Application of Placebo Model in Drug Development—A Regulatory Perspective

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Disclaimer: My remarks today are my own personal views and do not represent those of the FDA
Outline

• Overview
• Case studies
  – Alzheimer’s Disease (AD)
  – Attention Deficit Hyperactivity Disorder (ADHD)
• Summary
Overview

• Many therapeutic areas still rely on placebo arm as the comparator
• Placebo effect exists in almost every therapeutic area
• Many factors contribute to the placebo effect
• Different placebo response patterns could happen under the same trial design
• In 2011, German Medical Association advised physicians to give out more placebos
  – Dr. Peter Scriba, chairman of the German Medical Association's advisory board, said that "placebos could help patients with mild anxiety, depression, chronic inflammatory problems, pain and asthma."

http://archive.boston.com/yourtown/cambridge/articles/2011/03/31/german_doctors_advised_to_give_out_more_placebos_1301580340/
Placebo Effect for Antidepressants

Placebo Response in Randomized Controlled Trials of Antidepressants for Pediatric Major Depressive Disorder, Jeffrey A. Bridge, et al. *Am J Psychiatry* 166:1, January 2009
Different Placebo Response Patterns

- QTcF Change from Baseline (msec)
- Change from Baseline in QTc (msec)

Time (hr):
- Period 1
- Period 2
- Period 3
- Period 4

Days:
- Day 1
- Day 7
Alzheimer’s Disease (AD)

• Currently available AD treatments only relieve symptoms
• New compounds targeted to prevent neuro-damages (i.e., disease-modifying) are under investigation
• More sophisticated clinical trials and alternative endpoints are needed to evaluate the disease-modification effect
• Quantifying the natural disease progression is critical for trial design
Amyloid Cascade Hypothesis
Database

• **Clinical Trials**
  – Patients: mild to moderate AD
  – Primary Endpoint: ADAS-cog
  – Duration: > 3 month
  – Observations/Subject: >2

• **Data**
  – Number of Trials: 10 (2 trials has treatment duration > 1 year).
  – Observations: 2479 patients with 6737 ADAS-cog score.
  – Baseline: median ADAS₀ = 24

*Only Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores observed from Week 10 and above from placebo group were included for AD modeling.*
Non-Linear Disease Progression Under Placebo

Scheduled Time [Week]

ADAS Score

LOW  M-LOW  M-HIGH  HIGH

Median  5-95th percentile

Drop-Out Model

Joint Efforts

• Coalition Against Major Diseases (CAMD)
  – Develop new tools (biomarkers and disease progression models) and methods that can be applied during the development of new treatments for neurodegenerative diseases

• Partners:
  Government:
  U.S. Food and Drug Administration
  European Medical Agency (EMA)
  Engelberg Center for Health Care Reform at the Brookings Institution
  National Institute of Neurological Disorders and Stroke (NINDS)
  National Institute on Aging (NIA)

  Industry:
  Abbott Laboratories
  AstraZeneca Pharmaceuticals LP
  Bristol-Myers Squibb Company
  Eli Lilly and Company
  F. Hoffmann-La Roche Ltd.
  Forest Research Institute
  Genetech, Inc.
  GlaxoSmithKline
  Johnson & Johnson, LLC
  Novartis Pharmaceuticals Corporation
  Pfizer, Inc.
  Sanofi-aventis U.S., Inc.

  Other:
  Alliance for Aging Research, Alzheimer’s Association
  Alzheimer’s Foundation of America, CHDI Foundation, Inc.
  National Health Council (NHC), Parkinson’s Action Network
  Parkinson’s Disease Foundation

http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm231134.htm
Other Disease Models for AD

1. Ito, et al, Alzheimer’s & Dementia, 2010

Data for 2 and 3:
https://www.loni.ucla.edu/ADNI
Fit-for-Purpose Model Qualification

• First drug development tool (DDT) submitted for qualification
  – AD trial simulation Tool
• A drug-disease-trial model that describes disease progression, placebo effect, drug effects, and dropout rates
• Data: literature, clinical trials, ADNI
• Multiple collaborators
• Multiple rounds of interactions between CAMD and FDA
• Comprehensive review of the submission by an interdisciplinary team
AD Trial Simulation Tool

• “Regulatory agencies in the U.S. and Europe have endorsed a quantitative simulation tool that allows researchers to model clinical trials in mild to moderate Alzheimer’s disease”

• “The Food and Drug Administration (FDA) declared the simulator a “fit-for-purpose” drug development tool on June 12, and the European Medicines Agency (EMA) qualified it for use on July 1”

• “The FDA encourages these kinds of pre-competitive collaboration among multiple companies to build a shared tool,” said Yaning Wang at the FDA, who worked on the project”

http://www.alzforum.org/new/detail.asp?id=3542
Guanfacine

• Intuniv™ (extended-release guanfacine, SPD503), approved for QD administration for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents age 6–17 years old.

• Initially approved dose in 2009: 1 to 4 mg

• Subgroup analyses suggested a lack of efficacy for adolescents (13-17)

• PMR study for adolescents (13-17)
Drug Concentrations Are Lower for Adolescents
Placebo Effects Are Larger for Adolescents

% Change From Baseline

Visit

GUAN 301 | GUAN 304

LYAC | LYAT

12<Age
6 < Age <= 12

12
6
0
-20
-40
0
1
2
3
4
5
6
2
4
6
8
2
3
4
5
6
4
6
8
10
12

Visit
Clinical Trial Simulation

Prior information (data from 9 trials)

Pediatrics (6-17)
- 5 trials - placebo and active SPD503
- 4 trials - placebo arms from different programs

Exposure-response model

Placebo model

Dropout model

Simulate experimental design

- 312 Protocol

Probability of Success 97%

<table>
<thead>
<tr>
<th>STUDY</th>
<th>301</th>
<th>304</th>
<th>312</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td>6 – 17</td>
<td>6 – 17</td>
<td>13 – 17</td>
</tr>
<tr>
<td># subjects</td>
<td>345 (~ 86 per group)</td>
<td>324 (~65 per group)</td>
<td>280 (140 per group)</td>
</tr>
<tr>
<td>Titration</td>
<td>Forced</td>
<td>Forced</td>
<td>Flexible</td>
</tr>
<tr>
<td>Target Doses</td>
<td>Placebo, 2, 3 or 4 mg/day</td>
<td>Placebo, 1, 2, 3, or 4 mg/day</td>
<td>Placebo, Based on weight, maximum 4-7 mg/day</td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>8</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Titration</td>
<td>5</td>
<td>3</td>
<td>7 (optimization)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0</td>
<td>3</td>
<td>6</td>
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<tr>
<td>Tapering</td>
<td>3</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Notes:</td>
<td></td>
<td></td>
<td>Min ADHD-RS IV of 32 at baseline</td>
</tr>
</tbody>
</table>
### Successful Study 312

Table 1: Summary of MMRM Analysis of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Week 13 (FAS) - Study SPD503-312

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=155)</th>
<th>SPD503 (N=157)</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>155</td>
<td>157</td>
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<tr>
<td>Mean (SD)</td>
<td>40.0 (6.11)</td>
<td>39.9 (5.57)</td>
</tr>
<tr>
<td><strong>Visit 13</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>106</td>
<td>109</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.3 (13.35)</td>
<td>14.1 (9.38)</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-19.5 (12.63)</td>
<td>-25.7 (10.09)</td>
</tr>
<tr>
<td><strong>Comparison to placebo</strong></td>
<td></td>
<td></td>
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<tr>
<td>LS mean</td>
<td>-18.527</td>
<td>-24.552</td>
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<tr>
<td>Difference in LS means</td>
<td>NA</td>
<td>-6.026</td>
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<tr>
<td>(95% CI)</td>
<td>NA</td>
<td>-8.865, -3.187</td>
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<tr>
<td>Effect Size</td>
<td>NA</td>
<td>0.52</td>
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<tr>
<td>p-value</td>
<td>NA</td>
<td>&lt;0.001</td>
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Summary

• Placebo effect is common in clinical trials
• To improve the chance of success for a clinical trial:
  – Understand the reasons for placebo effect
  – Quantify placebo effect
  – Conduct clinical trial simulation
Acknowledgements

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