A Seamless 2/3 Design Incorporating a Clinical Utility Index

Zachary Kulkarni Skrivanek, PhD

Eli Lilly and Company

October 10, 2008
1 Background

2 Study Design
   • Description of Study Design and Data Flow
   • Mathematics Behind Study Design

3 Simulations
   • Simulation Process
   • Simulation Results

4 Conclusion
Outline

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4 Conclusion
Under the FDA Modernization Act of 1997 (P.L. 105-115), Congress expanded the FDA mission to include the promotion of public health, not only through the timely and efficient review of clinical research, but also though collaborations with partners in government, academia, and industry to further medical product development. FDA’s Critical Path initiative (CPI) will stimulate industry-wide efforts to identify . . . improved clinical trial designs that will accelerate product development.

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diabetes was selected by Lilly and the FDA for a CPI project.
Diabetes is a well understood disease with biomarkers that have been used in clinical practice for decades to assess the safety and efficacy of diabetes therapies.

Consequently, adaptive designs are well suited for learning about the dose response of a diabetes drug and providing confirmatory evidence for the safety and efficacy of the optimal dose(s).
Objectives of Study

1. Identify up to two doses (Low and High doses) that have a high probability of meeting criteria for safety and efficacy.

2. Demonstrate that these doses show robust glycemic control compared to Active Comparator (AC) and placebo in patients with Type 2 Diabetes Mellitus at 12 months.

3. Primary objective is to demonstrate noninferiority to the AC for the High dose. Five other secondary objectives are included in the primary analysis. The family-wise Type I error is controlled by a modified tree-gatekeeping strategy.¹

This was a collaborative effort

- Medical Director, study physician
- biostatistician, statistical analyst
- PK/PD scientist, PK/PD modeler
- marketing director, marketing researcher
- Berry Consultants
- cluster computing computer scientist

- design finalized and turned into a protocol within 6 months
- met with the FDA 5 times (3 face to face meetings, 2 teleconference) and EMEA to discuss aspects of design
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An Adaptive Seamless Phase 2/3 Study
Two Stage Design

Stage 1 (n ≤ 400)

- 7 experimental doses ($d_1, \ldots, d_7$) and 2 comparators, placebo ($pbo$) and Active Comparator (AC)
- burn-in period of patients 5 per arm
- adaptive dose randomization after burn-in
- adapting on 2 safety ($S_1$ and $S_2$) and 2 efficacy ($E_1$ and $E_2$) endpoints
- bi-weekly updating of safety and efficacy data and randomization probabilities
- after 200 patients enrolled, assess decision alternatives
  - continue in Stage 1
  - stop for "futility" (efficacy and safety)
  - start Stage 2
Two Stage Design

Stage 2 (add approximately 800 patients)

- up to two doses, *pbo* and *AC*
- ≥ 70% of patients in each arm from Stage 2
- fixed allocation to all arms/fixed sample size
- same study schedule as in Stage 1

Final analysis

- Includes data from both stages for all of the arms continuing into Stage 2
- Strong control of Type I Error rate prospectively demonstrated via simulations
Two Stage Design

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Data Flow

**Sites**
- eCRF Data
- Central Lab Data
- Other Data*
  - Pharmacovigilence Data

**Blinded**
- Lilly
- Recommendations
  - Safety & Efficacy Data

**Unblinded**
- Independent DMC
- Independent SAC
  - bi-weekly randomization updates

**BLINDED**

**UNBLINDED**

*e.g. PK, adjudicated AE data
DMG = Data Movement Group
IVRS = Interactive Voice Response System
LRL = Lilly Research Laboratories
SAC = Statistical Analysis Center
DMC = Data Monitoring Committee
Components of Data Flow

There are 3 major components to the data flow:

1. update the longitudinal models and dose response models
2. update randomization probabilities
3. evaluate decision rules
Clinical Utility Index

**Derivation**
1. identify key biomarkers (2 efficacy, $E_1$ and $E_2$, and 2 safety measures, $S_1$ and $S_2$)
2. anchor at 1 for neutral
3. solicit expert opinion
4. validate with decision makers using simulation
5. multiplicative

**Background**
1. Deringer and Suich define desirability functions
2. geometric mean has optimal properties
Clinical Utility Index

Derivation

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Background

1. Deringer and Suich define desirability functions
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Clinical Utility Index

\[
CUI = E1 \cdot E2 \cdot S1 \cdot S2
\]

\[
CUI = \text{Efficacy} \cdot \text{Efficacy} \cdot \text{Safety} \cdot \text{Safety}
\]

**Figure:** After burn-in in Stage 1, safety and efficacy data accumulate, and the algorithm will minimize the chance that a subject is enrolled in either an unsafe or ineffective treatment arm.
Longitudinal Growth Model

Project out to 6 months for safety (S1 and S2) and 12 months for efficacy (E1 and E2)

$\theta_v(d)$ is the mean for endpoint $v$ and dose $d$

For $v = E1, E2, S1$ and $S2$ and treatment $d$, the mean effect at time $t$ is modeled by

- $e^{\gamma_v,t} \cdot \theta_v(d)$
- $\gamma_{v,t} = 0$ at $t = \text{endpoint time (6 mos or 12 mos)}$

priors on $\gamma_{v,t}$

- prior mean is Normal, $\leq 0$, and monotonically increasing
- informative, solicited from expert opinion
Longitudinal Growth Model

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**priors on $\gamma_{v,t}$**

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- informative, solicited from expert opinion
Dose Response Models

For \( v = E1, E2, S1 \) and \( S2 \) and \( d = d_1, pbo \) and \( AC \):

\[
\theta_v(d) \sim N(m_v(d), s^2_v(d))
\]

For \( v = E1, E2, S1 \) and \( S2 \) and treatment \( d = d_2, \ldots, d_7 \):

- Normal Dynamic Linear Model (NDLM)
- \( \theta_v(d_k) \sim N(\theta_v(d_{k-1}), \lambda^2_v) \)

Priors

- Informative priors on \( \theta_v(d) \), solicited from expert opinion
- Uninformative (flat) priors on \( \lambda^2_v \) and \( s^2_v(d) \)
Dose Response Models

For \( \nu = E_1, E_2, S_1 \) and \( S_2 \) and \( d = d_1, pbo \) and \( AC \)

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### Dose Response Models

For $v = E1, E2, S1$ and $S2$ and $d = d_1, pbo$ and $AC$

$$\theta_v(d) \sim N(m_v(d), s^2_v(d))$$

For $v = E1, E2, S1$ and $S2$ and treatment $d = d_2, \ldots, d_7$

- Normal Dynamic Linear Model (NDLM)
- $$\theta_v(d_k) \sim N\left(\theta_v(d_{k-1}), \lambda^2_v\right)$$

**priors**

- informative priors on $\theta_v(d)$, solicited from expert opinion
- uninformative (flat) priors on $\lambda^2_v$ and $s^2_v(d)$
Hierarchical model for individual effect of patient $i$, $Y_{ivt}$

$$Y_{ivt} = e^{\gamma_{ivt}} (\theta_v(d) + \delta_{iv}) + \epsilon_{ivt}$$

$$\delta_{iv} \sim N(0, \tau_v^2)$$

$$\epsilon_{ivt} \sim N(0, \sigma_v^2)$$

Attributes of hierarchical model

- mean for individual $i$ is $\theta_v(d) + \delta_{vi}$
- induces intra-subject correlation
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Attributes of hierarchical model

- mean for individual $i$ is $\theta_v(d) + \delta_{vi}$
- induces intra-subject correlation
Definition of Terms for Randomization Probabilities

- **MUD** = the dose that has the maximum utility based on the current information
- **MAD** = the lowest dose that has a utility of at least 0.60
- **$P_{MUD}(d)$**: posterior probability that dose $d$ is MUD
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- **$PrU(d)$**: probability that dose $d$ has a utility of at least 0.60
Randomization Probabilities

The randomization probability for treatment $d$, $r_d$, is determined by

$$ r_d = \begin{cases} 
0.20 & \text{if } d = \text{comparator} \\
\frac{h_d + l_d}{\sum_{d=d_1}^{d_7} [h_d + l_d]} \times (0.60) & \text{if } d = d_1, \ldots, d_7
\end{cases} $$

where

$$ l_d = \frac{P_{MAD}(d)}{\sum_{d=d_1}^{d_7} P_{MAD}(d)}, \quad h_d = \frac{P_{MUD}(d)}{\sum_{d=d_1}^{d_7} P_{MUD}(d)} $$
Definition of Terms for Decision Rules

- **Max** = the most likely MUD dose
- **PPNI(d)\(_1\)** and **PPNI(d)\(_2\)**: predictive probability of noninferiority to AC at 12 months for \(n_1\) and \(n_2\) total patients per arm, respectively.
- **PPSUP(d)\(_1\)**: predictive probability of superiority to AC at 12 months with \(n_1\) total patients per arm
- **PrU(d)**: probability that dose \(d\) has a utility of at least 0.60
Decision Rules (200 < n < 400)

Stop for futility if at least 1 of the following holds for all \( d_1, \ldots, d_7 \):

1. \( PPNI(d)_2 < 0.05 \)
2. \( PrU(d) < 0.05 \)

Go to Stage 2 with Max dose as the High dose if \( PPNI(\text{Max})_1 > 0.85 \) and \( PrU(\text{Max}) > 0.60 \) and either a Low dose can be selected or it is futile to find a low dose as defined below.

1. Select the next highest dose, \( d \) that has \( PrU(d) > 0.60 \) for the Low dose
2. Futile to find Low dose if every dose lower than Max satisfies at least 1 of the futility rules defined previously.

Otherwise, continue with Stage 1
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Decision Rules (200 < n < 400)

Stop for futility if at least 1 of the following holds for all $d_1, \ldots, d_7$:

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Decision Rules \((n = 400)\)

Go to Stage 2 with Max dose as the High dose if

\[ PPNI(\text{Max})_1 > 0.7 \text{ and } PrU(\text{Max}) > 0.60 \]

and either a Low dose can be selected or it is futile to find a low dose as defined below.

1. Select the next highest dose, \(d\) that has \(PrU(d) > 0.60\) for the Low dose

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Go to Stage 2 with the highest dose as the High dose that satisfies

\[ PPNI(\text{High})_1 > 0.7 \text{ and } PrU(\text{High}) > 0.60 \]

Select dose as Low if:

\[ PrU(\text{Low}) > 0.60 \]

else go to Stage 2 with just the High dose

Otherwise, stop the study
Decision Rules ($n = 400$)

Go to Stage 2 with $\text{Max}$ dose as the $\text{High}$ dose if $\text{PPNI}(\text{Max})_1 > 0.7$ and $\text{PrU}(\text{Max}) > 0.60$ and either a $\text{Low}$ dose can be selected or it is futile to find a low dose as defined below.

1. Select the next highest dose, $d$ that has $\text{PrU}(d) > 0.60$ for the $\text{Low}$ dose.

2. Futile to find $\text{Low}$ dose if every dose lower than $\text{Max}$ satisfies at least 1 of the futility rules defined previously.

Go to Stage 2 with the highest dose as the $\text{High}$ dose that satisfies $\text{PPNI}(\text{High})_1 > 0.7$ and $\text{PrU}(\text{High}) > 0.60$. Select dose as $\text{Low}$ if:

- $\text{PrU}(\text{Low}) > 0.60$
- else go to Stage 2 with just the $\text{High}$ dose.

Otherwise, stop the study.
Decision Rules \((n = 400)\)

Go to Stage 2 with \textit{Max} dose as the \textit{High} dose if \(PPNI(\text{Max})_1 > 0.7\) and \(PrU(\text{Max}) > 0.60\) and either a \textit{Low} dose can be selected or it is futile to find a low dose as defined below.

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Go to Stage 2 with the highest dose as the \textit{High} dose that satisfies \(PPNI(\text{High})_1 > 0.7\) and \(PrU(\text{High}) > 0.60\). Select dose as \textit{Low} if:

\(PrU(\text{Low}) > 0.60\)

else go to Stage 2 with just the \textit{High} dose

Otherwise, stop the study
Stage 2 is conducted with a total sample size of at least $n_1$ or $n_2$ per arm.

If $PPSUP(d)_1 > 0.85$ then proceed with $n_1$, else proceed with $n_2$.

The sample sizes are augmented to ensure that $\geq 70\%$ of all patients in each arm are randomized in Stage 2.
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An Adaptive Seamless Phase 2/3 Study
Simulation Process

Overarching Quantitative Decision Criteria
"Design with the End in Mind"
Simulation Process

Virtual Patients → Trial Simulator → Operating Characteristics

Virtual Results
Simulation Process

Response Models
- PK/PD (alternative)
- Empirical statistical models (null or alternative)

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- Inclusion/exclusion criteria
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Trial Execution Models
- Drop out models
- Accrual models
- Decision models:
  - CUI
  - Futility threshold
- Predictive models:
  - Longitudinal model to predict patient outcomes for ongoing patients
  - Dose-response model to assess population effect

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**Data Analysis Model**
- ANCOVA
- LOCF
- Tree-gatekeeping
- Nominal alpha

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Trial Performance Metrics
- Power (Scenario in alternative)
- Type I error (Scenario in null)
- Probability of selecting correct dose(s)
- Probability of stopping for safety
- Probability of stopping for lack of efficacy

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**Operating Characteristics**

iterate
Simulation Process

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Data Analysis Model:
- ANCOVA
- LOCF
- Frequentist: nominal alpha

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iterate
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Operating Characteristics

Output

Simulation Report

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Simulation Results—Select Scenarios

- Probability increases with CUI
- Sample size depends on width of therapeutic window

Barplot of $P(\text{Enter Stage 2})$

- Red: no therapeutic window
- Yellow: narrow therapeutic window
- Green: wide therapeutic window

Sample Size

Trimmed mean CUI across all 7 doses

Median Sample Size/arm in Stage 1

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Scenario 1: increasing efficacy, no safety issues

- Probability increases with CUI
- Sample size increases with CUI
Scenario 2: narrow therapeutic window

- Probability increases with CUI
- Sample size increases with CUI
Scenario 3: narrow therapeutic window

- probability increases with CUI
- sample size increases with CUI
Scenario 4: wide therapeutic window

- Probability increases with CUI
- Sample size increases with CUI
Fixed Design Comparison

<table>
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<tr>
<th>Fixed design</th>
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<tbody>
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<td>4. 50 patients/arm</td>
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Assess both fixed design and adaptive design using the same pharmacodynamic models for *E1*, *E2*, *S1* and *S2*

- fixed design: 6% or 12% (12 or 26 weeks) successfully selected dose(s)
- adaptive design: 90% success rate (mean duration 56 weeks, mean total sample size 279 patients)
Fixed Design Comparison

**Fixed design**

1. 4 doses and pbo
2. 12 or 26 weeks (2 scenarios)
3. no dropouts
4. 50 patients/arm

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2. adaptive design: 90% success rate (mean duration 56 weeks, mean total sample size 279 patients)
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Advantages of Seamless, Adaptive Design

The adaptive dose finding aspect allows for:

1. patients allocated more often to optimal doses rather than doses that do not demonstrate a good safety/efficacy profile
2. more doses studied (7 vs the typical 3 to 4 doses studied in a fixed design)
3. better decisions (dose selection, futility)

The seamless aspect of the design:

1. is more efficient use of patient data
2. eliminates white space
3. provides longer term safety data sooner
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Acknowledgements

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Select References