A Bayesian Analysis of Disease Modification Using Doubly Randomized Delayed-Start and Matched-Control Design Paradigms

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Outline

- Introduction
- Scientific/Regulatory Considerations
- Existing Trial Designs and Statistical Methods
- Research Initiatives
- Discussion
How do Disease Progression and Disease Modification Differ?

- Disease progression: worsening of a disease in terms of symptom severity, underlying pathology, or outcome. The term “disease progression” is most commonly used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis.

- Disease modification: alteration of the underlying disease pathophysiology that results in a beneficial outcome.
Neurodegenerative Disease

- Amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease
- Multiple sclerosis (MS)
- Parkinson’s disease (PD)
- Alzheimer’s disease (AD)
Neurodegenerative Disease
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Challenges to Drug Development
- Unmet need for efficacious disease modification drugs over management of symptoms
- Driven by fruitful scientific research and discoveries
- Additional research objectives
  - To establish disease mediation biomarkers
  - To demonstrate clinical evidence of disease modifications
Basic Research in Disease Biology

- Associations of biomarkers and clinical outcomes from observational studies
- Causality via designed experiments
- Targeted drugs with effects on mediation biomarkers
Basic Research in Disease Biology

- Associations of biomarkers and clinical outcomes from observational studies
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Mediation Biomarkers

- Direct measure of biological or physiological state of disease progression associated with clinical outcomes
- Direct targeted drug effects on biomarkers
- Indirect drug effects on clinical outcomes
- Indirect drug effects on clinical outcomes explained by direct biomarker effects
Randomized Delayed-Start Design

  - Two basic treatment sequences TT and PT
  - Clinical effects in period 1 between T and P, sustained effects between TT and PT after delayed-start in period 2
  - More “ethical” than randomized withdrawal?
FIG. 2. Randomized start design.

Alzheimer Disease and Associated Disorders, Vol. 10, Suppl. 1, 1996
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  - Adequate duration required to allow meaningful interpretation
  - An order of magnitude too big for non-inferiority margin for the second period
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  - Too complicated to interpret
  - Disease modifying effect to reflect physiological changes
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  - Suitable for drugs with large effect
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- D’Agostino
  - Second phase observational study with differential drop-out
  - Careful to buy into this design
Period 1 Issues

- **Slope Analysis**
  - Disease progression generally non-linear; instruments with ceiling effects
  - Specification of duration of exclusion (Fleming) or “data-not-used zone” (D’Agostino)
  - Bias due to early differential dropouts
Period 1 Issues

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- **Last-Visit Analysis**
  - Biased “completer analysis” (consider, MMRM with treatment contrast for the last visit)
  - “Sensitivity analysis” with un-verifiable assumptions (consider, multiple imputation or pattern mixture models)
  - Lacking serious evaluations of robustness of any analytical method under a range of plausible MNAR models or assumptions
Period 2 Issues

- Analysis of clinical evidence of disease modifications
  - Slope analysis difficult to interpret due to non-linear response curves
  - Bias due to excessive missing data (in period 1) and lack of blinding with controls

- Clinical trial design
  - Presumption of delayed-start effects
  - Lacking mechanisms for the verification and quantification of the delayed-start effects
Period 2 Issues

- Analysis of clinical evidence of disease modifications
  - Slope analysis difficult to interpret due to non-linear response curves
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Adaptations with Potential Mediation Biomarkers

- Early futility, modification of enrollment criteria, or sample size adjustment
- Bias mediation analysis
- Validity of design established mathematically, not via limited and potentially biased simulation studies
Case 1: Disease Modification Effects

Oral Paliperidone ER

Part I

2-month Lead-In

Part II

9-month

Part III

9-month

Research Initiatives
Case 1: Disease Modification Effects

δ_{21}: Treatment effect on disease progression;

Part I
- 2-month
- Lead-In
- randomization

Part II
- 9-month
- Disease Progression
- 1:2 Rand

Part III
- 9-month

Oral Paliperidone ER

Oral APs

PP

δ_{21}
Case 1: Disease Modification Effects

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Case 1: Disease Modification Effects

δ_{21}: Treatment effect on disease progression;

Part I
- 2-month Run-In
- Randomization

Part II
- 9-month Disease Progression

Part III
- 9-month Disease Progression
- Exploratory Disease Interception
- Delayed-start PP
Case 1: Disease Modification Effects

δ_{21}: Treatment effect on disease progression; δ_{31}: Lead treatment effect;
Case 1: Disease Modification Effects

- $\delta_{21}$: Treatment effect on disease progression
- $\delta_{31}$: Lead treatment effect
- $\delta_{32}$: Delayed-start treatment effect on disease progression

Part I: 2-month Run-In
- Oral Paliperidone ER

Part II: 9-month Disease Progression
- 1:2 Rand
- Oral APs
- $\delta_{21}$

Part III: 9-month Disease Progression
- 1:1 Rand
- Delayed-start PP
- Oral APs
- $\delta_{31}$
- $\delta_{32}$
Case 1: Disease Modification Effects

\[ \delta_{21} : \text{Treatment effect on disease progression; } \delta_{31} : \text{Lead treatment effect; } \delta_{32} : \text{Delayed-start treatment effect on disease progression; } \delta_{33} : \text{Overall effect of treatment.} \]
Case 2: Delayed-Start Effects

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Biomarkers

- Brain MRI Scans
- ICM volume will be measured - Cortical thickness, gray matter and white matter volumes

- No correlations
- No path analysis

Lingering Issues

- Missing data
- Multiplicity
Three Key Innovations

- Randomized Matched Controls
  - Prospective run-in with static and dynamic prognostic factors
  - Matched control or causal inference to quantify retention effect

- Managed Withdrawal with Re-entry
  - Patients who decide to drop out are given necessary medicine(s) other than the study drug for best possible care, and are allowed to re-enter into Part III
  - On-going trials

- Randomized Delayed-Start
  - Verification and quantification of delayed-start effect
  - Disease modification as a clinical judgment based on the totality of evidence (i.e., effect on progress $\delta_{21}$, lead effect after early-start $\delta_{31}$, delayed-start effect $\delta_{32}$, cumulative effect on progression $\delta_{33}$, and biomarker effects)
Recall: Disease Modification

δ_{21}: Treatment effect on disease progression; δ_{31}: Lead treatment effect; δ_{32}: Delayed-start treatment effect on disease progression; δ_{33}: Overall effect of treatment.
• $\delta_{21}$ is the month 9 treatment effect on disease progression
  \[ \delta_{21} = \mu_{9}^{(PP)} - \mu_{9}^{(AP)} \]

• $\delta_{31}$ is a measure of how much the $AP / PP$ (delayed start with $PP$ or lead treatment effect) subjects caught to the PP/PP subjects
  \[ \delta_{31} = \mu_{18}^{(PP,PP)} - \mu_{18}^{(AP,PP)} \]

• $\delta_{32}$ is delayed start treatment effect on disease progression. The amount you may gain switching to $PP$
  \[ \delta_{32} = \mu_{18}^{(AP,PP)} - \mu_{18}^{(AP,AP)} \]

• $\delta_{33}$ is the overall effect of treatment
  \[ \delta_{33} = \mu_{18}^{(PP,PP)} - \mu_{18}^{(AP,AP)} \]
We will examine catching up by estimating the posterior probabilities:

\[ P(\delta_{31} > 0.75\delta_{21}); \quad P(\delta_{31} > 0.50\delta_{21}); \quad P(\delta_{31} > 0.25\delta_{21}) \]

This is like

\[ H_0: \quad \delta_{31} \leq 0.75\delta_{21} \]

\[ H_1: \quad \delta_{31} > 0.75\delta_{21} \]

indicating that at least 75% of the treatment difference observed at the end of the Part II has been preserved at the end of delayed start period.

We will also examine Significant Treatment differences by estimating the posterior probabilities:

\[ P(\delta_{21} > 0); \quad P(\delta_{31} > 0); \quad P(\delta_{32} > 0); \quad P(\delta_{33} > 0) \]
Notation

- We observe $Y_{ij}^{(AP)}$, $Y_{ij}^{(PP)}$, and $Y_{ij}^{(APP)}$; for subject $i$ ($i = 1, ..., n$)

\[ Y_{ij} = \mu_{ij} + \varepsilon_{ij}; \quad \varepsilon_{ij} \sim N(0, \tau^2_j) \quad j = 0, 3, 6, 9, 12, 15, 18 \]
\[ \mu_{ij} = \theta + \alpha_i + \beta_{ij}M_j \]
\[ \beta_{ij} = \beta_j + f_{ij}; \quad f_{ij} \sim N(0, \Sigma) \]

- $\mu_{ij}$ is the average response of patient $i$ at month $j$
- $\alpha_i$ is the random intercept for patient $i$
- $\theta$ is the baseline response
- $\beta_j$ is the rate of change exhibited by patient $i$ at month $j$
- $\beta_{ij}$ is the aggregated average rate of change
- $\varepsilon_{ij}$ is the residual error for response $Y_{ij}$
- $\tau_j$ is the standard deviation of the error
- $f_{ij}$ is the residual error for the rate of change exhibited by patient $i$ at month $j$
- $\Sigma$ is the covariance matrix for residual errors
Notation

- Likelihood for the general model under a generic treatment regime

\[
L \propto \exp \left\{ - \frac{\sum (Y_{ij} - \mu_{ij})^2}{2\tau_j^2} \right\} \times \exp \left\{ - \frac{\sum_i (\beta_{i,.} - \beta_{.})'\Sigma^{-1}(\beta_{i,.} - \beta_{.})'}{2} \right\} \times \frac{1}{\left| \Sigma \right|^{\frac{n+8}{2}}} \exp \left\{ - \frac{\sum_j (\beta_j - \mu_{\beta} - \psi(\beta_{j-1} - \mu_{\beta}))^2}{2\sigma^2} \right\}
\]
Models of Interest

- Linear
- Random Intercept
- Random Intercept and Random Slope
- Autoregressive

Nonlinear Models
- Spline models with random intercept
- Spline models with random intercept and random slope
Model Evaluation

- Deviance Information Criterion (DIC)

\[
D(\mu, \tau) = \sum_{i,j} \frac{(Y_{ij} - \mu_{ij})^2}{\tau_j^2}, \quad D(\bar{\mu}, \bar{\tau}) = \sum_{i,j} \frac{(Y_{ij} - \bar{\mu}_{ij})^2}{\bar{\tau}_j^2}
\]

DIC is defined as the posterior average of:

\[
DIC^* = 2 \times D(\mu, \tau) - D(\bar{\mu}, \bar{\tau})
\]

- Bayesian p-value is based on comparing predictive posterior residual with their observed counterparts

Predicted Residuals \[ resid_{ij}^* = \frac{(Y_{ij}^* - \mu_{ij})}{\tau_j} \],

Observed Residuals \[ resid_{ij} = \frac{(Y_{ij} - \mu_{ij})}{\tau_j} \]

Bayesian p-value \[ P \left\{ \sum_{i,j} \frac{(Y_{ij}^* - \mu_{ij})^2}{\tau_j^2} > \sum_{i,j} \frac{(Y_{ij} - \mu_{ij})^2}{\tau_j^2} \right\} \]
Central parameters have the prior distributions

\[ \Sigma \sim IW(8, \frac{I}{\varepsilon}) \]
\[ \beta_j \sim N(0, \frac{I}{\varepsilon}) \]
\[ \tau_j^2 \sim \frac{\varepsilon}{\chi_1^2}; \quad \sigma^2 \sim \frac{\varepsilon}{\chi_1^2} \]
Posteriors will be computed for

$\theta$

$\alpha_i$

$\beta_{ij}$

$\beta_j$  aggregated rate of change for treatment groups

$\Sigma$

$\tau_j^2$
We assume that

\[ Y_{ij} = \mu_j + \varepsilon_{ij} ; \quad \varepsilon_{ij} \sim N(0, \tau_j^2) \]
\[ \mu_{ij} = \theta I(j = 0) + \beta_{j>0} M_{j>0} \]

- \( \theta \) is the means for subjects at month 0
- \( \beta_j \) is the rate of change for month \( j \)
- \( \varepsilon_{ij} \) is the residual error assumed to be normal with standard deviation \( \tau_j \)
- Priors: We assume standard normal indifference priors for \( \theta \) and \( \beta_j \), and standard chi-square indifference priors for \( \tau_j \)
Linear Model under generic treatment regime, Likelihood

\[ Y_{ij} = \mu_j + \varepsilon_{ij} \]
\[ \mu_{ij} = \theta I(j = 0) + \beta_j M_j \]

\[ L \propto \frac{1}{\prod_{j=1}^{7} \tau_j^n} \exp \left\{ -\sum_i \frac{(Y_{i0} - \theta)^2}{2\tau_0^2} - \sum_i \sum_{j>0} \frac{(Y_{ij} - \beta_j M_j)^2}{2\tau_j^2} \right\} \]
Linear Model under generic treatment regime, Posteriors

\[
\theta \sim N \left\{ \frac{\sum_{i} Y_{i0}}{n / \tau_0^2}, \sqrt{\frac{1}{n / \tau_0^2}} \right\}
\]

\[
\beta_j \sim N \left\{ \frac{M_j \sum_{i} Y_{ij}}{nM_j^2 / \tau_j^2}, \sqrt{\frac{1}{nM_j^2 / \tau_j^2}} \right\}
\]

\[
\tau_0^2 \sim \frac{\sum_{i} (Y_{i0} - \theta)^2}{\chi_n^2}
\]

\[
\tau_j^2 \sim \frac{\sum_{i} (Y_{ij} - \beta_j M_j)^2}{\chi_n^2}
\]
Linear Model under generic treatment regime, Model Check

- **DIC** = \(2 \times D(\theta, \beta, \tau) - D(\overline{\theta}, \overline{\beta}, \overline{\tau})\)

\[
D(\theta, \beta, \tau) = \sum_{ij} \frac{(Y_{ij} - \theta - \beta_jM_j)^2}{\tau_j^2}
\]

\[
D(\overline{\theta}, \overline{\beta}, \overline{\tau}) = \sum_{ij} \frac{(Y_{ij} - \overline{\theta} - \overline{\beta}_jM_j)^2}{\overline{\tau}_j^2}
\]

- Bayesian p-value

\[
P\left\{ \sum_{ij} \frac{(Y_{ij}^* - \theta - \beta_jM_j)^2}{\tau_j^2} > \sum_{ij} \frac{(Y_{ij} - \theta - \beta_jM_j)^2}{\tau_j^2} \right\}
\]
Random Intercept

- \( Y_{ij} = \mu_{ij} + \varepsilon_{ij} \)

\[ \mu_{ij} = \theta + \alpha_i + \beta_j M_j \]

\( \alpha_i \) is the random intercept for patient \( i \)

\( \beta_j \) is the rate of change per month

\( \varepsilon_{ij} \) is the residual assumed to be normal with mean 0 and standard deviation \( \tau_j \)

Here we assume standard normal indifference priors for \( \alpha_i \) and \( \beta_j \), and standard chi-square indifferece priors for \( \tau_j \)
Random Intercept and Random Slope

- \( Y_{ij} = \mu_{ij} + \epsilon_{ij} \)

\[ \mu_{ij} = \theta + \alpha_i + \beta_{ij}M_j \]

\[ \uparrow \quad \uparrow \]

Random slope prior is \( \beta_{ij} = \beta_j + e_{ij} \)

\[ e_{ij} \sim N(0, \Sigma) \] and standard indifference priors on \( \beta_j \) and \( \Sigma \)

- \( L \propto \frac{1}{\prod_n^{j=1} \tau_j} \exp \left\{ - \sum_i \frac{(Y_{i0} - \theta - \alpha_i)^2}{2\tau_0^2} - \sum_i \sum_{j>0} \frac{(Y_{ij} - \alpha_i - \beta_{ij}M_j)^2}{2\tau_j^2} \right\} \times \exp \left\{ -\frac{1}{2} \sum_i (\beta_i, \bullet - \beta_j)' \Sigma^{-1} (\beta_i, \bullet - \beta_j) \right\} \)
\[ Y_{ij} = \mu_{ij} + \varepsilon_{ij} \]
\[ \mu_{ij} = \theta + \alpha_i + \beta_{ij}M_j \]

Random slope prior is \( \beta_{ij} = \beta_j + \varepsilon_{ij} \)

\[ \varepsilon_{ij} \sim N(0, \Sigma) \]

Assume lower level correlation \( \psi \) and lower level mean \( \mu_\beta \)

\[
\beta_j = \begin{cases} 
\mu_\beta + \psi (\beta_{j-1} - \mu_\beta) + \varepsilon_j, & \text{if } j > 0 \\
\mu_\beta + \varepsilon_0, & \text{if } j = 0 
\end{cases}
\]
Autoregressive Model

\[
\begin{align*}
Y_{ij} &= \begin{cases} 
\mu_j + \rho(Y_{i,j-1} - \mu_{j-1}) + \varepsilon_{i,j}, & \text{if } j > 0 \\
\mu_0 + \varepsilon_{i,0}, & \text{if } j = 0 
\end{cases}
\end{align*}
\]

\[
\mu_j = \theta + \beta_j M_j
\]

The residual errors are assumed to be \( \varepsilon_{i,j} \sim \mathcal{N}(0, \tau_j^2) \)

Assume indifference priors for the hyperparameters \( \rho, \beta, \theta, \tau_j \).
Autoregressive Model

\[ \mu_j = \begin{cases} 
\mu_j + \rho(Y_{i,j-1} - \mu_{j-1}) + \varepsilon_{i,j}, & \text{if } j > 0 \\
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- \[ Y_{ij} = \begin{cases} 
\mu_j + \rho(Y_{i,j-1} - \mu_{j-1}) + \varepsilon_{i,j}, & \text{if } j > 0 \\
\mu_0 + \varepsilon_{i,0}, & \text{if } j = 0 
\end{cases} \]

\[ \mu_j = \theta + \beta_j M_j \]

Compute posteriors for all the parameters

\[ \rho \sim N_{-1,1} \left\{ \sqrt{\frac{\sum_{i,j=2:7} (Y_{i,j} - \mu_j)(Y_{i,j-1} - \mu_{j-1})/\tau_j^2}{\sum_{i,j=2:7} (Y_{i,j-1} - \mu_{j-1})/\tau_j^2}} \right\} \]
The spline model of order $q$ without random slopes or intercepts

$$Y_{ij} = \theta I(j = 0) + \sum_{h=1}^{q} \beta_{h} M_{j}^{h} + \sum_{g=1}^{q} \gamma_{g} (M_{j} - \nu_{g})_{+}^{q} + \epsilon_{ij}$$

- $\beta_{h}$ is slope for polynomial $M_{j}^{h}$
- $\gamma_{g}$ is slope for spline polynomial
- $\nu_{g}$ is the breakpoint (node)
- $\alpha_{i}$ and $\beta_{ih}$ can be included
Scenarios
Scenario – No Disease Modification
Table 2 WCGB Score: Mixed Model Repeated Measures (MMRM) ANOVA, Actual Score and Difference at Each Visit Including Month 18 between PPPP and APAP; Subjects with Treatment PPPP or APAP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PPPP Estimate(SE)</th>
<th>APAP Estimate(SE)</th>
<th>Difference (PPPP vs APAP) Estimate(SE)</th>
<th>95% CI</th>
<th>DF</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Repeated Measures Model</td>
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<td>Treatment</td>
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<td>Visit</td>
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<td>6, 148</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Treatment*Visit Interaction</td>
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<td>6, 143</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Model Estimates/Treatment</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>29.7 (1.25)</td>
<td>29.7 (1.25)</td>
<td>-0.0 (1.75)</td>
<td>(-8.49; 3.49)</td>
<td>148</td>
<td>1.000</td>
</tr>
<tr>
<td>Month 3</td>
<td>32.7 (1.39)</td>
<td>20.8 (1.39)</td>
<td>11.9 (1.97)</td>
<td>(8.03; 15.81)</td>
<td>148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 6</td>
<td>31.5 (1.80)</td>
<td>25.5 (1.80)</td>
<td>6.0 (1.64)</td>
<td>(2.36; 9.61)</td>
<td>148</td>
<td>0.001</td>
</tr>
<tr>
<td>Month 9</td>
<td>35.9 (1.25)</td>
<td>19.1 (1.25)</td>
<td>17.8 (1.75)</td>
<td>(14.32; 21.28)</td>
<td>148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 12</td>
<td>32.4 (1.25)</td>
<td>18.6 (1.26)</td>
<td>13.7 (1.79)</td>
<td>(10.17; 17.25)</td>
<td>148</td>
<td>&lt;0.001</td>
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<tr>
<td>Month 15</td>
<td>38.8 (1.25)</td>
<td>18.1 (1.26)</td>
<td>16.7 (1.78)</td>
<td>(12.17; 21.21)</td>
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<tr>
<td>Month 18</td>
<td>29.4 (1.16)</td>
<td>17.7 (1.16)</td>
<td>11.6 (1.64)</td>
<td>(6.82; 16.00)</td>
<td>148</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Note: DF stands for degrees of freedom. The estimate, standard error, 95 percent CI, and p-value are based on a repeated measures mixed effects ANOVA model with treatment and visit as fixed effect (categorical) factors; and treatment-by-visit interaction. The correlation of the repeated measures is modeled with an unstructured covariance structure. Use DREAMSCENARIOS dataset.
Table 3.2 MCOB Score: Mixed Model Repeated Measures (MMRM) ANOVA, Actual Score and Difference at Each Visit including Month 18 between PPPP and APPP; Subjects with Treatment PPPP or APPP

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<td>Model Estimates/Treatment Comparison (PPPP - APPP) at Each Visit</td>
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</tr>
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<td>0.001</td>
</tr>
<tr>
<td>Month 9</td>
<td>36.9 (1.25)</td>
<td>19.1 (1.25)</td>
<td>17.8 (1.76)</td>
<td>(14.32; 21.28)</td>
<td>148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 12</td>
<td>32.4 (1.28)</td>
<td>22.5 (1.28)</td>
<td>9.9 (1.61)</td>
<td>(6.50; 13.83)</td>
<td>148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 15</td>
<td>33.6 (1.29)</td>
<td>26.8 (1.29)</td>
<td>6.8 (1.63)</td>
<td>(4.36; 11.59)</td>
<td>148</td>
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<tr>
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<td>29.4 (1.19)</td>
<td>-0.0 (1.68)</td>
<td>(-3.32; 3.32)</td>
<td>148</td>
<td>1.000</td>
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</table>

Note: DF stands for degrees of freedom. The estimate, standard error, 95 percent CI, and p-value are based on a repeated measures mixed effects ANOVA model with treatment and visit as fixed effect (categorical) factors; and treatment-by-visit interaction. The correlation of the repeated measures is modeled with an unstructured covariance structure. Use DREAM/SCENERIO5 dataset.
### Scenario – No Disease Modification, Posterior Means

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Random Intercept</th>
<th>Random Intercept and Slope</th>
<th>Autoregressive</th>
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<td>BASELINE (PART III)</td>
<td>29.8</td>
<td>29.7</td>
<td>29.7</td>
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<td>(27.8-31.9)</td>
<td>(27.7-31.7)</td>
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<td>(30.4-35.0)</td>
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<td>(19.2-26.9)</td>
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<td>(23.4-27.7)</td>
<td>(29.4-33.8)</td>
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<td>(17.0-20.8)</td>
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<td>19.1</td>
<td>17.9</td>
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<td>19.1</td>
<td>17.9</td>
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<td>(30.3-34.5)</td>
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<td>(31.6-36.1)</td>
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<tr>
<td>MONTH 18 (PART III)</td>
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<td>29.4</td>
<td>29.5</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>(15.8-19.4)</td>
<td>(27.4-31.3)</td>
<td>(27.6-31.3)</td>
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**Scenario – No Disease Modification, Posterior Mean Diffs**

<table>
<thead>
<tr>
<th>Contrasts</th>
<th>Linear Model</th>
<th>Random Intercept</th>
<th>Random Intercept and Slope</th>
<th>Autoregressive</th>
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<td>DELTA21</td>
<td>-17.8 (-20.3, -15.3)</td>
<td>-8.8 (-13.7, -4.3)</td>
<td>-16.3 (-17.6, -14.7)</td>
<td>-17.4 (-25.0, -10.2)</td>
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<tr>
<td>DELTA31</td>
<td>-0.0 (-2.9, 2.6)</td>
<td>4.0 (-2.0, 10.2)</td>
<td>0.2 (-1.1, 2.1)</td>
<td>0.0 (-4.5, 4.3)</td>
</tr>
<tr>
<td>DELTA32</td>
<td>11.8 (9.3, 14.3)</td>
<td>9.7 (5.4, 13.7)</td>
<td>13.8 (12.1, 15.5)</td>
<td>11.5 (6.6, 16.5)</td>
</tr>
<tr>
<td>DELTA33</td>
<td>11.8 (9.0, 14.6)</td>
<td>13.7 (10.0, 17.9)</td>
<td>14.0 (13.1, 14.6)</td>
<td>11.5 (6.2, 16.5)</td>
</tr>
</tbody>
</table>

**Note:** Delta21: Treatment effect on disease progression; Delta31: Lead treatment effect; Delta32: Delayed-start treatment effect on disease progression; Delta33: Overall effect of treatment.
Scenario – No Disease Modification, AR(1) Posterior Means

![Graph showing mean with 90% credible interval MCCB score over months for different treatments.](image)
Scenario – No Disease Modification, 2 Nodes Posterior Means
Scenario – No Disease Modification, DIC

Means: 32.89 24.07 23.53
Summary

- Huge unmet medical need for disease modification drugs
- Existing clinical development and trial design approaches are not adequate
- Doubly-randomized matched control design with proposed analytical plans addresses many existing issues for demonstrating clinical evidence of disease modification
- Bayesian inference is a natural fit
- Strong preference for simpler designs to establish mediation biomarkers, especially for drugs with modest effects