Bayesian Adaptive Trial Design: A New Approach for Phase 2 Clinical Trials in Alzheimer’s Disease

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We Need to Rethink Study Design for AD Trials

**Motivation**
- Several Phase 3 failures
- Need proof-of-concept before Phase 3 – Identify the right dose

**Inherent Challenges**
- Studies shifting to earlier disease
  - Progression slow = large sample sizes, long trials
- Multiple uncertainties
  - Dose/regimen, treatment effect size, sample size, etc.

**Novel Approach**
- Bayesian adaptive design allows informed and efficient decision making through ongoing analysis of existing study data
  - Opportunity to make decisions earlier
Bayesian Adaptive Design helps us to drive with our eyes open

- Adaptive design algorithm uses probability distributions for dose effects
- Longitudinal model imputes later endpoints based on effects at earlier points
- Multiple planned interim analyses (IA) update the probability distributions and longitudinal model
- Based on IA results, the trial can be stopped for futility, or accrual can be stopped for early success, leading to faster initiation of Phase 3
- To find the most effective dose with fewer subjects
  - Can start trial with larger number of active treatment arms than a traditional Phase 2 trial
  - Response adaptive randomization assigns patients to more favorable doses based on IA results

*Bayesian Adaptive Design helps mitigate risk of multiple unknowns*
Eisai decided on a Bayesian adaptive design for its Phase 2 trial of a disease-modifying antibody

- **Investigational agent:** BAN2401
  - Monoclonal antibody directed at amyloid protofibrils
- **Objectives**
  - Demonstrate clinical efficacy (PoC)
  - Learn whether effect may be disease-modifying
  - Assess dose response and safety
- **Subjects**
  - MCI due to AD and Mild AD (Early AD, collectively)
Drug Effect and Boundary Definitions

Treatment Effect Size

- Cut-point for estimated meaningful difference in change from baseline on primary endpoint for drug compared to placebo
  
  = 25%

- Key underlying design component that guides decision making
- Used in the adaptive model to define boundaries for futility and success

**Futility:** Probability that any dose is better than PBO by 25% at IA is less than X%

**Early Success:** Probability that a dose is better than PBO by 25% at IA is at least Y%

- Selection of “X” and “Y” using simulation
Role of Simulations in Adaptive Design Process

- **Known Study Characteristics**
  - Dose arms
  - 1° endpoint and timing
  - Patient population

- **Design Components**
  - Futility/success boundaries
  - Treatment effect size
  - Sample size
  - Allocation rules
  - Existing data/Modeling

- **Dose Effect Scenarios**
  - 13 total

- **Simulations**

- **Objective**
  - POC
  - Dose-Finding

- **Execution**
  - Accrual Rate
  - Drop out rate

- **Operating Characteristics**
  - Type I and II error
  - Interim analysis timing
  - Probability of futility
  - Probability of early success
  - Probability of overall success
  - Probability Phase III go decision

- **Final Trial Design**
  Confirm Design Performance and Credibility
Simulating Futility Boundaries Over Multiple Dose/Effect Scenarios

- **Futility Boundary**: cut-point for making decision on ineffective drug
- Final boundary **trade-off** for stopping ineffective drug vs. stopping effective drug

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**Null Scenario**

- Futility Bound: 15%, 12.5%, 10%, 7.5%, 5%, 2.5%, 0%

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cumulative Probability Stop for Futility</th>
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<tbody>
<tr>
<td>1</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>12.5%</td>
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<tr>
<td>3</td>
<td>10%</td>
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<tr>
<td>4</td>
<td>7.5%</td>
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<td>5</td>
<td>5%</td>
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<td>6</td>
<td>2.5%</td>
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<tr>
<td>7</td>
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**Dose Response: 1 Robust Dose**

- Futility Bound: 15%, 12.5%, 10%, 7.5%, 5%, 2.5%, 0%

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Simulating Early Success Boundaries Over Multiple Dose/Effect Scenarios

- **Early Success Boundary**: cut-point for making decision on effective drug
- **Final boundary trade-off** for false positive vs. false negative decision
Final Design Performance Across Dose/Effect Scenarios

- **Null Effect**: 45% probability of early futility if no effect
- **1 Dose Strong Effect, Others Null**: 66% probability of early success if robust effect
- **Dose Response 1 Dose Strong Effect**: 80% probability of overall success if robust effect

800 Subjects Max

Pr(Stop Early Futility)
Pr(Stop Early Success)
Pr (Success)
Adaptive Trial Recruitment and Interim Analyses

- **Burn-in:**
  - Accrue 196 with fixed allocation:
    - 56 to PBO
    - 28 to each of 5 active doses

- **Interim Analyses every 50 patients**
  - Model current data
  - Adapt Randomization

- **200 onwards - Stop for EARLY FUTILITY?**

- **350 onwards - Stop for EARLY SUCCESS?**
  - IAs quarterly once 800 patients recruited
Example of stopping accrual early for success

Total n = 550
Example of stopping accrual early for futility

Total n = 500

Number Randomized

Probability of superiority to placebo by CSD
Final Design Sample Size Distribution Across Dose/Effect Scenarios

Simulation results for final design parameters

- 800 subjects max

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<tr>
<th>Scenario</th>
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<th>Dose Response 1 Robust Dose</th>
<th>Average Across All 13</th>
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<tr>
<td>Subjects to Decision (average)</td>
<td>683</td>
<td>669</td>
<td>657</td>
<td>626</td>
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- Almost never reach 800 subjects
- Time to decision with fewer subjects = shorter trial duration
  - On average, decision reached 17 months earlier
Phase 2 clinical trials should demonstrate proof-of-efficacy before proceeding to Phase 3.

BAN2401 is an amyloid-based investigational therapy predicted to work best in an early AD population where disease progression is slow and sample size requirements are therefore large for a traditional trial.

Bayesian adaptive design utilizes interim analyses to update randomization allocation and assess futility or success.

Bayesian design mitigates risks associated with larger and longer trials:
- Early termination if ineffective
- Early advancement to successful Phase 3
- Better dose selection

Approach is encouraged by regulatory authorities.

A similar approach is now being used for Phase 2 with a BACE1 inhibitor.