Quantitative Approaches in Drug Development: A Disease Progression Meta-Analysis Model in Alzheimer’s Disease

Kaori Ito Ph.D.
Pfizer Inc. Global Pharmacometrics, USA

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Today’s Topic

1. Model-based drug development
   Concept and methods

2. Applications in Alzheimer’s disease
   Literature data model (study level)¹
   Individual data model (patient level)²
   Combined model³
   ....How it has been used in Pfizer?

3. CAMD activities: Critical Path (FDA)

1. Ito K et al. Alzheimer’s & Dementia 2010; 6: 39-53
2. Ito K et al. Alzheimer’s & Dementia, accepted March 22nd 2010
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Attrition in Clinical Drug Development

Success Rate from FIH to Registration (1991 – 2000)

Lack of Efficacy is the Predominant Root-Cause of Phase III Failures

<table>
<thead>
<tr>
<th>Driver</th>
<th>Description</th>
<th>Percent of overall failures (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy vs. placebo</strong></td>
<td>- Failure to demonstrate significant difference from placebo in treatment effects</td>
<td>50</td>
</tr>
<tr>
<td>Safety vs placebo</td>
<td>- Confirmation of early safety concerns</td>
<td>31</td>
</tr>
<tr>
<td>Safety vs placebo</td>
<td>- Unclassifiable</td>
<td>23</td>
</tr>
<tr>
<td>Lack of differentiation</td>
<td>- Efficacy</td>
<td>16</td>
</tr>
<tr>
<td>Safety</td>
<td>- Given similar safety profile, failure to demonstrate superior efficacy versus an active comparator</td>
<td>19</td>
</tr>
<tr>
<td>Safety</td>
<td>- Given similar efficacy, failure to demonstrate superior safety versus an active comparator</td>
<td>3</td>
</tr>
</tbody>
</table>

66% of failures from insufficient efficacy versus placebo or comparators

In Vivo 2006;24;49-54.
Models and Clinical Trial Simulations

Evaluate “what if” scenarios……
Run Multiple Replications of Trial

Drug/Disease Model

Trial Designs
- Doses/arms/N
- Duration/Sampling
- Freq and time
- Enrichment strategies

Range of Outcomes

Statstics
Effect of Dose and Number of Subjects on Power to Estimate Significant Effect of Drug vs Placebo

<table>
<thead>
<tr>
<th>N</th>
<th>1 mg</th>
<th>2 mg</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>4.5</td>
<td>6.5</td>
<td>18</td>
<td>48.5</td>
<td>73.5</td>
</tr>
<tr>
<td>40</td>
<td>13</td>
<td>29</td>
<td>76</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>50</td>
<td>27.5</td>
<td>52</td>
<td>85</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>60</td>
<td>40.5</td>
<td>62</td>
<td>90</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>70</td>
<td>55.5</td>
<td>71</td>
<td>94</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>
Predicted Difference Between New Drug and Marketed Compound

Response of New Drug Relative to Marketed Drug at the Recommended Dose

Probability mean response is 5% worse (i.e., inferior), within 5% (i.e., equivalent), or >5% (i.e., superior) relative to marketed drug

<table>
<thead>
<tr>
<th>New Drug (mg)</th>
<th>Inferior</th>
<th>Equal</th>
<th>Superior</th>
</tr>
</thead>
<tbody>
<tr>
<td>300.00</td>
<td>10.0%</td>
<td>89.9%</td>
<td>0.1%</td>
</tr>
<tr>
<td>450.00</td>
<td>0.0%</td>
<td>53.5%</td>
<td>46.5%</td>
</tr>
<tr>
<td>600.00</td>
<td>0.0%</td>
<td>7.2%</td>
<td>92.8%</td>
</tr>
<tr>
<td>900.00</td>
<td>0.0%</td>
<td>2.8%</td>
<td>97.3%</td>
</tr>
</tbody>
</table>

Helps team address critical clinical development questions: confidence in dose-response, probability of a particular response at a given dose, probability of superior response versus comparators.
Quantitative Decision Criteria

LRV: lower reference value (e.g. placebo)
TV: target value (e.g. minimum needed for clinical and commercial success)

Figure 3 Example of a decision rule based on the dual criteria. The criteria and decisions will vary depending on the target responses that are important for a particular compound and the phase of clinical development.

Lalonde RL et al., Clin Pharmacol Ther 2007;82:21-32
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   Combined model\(^3\)
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Disease Progression Model in Clinical Trial

\[ S(t) = S_0 + \alpha \cdot t + f_{pbo}(t) + f_{drug}(t) + \varepsilon \]

- \( S_0 \): baseline disease “state”
- \( S(t) \): expected “state” at a time “t”
- \( \alpha \): disease progression rate
- \( t \): time
- \( \varepsilon \): prediction variability
- \( f_{pbo}(t) \): placebo effect
- \( f_{drug}(t) \): symptomatic drug effects

Note: if the drug is disease modifying (DM) type, the effect is on the slope (\( \alpha \)):

\[ S(t) = S_0 + \alpha \cdot f_{DM}(t) \cdot t + f_{pbo}(t) + \varepsilon \]

..or combination with symptomatic effect
Donepezil Phase III (302 study)
24-week DB, 6-week washout, followed by Open study

“Off-set” effect
Literature meta-analysis model development

- Develop a model to describe disease progression to understand the disease
  - AChE inhibitors (donepezil, rivastigmine, galantamine) are “symptomatic drug” to treat mild to moderate AD patients.
  - Endpoint: ADAS-cog (change from baseline)
- Leverage all available literature information
- Apply to drug development/decision making
What is ADAS-cog?

Alzheimer’s Disease Assessment Scale-Cognitive

- The ADAS-cog is a 0 to 70 point scale designed to measure, with the use of questionnaires, the progression and the severity of cognitive decline as seen in AD.

- The 11 cognitive items include spoken language ability, comprehension of spoken language, recall of test instructions, word-finding difficulty in spontaneous speech, following commands, naming objects and fingers, constructional praxis, ideational praxis, orientation, word-recall task and word-recognition task.

- The ADAS-cog is used as a primary endpoint in most AD clinical trials and the standard scale for the monitoring of cognitive function in AD patients.
Literature search/database building strategy

Step 1 – Literature search criteria
- Sources: all available clinical trials in NICE, MEDLINE, EMBASE, SBAs at FDA's CDER website (years 1990–2008)
- Key search terms: acetylcholinesterase inhibitors (AChEIs), endpoints (ADAS-cog, MMSE, CIBIC, etc.) and clinical trials definitions (double-blind, randomized, etc.)

Step 2 – Literature acceptance criteria
- Literature with ADAS-cog reported
- If placebo group data are available from non-AChEI study (i.e., vitamin E study), keep only placebo data from that literature
- Deleted any duplications
- Deleted exploratory studies (i.e., open study with patients N <= 20)

Step 3 – Further refinement
One Study was removed from the analysis: only week 52 result (change from baseline) was reported, baseline ADAS-cog was not reported, and the drop-out rate was high (from 173 at baseline to 95 at week 52), open rivastigmine study

LIKE: Literature Information Knowledge Explorer (Pfizer literature database)
Longitudinal data obtained

ADAS-cog was reported in most literature as “change from baseline”, not as raw data.
Plot point size is proportional to the size of the treatment arm and smooth lines in the plot are loess.
Baseline MMSE, ADAS-cog, AGE compared with publication year

Plot point size is proportional to size of treatment arm.
Linear regression for top-left panel, others are loess lines.

ADASCog = 60.9 - 1.85 * MMSE
(R = 0.86, p = 0.0000)
Modeling Plan

• Disease progression model

\[ S(t) = S_0 + \alpha \cdot t + f_{pbo}(t) + f_{drug}(t) + \frac{\epsilon}{\sqrt{N}} \]

• Placebo effects \((PD_{pbo})\)

\[ PD_{pbo}(t) = \beta_p \cdot \left( e^{-Ke_p \cdot t} - e^{-Keq_p \cdot t} \right) \]

• Drug effects \((PD_{drug})\)
  – Linear, Emax, or sigmoid Emax as function of TIME

\[ PD_{drug}(t) = \text{Slope} \cdot t, \quad PD_{drug}(t) = \frac{E_\Delta \cdot t}{ET_{50} + t} \]

• Covariates
  – Baseline ADAS-cog, Baseline MMSE, AGE
  – Study design (double-blind vs. open study)
  – LOCF vs OC
  – Publication year
Parameter Estimates

\[ S(t) = S_0 + \alpha \cdot t \cdot \left( \frac{ADAS_{BSL}}{25} \right)^{\theta_{BSL}} + PD_{pbo} + PD_{drug} + \frac{\varepsilon}{\sqrt{N}} \]

<table>
<thead>
<tr>
<th>Parameter Estimate (SE)</th>
<th>Estimate (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Progression</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline (points) 0 fix</td>
<td></td>
</tr>
<tr>
<td>Slope (α) (points/year) 5.49 (0.299)</td>
<td></td>
</tr>
<tr>
<td>Baseline ADAS-cog effect on slope 0.669 (0.357)</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo Effect</strong></td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>-2.1 (0.946)</td>
</tr>
<tr>
<td>Kel (week⁻¹)</td>
<td>0.0306 (0.00956)</td>
</tr>
<tr>
<td>Keq (week⁻¹)</td>
<td>0.127 (0.0551)</td>
</tr>
<tr>
<td><strong>Drug Effect</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Donepezil</strong></td>
<td></td>
</tr>
<tr>
<td>ΔEmax (points)</td>
<td>-2.26 (0.296)</td>
</tr>
<tr>
<td>ET₅₀ (week)</td>
<td>1.42 (1.21)</td>
</tr>
<tr>
<td>Dose effect: (dose/5 mg)⁰</td>
<td>0.231 (0.0948)</td>
</tr>
<tr>
<td><strong>Galantamine</strong></td>
<td></td>
</tr>
<tr>
<td>ΔEmax (points)</td>
<td>-4.88 (0.498)</td>
</tr>
<tr>
<td>ET₅₀ (week)</td>
<td>13.1 (3.8)</td>
</tr>
<tr>
<td><strong>Rivastigmine</strong></td>
<td></td>
</tr>
<tr>
<td>ΔEmax (points)</td>
<td>-1.6 (0.566)</td>
</tr>
<tr>
<td>ET₅₀ (week)</td>
<td>9.37 (9.88)</td>
</tr>
<tr>
<td>Dose effect: (dose/6 mg)⁰</td>
<td>1.17 (0.58)</td>
</tr>
<tr>
<td><strong>Random effect</strong></td>
<td></td>
</tr>
<tr>
<td>ETA (η₁) on intercept 0.669 (0.282)</td>
<td></td>
</tr>
<tr>
<td>ETA (η₂) on slope 7.51E-04 (2.64E-04)</td>
<td></td>
</tr>
<tr>
<td>ETA (η₃) on ET₅₀ 1.33 (0.735)</td>
<td></td>
</tr>
<tr>
<td><strong>Standard Deviation (SD)</strong></td>
<td>8.51 (0.823)</td>
</tr>
</tbody>
</table>

α = rate of change of ADAS-cog
β = coefficient of placebo effect
ET₅₀ = half time to reach maximum drug effect

<table>
<thead>
<tr>
<th>Baseline ADAS-cog</th>
<th>Baseline MMSE*</th>
<th>Slope estimate (point/year)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>&gt;27</td>
<td>2.97</td>
<td>2.39–3.56</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>3.90</td>
<td>3.31–4.49</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>4.73</td>
<td>4.14–5.31</td>
</tr>
<tr>
<td>25</td>
<td>19</td>
<td>5.49</td>
<td>4.90–6.08</td>
</tr>
<tr>
<td>30</td>
<td>17</td>
<td>6.20</td>
<td>5.62–6.79</td>
</tr>
<tr>
<td>35</td>
<td>14</td>
<td>6.88</td>
<td>6.29–7.46</td>
</tr>
<tr>
<td>40</td>
<td>&lt;12</td>
<td>7.52</td>
<td>6.93–8.10</td>
</tr>
</tbody>
</table>

* Baseline MMSE was approximately calculated based on the linear regression relationship with baseline ADAS-cog

c.f. disease progression estimate previously reported: 6.17/ year (Holford et al, 1992)
3.38/ 26 weeks (Doraiswamy et al, 1997)
Model Evaluation (n=1000 simulation)

**placebo**

![Graph showing ADAS-cog scores over time for placebo treatment.]

**donepezil**

![Graph showing ADAS-cog scores over time for donepezil treatment.]

**galantamine**

![Graph showing ADAS-cog scores over time for galantamine treatment.]

**rivastigmine**

![Graph showing ADAS-cog scores over time for rivastigmine treatment.]

dotted line: 90% predicted interval
Summary

Literature model-based meta-analysis

- A disease progression model was developed to describe ADAS-cog changes with AD patients, based on data obtained from the literature (1990–2008)
- AChEIs were modeled as symptomatic effect (not disease modifying)
- An $E_{\text{max}}$ model was used to describe the data
- Mean slope estimate (disease progression) was **5.5 points/year**
- Baseline ADAS-cog on slope was selected as a covariate in the final model
  - Slope changes as disease progresses
How it has been used?

- Evaluate due diligence compound
  - Dimebon
  - TauRx
  - Flurizan
  - Neurokos

- Benchmark outcomes for new clinical studies
  - Dimebon (Phase 3)
  - SAM-531

- Simulate the probability of success of clinical trial
Due Diligence compound (1)
Due Diligence compound (2)

The size of points represent clinical-trial sample size (each open circle is drawn in proportion to number of patients in trial arm)
Probability of Success?

What is the magnitude of change from placebo at 6, 12, 26 wks?

What is the probability to observe the effect (e.g. 50% of maximum* effect) in early time?

* Maximum effect = effect at 26 weeks

Note: Figure includes both open and double blind, 5 and 10 mg studies
Approach

- **Using parameter estimates from the meta-data model**
  - Model-based approach can predict any time point, with different assumption for drug potency/mechanism
  - The parameters were estimated by fitting all available data (double-blind, open, all AChE-inhibitors, placebo group data from Vitamin E, COX2-inhibitor studies etc)
  - Between study variability and within study variability

- **Calculate probability distribution from the observed data**
  - (using double blind, placebo controlled donepezil studies)
  - direct way to answer the question
  - may be more conservative (no question for model 😊)
  - Can not calculate the probability where little/no data available (e.g. 52 weeks)
Probability of Success?

Let’s look at double blind, placebo controlled study with donepezil (10mg) at 6, 12, 26 wks

Calculate “change from placebo” in each study
Concept of probability to observe “effects” (change from placebo)

Mean change from placebo (donepezil 10 mg)

Pr (>x) = “area under the curve of >x”

Let’s assume 26-wk effect as “maximum effect” (100%)

Note: size of points is proportional to square root of N of patients in the study
Probability to observe “effects” at 6 and 12 weeks (change from placebo)

**Probability to observe 50% effect:**
(-1.45 change from placebo)
6 wks: 63%  12 wks: 97%

**Probability to observe 80% effect:**
(-2.31 change from placebo)
6 wks: 37%  12 wks: 70%

**Probability to observe 90% effect:**
(-2.6 change from placebo)
6 wks: 28%  12 wks: 53%

Note: size of points is proportional to square root of N of patients in the study
### Literature database/Modeling Approach

#### Indications Currently Available in the Database

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions/Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain/Inflammation</strong></td>
<td>OA-pain / opiates / COX II Inhibitors, NSAIDS, Neuropathic Pain, Fibromyalgia, Rheumatic Arthritis, Anemia Syndrome, Kidney Transplant Rejection</td>
</tr>
<tr>
<td><strong>Neuroscience</strong></td>
<td>Alzheimer’s, Bipolar, Attention Deficit Hyperactivity Disorder, Generalized Anxiety Disorder, Schizophrenia, Depression, Epilepsy, Insomnia, Narcolepsy, Post Traumatic Stress Disorder, Restless Legs Syndrome</td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
<td>Glaucoma, Diabetic Macular Edema, Dry Eye Syndrome, Age Related Macular Degeneration (wet and dry)</td>
</tr>
<tr>
<td><strong>CVMED</strong></td>
<td>Diabetes Mellitus type 2, Obesity, Acute Coronary Syndrome, Myocardial Infarction, Osteoporosis, Frailty, Thrombosis VTE, Ventricular Tachycardia</td>
</tr>
<tr>
<td><strong>Oncology</strong></td>
<td>Breast Carcinoma, Gastric Cancer, Non Small Cell Lung Cancer, Pancreatic Cancer (in the process), Chronic Myelogenous Leukemia (in the process)</td>
</tr>
<tr>
<td><strong>Sexual Health/Urology</strong></td>
<td>Benign Prostatic Hyperplasia, Cystitis Interstitial, Endometriosis, Prostatitis, Urinary Incontinence</td>
</tr>
<tr>
<td><strong>Allergy and Respiratory</strong></td>
<td>Asthma, Chronic Obstructive Pulmonary Disease, Pulmonary Arterial Hypertension</td>
</tr>
<tr>
<td><strong>Infectious Diseases</strong></td>
<td>HIV infection, Hepatitis C Virus</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Hepatic Fibrosis</td>
</tr>
</tbody>
</table>
Pros and Cons of Study Level Analysis

Pros:
- **Meta-analysis enhances drug development**
  - Applies quantitative decision-making for critical questions early in development
  - Provides integrated approach for comparing treatment effect of new compound relative to marketed compounds
  - Useful for dose selection or product profiling

Cons:
- **Limitation of the data**
  - Data may not available with enough information (i.e. change from baseline is reported, but not actual value)
  - Difficult to get the individual response predictions
  - Low power to detect covariate relationship due to small between-study variability in covariate values (means), and correlations among covariates may not be found due to the use of summary statistics
Other models…

- Individual data model (patient level)
- Combined model
Disease Progression Model for ADNI*

Base structure:

\[ S(t) = S_0 + \alpha \cdot t + \varepsilon \]

- \( S(t) \): expected state at a given point in time
- \( S_0 \): baseline disease state
- \( \alpha \): disease progression rate
- \( \varepsilon \): prediction variability

- ADNI is a no intervention study to evaluate natural disease progression in normal, MCI, and AD patients
- Individual data make it able to evaluate covariate effect on disease progression
  - Age, ApoE4, gender, education year, family history etc.

*Alzheimer’s Disease Neuroimaging Initiative (ADNI): [http://www.ioni.ucla.edu/ADNI](http://www.ioni.ucla.edu/ADNI)
### Baseline characteristics of patients in the ADNI database (as of Dec 2009)

<table>
<thead>
<tr>
<th></th>
<th>AD N=186*</th>
<th>MCI N=402</th>
<th>NL N=229</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>75.3 ± 7.6</td>
<td>74.8 ± 7.4</td>
<td>75.9 ± 5.0</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>47.3</td>
<td>35.6</td>
<td>48.0</td>
</tr>
<tr>
<td><strong>Baseline ADAS-cog</strong></td>
<td>18.7 ± 6.3</td>
<td>11.5 ± 4.4</td>
<td>6.2 ± 2.9</td>
</tr>
<tr>
<td><strong>Baseline MMSE</strong></td>
<td>23.3 ± 2.0</td>
<td>27.0 ± 1.8</td>
<td>29.1 ± 1.0</td>
</tr>
<tr>
<td><strong>Education (yr)</strong></td>
<td>14.7 ± 3.2</td>
<td>15.7 ± 3.0</td>
<td>16.0 ± 2.9</td>
</tr>
<tr>
<td><strong>ApoE4 status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε4 non-carrier (%)</td>
<td>63 (33.9)</td>
<td>187 (46.5)</td>
<td>186 (73.4)</td>
</tr>
<tr>
<td>ε4 carrier (%)</td>
<td>123 (66.1)</td>
<td>215 (53.5)</td>
<td>61 (26.6)</td>
</tr>
</tbody>
</table>

*; mild=171, moderate=13, severe=1, NA=1
Longitudinal data from ADNI

ADAS-cog Score vs Time (months)

- AD
- MCI
- NL

Visit values (month) were slightly jittered to aid visual interpretation in the figure.
Lines: loess
There is an approximate linear relationship between ADAS-cog and MMSE (10–30)

ADNI data

Baseline ADAS-cog Score vs. Baseline MMSE

\[ \text{ADAS-cog} = 56.4 - 1.86 \times \text{MMSE} \]

R-squared: 0.4815, p<0.0001

Patient population in ADNI

Parameter Estimates

\[ S(t) = \left( Int_p - \theta_3 \cdot \frac{MMSE_{BSL}}{25} + \eta_1 \right) + \left( \alpha \cdot f(ADAS_{BSL}, \theta_5) \cdot \left( \frac{AGE}{75} \right)^{\theta_6} \cdot \theta_7^{APOE4} \cdot \theta_8^{SEX} + \eta_2 \right) \cdot t + \varepsilon \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>RSE (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Progression (α) (point/yr)</td>
<td>4.83</td>
<td>11.9</td>
<td>[3.63, 6.00]</td>
</tr>
<tr>
<td>ADAS_{t=0}-Intercept</td>
<td>56.4</td>
<td>2.98</td>
<td>[53.4, 59.9]</td>
</tr>
<tr>
<td>ADAS_{t=0}-Slope</td>
<td>-1.68</td>
<td>3.58</td>
<td>[-1.80, -1.58]</td>
</tr>
<tr>
<td><strong>Covariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline ADAS-cog</td>
<td>3.45</td>
<td>9.57</td>
<td>[2.82, 4.07]</td>
</tr>
<tr>
<td>Age</td>
<td>-1.80</td>
<td>35.2</td>
<td>[-3.24, -0.593]</td>
</tr>
<tr>
<td>ApoE4 effect (MCI) ††</td>
<td>1.21</td>
<td>21.9</td>
<td>[0.823, 2.24]</td>
</tr>
<tr>
<td>ApoE4 effect (AD) † †</td>
<td>1.22</td>
<td>23.0</td>
<td>[0.775, 2.03]</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>0.893</td>
<td>13.2</td>
<td>[0.684, 1.11]</td>
</tr>
<tr>
<td><strong>Random Effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sqrt of ( \eta_1 ) on ADAS_{t=0}</td>
<td>3.78</td>
<td>10.0</td>
<td>[3.42, 4.16]</td>
</tr>
<tr>
<td>sqrt of ( \eta_2 ) on ( \alpha ) (point/yr)</td>
<td>2.47</td>
<td>18.4</td>
<td>[2.04, 2.90]</td>
</tr>
<tr>
<td>covariance of random effect</td>
<td>-0.099</td>
<td>58.7</td>
<td>[-0.20, 0.0056]</td>
</tr>
<tr>
<td><strong>Residual Error</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Deviation (SD)</td>
<td>2.83</td>
<td>2.33</td>
<td>[2.72, 2.96]</td>
</tr>
</tbody>
</table>

*95% CI are obtained from non-parametric bootstrap (n=500)
††: estimated within the patient population
‡ : not estimated (covariates are not included in the Base Model)
Random Effect (Inter Individual Variability) on Slope (Base Model vs. Final Model)

Base Model

Final Model
### Slope Estimates

“the more severe the cognitive impairment, the faster the deterioration”

<table>
<thead>
<tr>
<th>Baseline ADAS\textsubscript{cog}</th>
<th>Baseline MMSE*</th>
<th>Age</th>
<th>Slope Estimate [95% CI] (point/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>30</td>
<td>75</td>
<td>0.10 [−1.02, 1.22]</td>
</tr>
<tr>
<td>10</td>
<td>&gt; 27</td>
<td>75</td>
<td>0.83 [−0.29, 1.95]</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>75</td>
<td>2.49 [1.36, 3.61]</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>75</td>
<td>4.83 [3.71, 5.95]</td>
</tr>
<tr>
<td>25</td>
<td>19</td>
<td>75</td>
<td>7.25 [6.13, 8.37]</td>
</tr>
<tr>
<td>30</td>
<td>16</td>
<td>75</td>
<td>9.06 [7.94, 10.2]</td>
</tr>
<tr>
<td>35</td>
<td>13</td>
<td>75</td>
<td>9.73 [8.60, 10.9]</td>
</tr>
<tr>
<td>40</td>
<td>&lt; 10</td>
<td>75</td>
<td>9.06 [7.94, 10.2]</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>65</td>
<td>6.25 [5.13, 7.37]</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>70</td>
<td>5.47 [4.35, 6.59]</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>75</td>
<td>4.83 [3.71, 5.95]</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>80</td>
<td>4.30 [3.18, 5.42]</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>85</td>
<td>3.86 [2.73, 4.98]</td>
</tr>
</tbody>
</table>

*: Baseline MMSE was approximately calculated based on the linear regression relationship with baseline ADAS-cog

Note: modified inverse-U function for baseline ADAS-cog (covariate) was used

\[
f(ADAS_{BSL}, \theta_5) = \left( \frac{ADAS_{BSL}}{20} \cdot \frac{70 - ADAS_{BSL}}{50} \right)^{\theta_5}
\]
Visual Predictive Check – 100 simulations from the final model

Shaded area: 90% Prediction Intervals
Dashed lines: 95% Prediction Intervals
Summary
ADNI model-based patient-level analysis

• Baseline disease severity is most influential covariate
• Age, ApoE4 status and gender are also important potential covariates
• There is an approximate 5.5-point change in ADAS-cog per year for mild to moderate AD patients*
• Results for yearly disease progression are consistent with those of the model-based literature meta-analysis and previous studies1–4

* Dispositions of gender and ApoE4 are adjusted with ADNI AD patients

Combined Model

• Fusion model (using WinBUGS)\(^3\)
  – Error structure that allows simultaneous modeling of summary-level data and patient-level data
  – Statistically sound “weighting” of residuals and random effects based on sampling theory
  – Accurately predicts observed correlations between
    • Time points – important in simulating adaptive trials, and
    • Changes in marginal variance over time – important in simulating any clinical trial

• Resulting model is suitable for fitting/simulating either individual patient data or summary statistics

Clinical Trial Simulation

What if PoC (Proof of Concept) study would be…..

– parallel or cross over study?
– How long? 6 weeks or 12 weeks?
– Disease modifying effect?
– target patents….mild AD? Moderate AD?
– How many dose/patient?
…etc.
Simulated X-Over Trial with Drug 1

Sequence 1: Treatment then Placebo
Sequence 2: Placebo then Treatment
Hypothetical Continuous Placebo

Simulated X-Over Trial with Drug 2

Sequence 1: Treatment then Placebo
Sequence 2: Placebo then Treatment
Hypothetical Continuous Placebo

* Since these graphics are only meant to address the issue of bias, extremely large trials were simulated (100000 patients / group); by contrast, operating characteristics described on other slides were based on simulated trials with realistic sample sizes (30 patients / group).
Today’s Topic

1. Model-based drug development
   Concept and methods

2. Applications in Alzheimer’s disease
   Literature data model (study level)¹
   Individual data model (patient level)²
   Combined model³

   How it has been used in Pfizer?

3. CAMD activities: Critical Path (FDA)

1. Ito K et al. Alzheimer’s & Dementia 2010; 6: 39-53
2. Ito K et al. Alzheimer’s & Dementia, accepted March 22\textsuperscript{nd} 2010
March 2004

- Facilitate infrastructure and “toolkit” development

- Encourage collaborative efforts among government, academia, industry, and patient groups

- Develop relevant standards (regulatory and data)

- Build support for academic science bases in relevant disciplines

Create opportunities to share existing knowledge and databases
CAMD (Coalition Against Major Diseases)

Sharing pre-competitive information in Alzheimer’s Disease (AD) and Parkinson’s Disease (PD).

Currently CAMD has 12 member companies, 6 patient groups and 1 research foundation

http://www.c-path.org
http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm
Purpose

To develop a quantitative model of the progression in AD to test and optimize operating characteristics of trial designs for AD

• (via simulations based on the model), but NOT to replace clinical trial execution.

To submit the results of the analyses outlined in the research plan for review and qualification for potential use of these trial designs in AD drug development (Context of use)
• CAMD member companies provide patient-level control arm data from legacy clinical trials in AD (total n≈4000 patients)
• Development of CDISC standards to combine such legacy data and to collect prospective data in AD
• Additional information from other databases will be used for M&S purposes (ADNI was the foundation for the current disease progression model)
• Literature summary data will be incorporated when patient-level data is unavailable
• Cross-evaluation by member companies
• The model will evolve in future iterations with new data
Conclusions and Key Messages

• Most drugs fail in clinical drug development and they fail most often for lack of efficacy
• We need to use all available data to make informed decisions
• Drug and disease models help us turn data into knowledge and provide a quantitative basis for drug development and regulatory decision-making
• Model-based drug development is a key opportunity to help address some of the current drug development challenges, as described in the US FDA Critical Path document
Acknowledgement

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• Bill Billing
• Richard Anziano

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• Bill Gillespie (Metrum)