y \leq 0.2 \\ -2y + 1.4 & \text{if } 0.2 < y < 0.7 \\ 0 & \text{if } 0.7 < y \leq 1 \end{cases}$$

Piece-wise Continuous Function

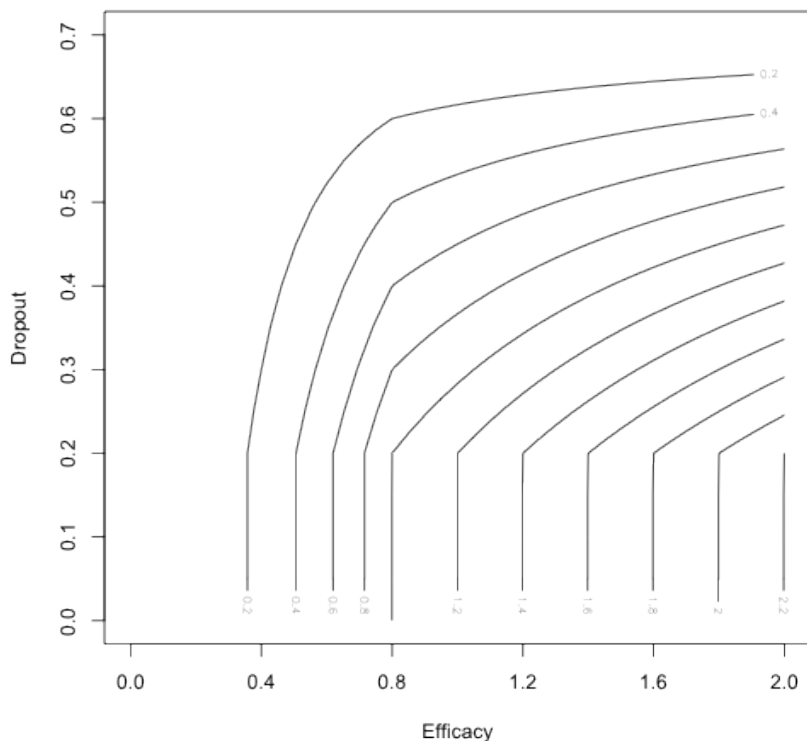


## Efficacy and Safety Separately

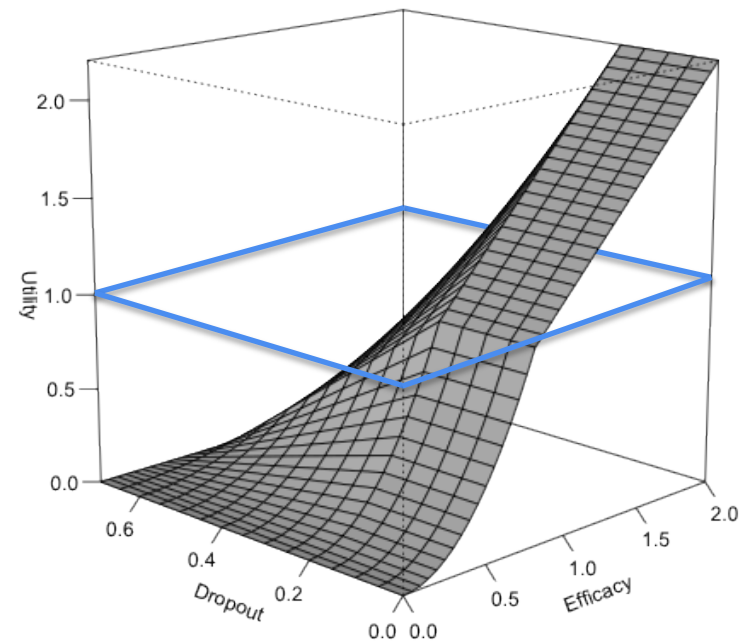
# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – CSMU (4)

## Combining Utilities

Contour Plot of Utility by Efficacy and Dropout



3D Plot of Utility by Efficacy and Dropout



**Clinically Significant Minimum Utility (CSMU)**

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – Stopping for Futility

## Stopping for Futility

A trial can be terminated early due to futility during interim monitoring.

Sample stopping rules:

- Probability that  $d_{U_{\max}}$  would be superior to placebo in a future randomized Phase 3 trial

$$\Pr (\text{Success in Phase 3 for } d_{U_{\max}}) < 0.10$$

$d_{U_{\max}} \equiv$  maximum effective utility dose

- Probability that  $d_{U_{\max}}$  would have a clinically significant difference (CSD) over placebo

$$\Pr (\vartheta_{d_{\max}} - \vartheta_0 > \text{CSD}) < 0.10$$

- Probability that the utility function  $U$  for the dose with the best utility value ( $d_{U_{\max}}$ ) is better than the clinically significant minimum utility (CSMU)

$$\Pr (U > \text{CSMU}) < 0.10$$

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – Stopping for Success

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## Stopping for Success

The trial can be stopped for success if ALL success criteria are met:

Sample stopping rules:

- $\Pr(\text{Success in Phase 3 for } d_{U_{\max}}) > 0.85$
- $\Pr(\vartheta_{d_{\max}} - \vartheta_0 > \text{CSD}) > 0.85$
- $\Pr(U > \text{CSMU}) > 0.85$



# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – ENPV (1)

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## Calculation of NPV

- For each simulated Phase 2b trial where a dose was selected to carry into Phase 3 trials:
  - Analytically calculate predictive PoS =  $\Pr(\text{Both Phase 3 trials show significance})$  using Normal priors for Phase 3 trials with mean and SD of Phase 2b posterior distribution
  - Use this probability to calculate  $E(\text{NPV})$  for the simulated Phase 2b trial by combining
    - NPV calculated from commercial model when there is Success
    - Negative NPV calculated from Phase 2b and Phase 3 trial costs when there is No Success
- Estimate  $E(\text{NPV})$  by averaging over all Phase 2b simulated trials

# Designing a Cost-effective Dose-finding Phase 2 Trial with Adaptive Design – ENPV (2)

## Calculation of NPV (con'd)

- Let  $e(d_i)$  denote the true mean diff. in efficacy from placebo for dose  $d_i$
- Let  $s(d_i)$  denote the true nuisance AE rate (tolerability) for dose  $d_i$

Table shows fifth year net revenue (\$B) from marketing a single dose that reflect trade-offs between efficacy and tolerability

$e(d_i)$	$s(d_i)$					
	0.2	0.3	0.4	0.5	0.55	0.6
0.4	0.25	0.2	0.15	0.1	0.075	0.05
0.6	0.5625	0.45	0.3375	0.225	0.16875	0.1125
0.8	1	0.8	0.6	0.4	0.3	0.2
1.0	1.2	0.96	0.72	0.48	0.36	0.24
1.2	1.4	1.12	0.84	0.56	0.42	0.28
1.4	1.6	1.28	0.96	0.64	0.48	0.32

# SIMULATION RESULTS



## Simulation Results – Probabilities of Futility and Success

Dose Response Scenario	Phase 2 Sample Size		Prob of Going to Phase 3		Prob of Phase 3 Success	
	Fixed	Adaptive	Fixed	Adaptive	Fixed	Adaptive
No Signal	400	<b>338</b>	0.002	<b>0.004</b>	0.000	<b>0.000</b>
12 Level Off	400	<b>366</b>	0.553	<b>0.587</b>	0.552	<b>0.587</b>
12 Drug	400	<b>372</b>	0.481	<b>0.526</b>	0.481	<b>0.523</b>
9 Level Off	400	<b>385</b>	0.157	<b>0.155</b>	0.153	<b>0.152</b>
9 Level Slow	400	<b>374</b>	0.429	<b>0.453</b>	0.429	<b>0.452</b>
9 Drug	400	<b>380</b>	0.358	<b>0.389</b>	0.358	<b>0.388</b>
15 Drug	400	<b>381</b>	0.308	<b>0.341</b>	0.307	<b>0.339</b>
18 Drug	400	<b>380</b>	0.305	<b>0.316</b>	0.304	<b>0.316</b>
18 Super	400	<b>360</b>	0.621	<b>0.671</b>	0.620	<b>0.671</b>

**Smaller**

**Higher**

**Higher**

## Simulation Results – Total Development Time and ENPV

Dose Response Scenario	Total Dev Time (in yrs)		ENPV (\$B)	
	Fixed	Adaptive	Fixed	Adaptive
No Signal	7.0	6.8	0.00	0.00
12 Level Off	7.1	7.0	2.20	2.36
12 Drug	7.1	7.0	2.22	2.42
9 Level Off	7.1	7.0	0.36	0.36
9 Level Slow	7.1	7.0	1.46	1.56
9 Drug	7.1	7.0	1.38	1.52
15 Drug	7.1	7.0	1.06	1.18
18 Drug	7.1	7.0	1.05	1.14
18 Super	7.1	7.0	2.75	3.02

Similar Duration

Higher Revenue

## Conclusions and Discussion

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- **Adaptive randomization with utility function appears to be a more efficient approach for the characterization of the dose-response profile of an experimental drug.**
- **ENPV is generally higher for adaptive design than fixed-arm design.**
- **Expected sample size for Phase 2 trials is overall smaller for adaptive design.**
- **Predicted probability of success of Phase 3 trials is higher for adaptive design.**
- **ENPV is directly related to clinical utility, so it can be thought of as optimizing for clinical utility.**
- **Work is ongoing to refine/finalize the design parameters for the adaptive randomization with utility function framework to enable selection of ED dose(s) with maximum probability of success in Phase 3.**

## References

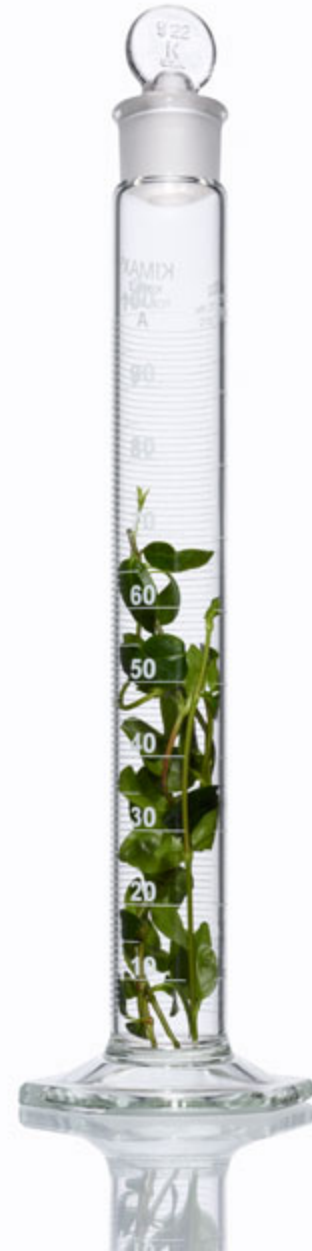
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BACK UP



# Designing a Cost-effective Dose-finding Phase 2 Trial – Dose-respond Models for Efficacy

## Dose-Response Models for Efficacy

- Normal Dynamic Linear Model (NDLM)
- A flexible and robust model for capturing non-monotonic curves.
- Let  $i = 1, \dots, k$  be the subject indices. Let subject  $i$  have dose  $d_i = 0, 1, \dots, D$ , in which the placebo control is labeled as  $d = 0$ , the active comparator is labeled as  $d = D$ ,  $Y_i \sim \vartheta_d + N(0, \sigma^2)$ .
- The prior distribution for the first dose,  $d = 1$ , is  $\theta_1 \sim N(\mu_1, \nu_1^2)$  and  $\theta_d \sim N(\theta_{d-1}, \tau_{d-1}^2)$  for  $2 < d < D$
- The prior distribution of the drift term  $\tau$  is  $\tau^2 \sim IG\left(\frac{\tau_n}{2}, \frac{\tau_\mu^2 \tau_n}{2}\right)$
- The prior distribution of the error term  $\sigma$  is  $\sigma^2 \sim IG\left(\frac{\sigma_n}{2}, \frac{\sigma_\mu^2 \sigma_n}{2}\right)$
- The placebo and active are modeled separately with prior distributions of  $\theta_0 \sim N(\mu_0, \nu_0^2)$   $\theta_D \sim N(\mu_D, \nu_D^2)$

# Designing a Cost-effective Dose-finding Phase 2 Trial – Longitudinal Models for Efficacy

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## Longitudinal Models for Efficacy

- Design the trial with multiple visits instead of a single visit.
- A longitudinal model will be employed to enable final observations to be imputed for those subjects that only have intermediate responses.
- Separate longitudinal models might be fitted to various doses.
- We use the simple linear regression model to accommodate the correlation between final observations and intermediate responses.
- A common model is used for each dose and a separate model for the placebo and one for the active comparator arm.
- The primary end point is modeled as  $Y_i | y_{it} \sim \alpha_t + \beta_t y_{it} + N(0, \lambda_t^2)$
- The prior distributions of  $\alpha_t$ ,  $\beta_t$ , and  $\lambda_t$  are

$$\alpha_t \sim N(\alpha_\mu, \alpha_\sigma^2)$$

$$\beta_t \sim N(\beta_\mu, \beta_\sigma^2)$$

$$\lambda_t^2 \sim IG\left(\frac{\lambda_n}{2}, \frac{\lambda_\mu^2 \lambda_n}{2}\right)$$

# Simulation Set-up: Dose Response Model

## Simple Normal Dynamic Linear Model (NDLM)

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- 5 doses of ED are labeled as  $d = 1, 2, 3, 4$  and 5. The placebo is labeled as  $d = 0$  and the active is labeled as  $d = 6$ .
- For subject  $i$  on dose  $d$ ,
  - $Y_{12,i,d} \sim N(\vartheta_d, \sigma^2)$
- The prior distribution for the first dose,  $d = 1$ , is
  - $\vartheta_1 \sim N(1.8, 2.5^2)$  and
  - $\vartheta_d \sim N(\vartheta_{d-1}, \tau^2)$  for  $d = 2, 3, 4, 5$
- The prior distribution of the drift term  $\tau$  is  $\tau^2 \sim IG(0.5, 8)$ .
- The prior distribution of the error term  $\sigma$  is  $\sigma^2 \sim IG(0.001, 1000)$ .
- The placebo and active are modeled separately with prior distributions of  $\vartheta_0 \sim N(1.8, 2^2)$  and  $\vartheta_6 \sim N(2.8, 2^2)$ , respectively.

# Simulation Set-up: Longitudinal Model

## Simple Linear Regression Model

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- Given the change from Baseline pain score at visit  $t$  (at least Week 2), the final response for subject  $i$  on dose  $d$  is modeled as,

- $Y_{i,d} / y_{i,d,t} \sim N(\alpha_t + \beta_t y_{i,d,t}, \lambda_t^2)$

- The prior distributions of  $\alpha_t$ ,  $\beta_t$ , and  $\lambda_t$  are

- $\alpha_t \sim N(0, 3^2)$

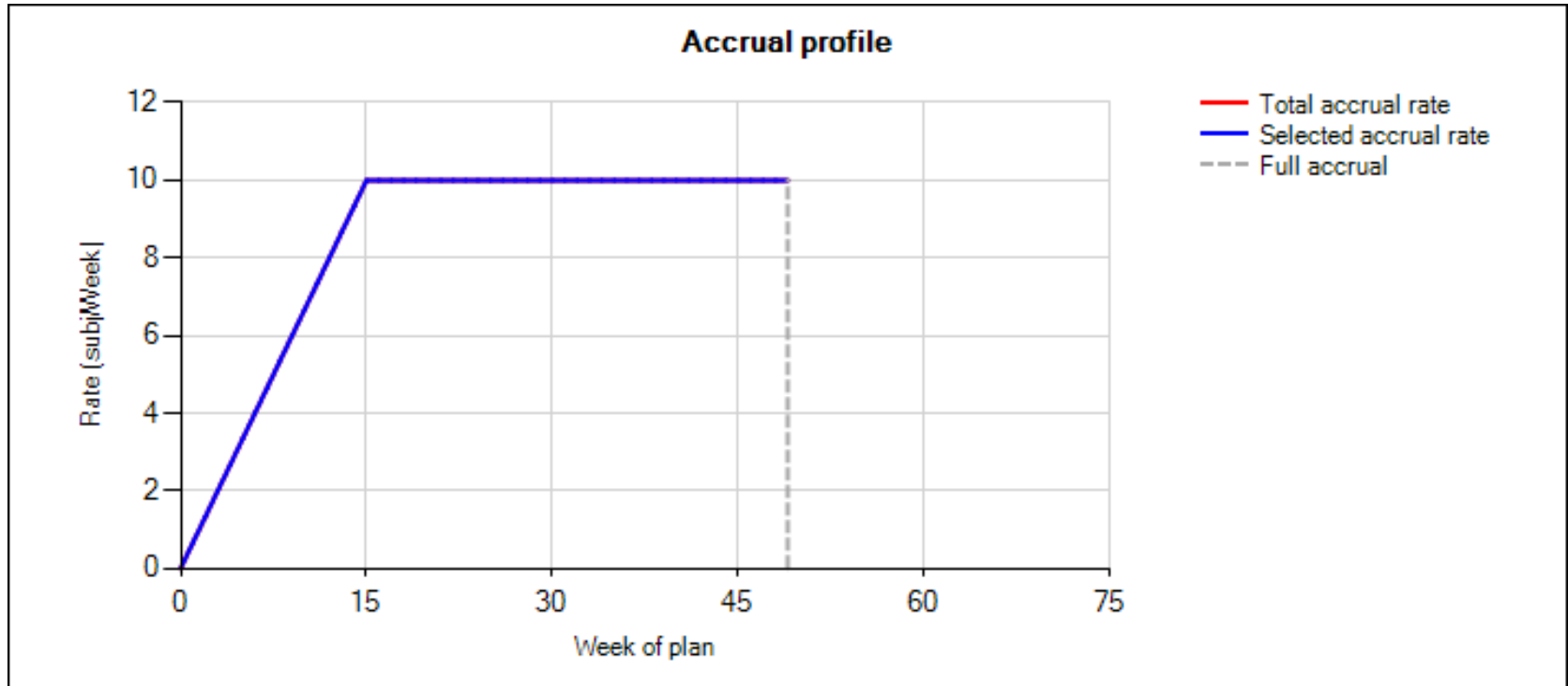
- $\beta_t \sim N(0.8, 0.25^2)$

- $\lambda_t^2 \sim IG(0.5, 1.36)$

- All the ED doses are modeled together. And the placebo and active are modeled separately.

## Simulation Set-up: Accrual Profile

- We assume that accrual will ramp-up starting for the first 14 weeks and then reach a peak accrual rate of 10 patients per week in week 15 until accrual is complete.



## Simulation Set-up: AE Rates

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- We assume a decreasing drop-out rate at each visit resulting in the requested overall drop-out rates as below for each treatment arm.

Visit	Placebo	6 mg	9 mg	12 mg	15 mg	18 mg	AC
Week 2	0.085	0.15	0.15	0.15	0.175	0.175	0.12
Week 4	0.04235	0.075	0.075	0.075	0.0875	0.0875	0.06
Week 6	0.02125	0.0375	0.0375	0.0375	0.04375	0.04375	0.03
Week 8	0.010625	0.01875	0.01875	0.01875	0.021875	0.021875	0.015
Week 12	0.010625	0.01875	0.01875	0.01875	0.021875	0.021875	0.015

## Simulation Set-up: Time and Cost Estimates

Factors	Value
Total patent life	17 years
Duration of development time prior to phase 2 trial that cuts into the patent life	2 years
Total number of sites in phase 2 trial	50
Time between completion of phase 2 trial and the 1st subject 1st visit in phase 3 trials	6 months
Patient accrual rate per month per site in phase 3 trials	1
Total number of sites in each phase 3 trial	80
Time between end of phase 3 trials and product launch	12 months
Upfront cost per site	1.5K
Cost per patient	3.5K
Startup cost of manufacturing	1M
Revenue model parameter b	0.1
Revenue model parameter c	0.5
Annual discount rate to be used to calculate ENPV	10%
Minimum number of subjects per dose in phase 2 and phase 3 trials necessary to satisfy ICHE1 requirement	1500
Proportion of phase 2 subjects completing 12 month long-term extension trial	50%

**Time and cost estimates used in ENPV calculations (all costs are in US dollars)**