FDA Webinar

*Early Alzheimer’s Disease Draft Guidance*

March 28, 2013

Nicholas A. Kozauer, MD
Acting Clinical Team Lead
Division of Neurology Products (DNP)
Center for Drug Evaluation and Research (CDER)
Outline

• Background
• Diagnostic Criteria
• Clinical Endpoints
• Biomarkers/Disease Modification
• Summary
Guidance for Industry
Alzheimer’s Disease:
Developing Drugs for the
Treatment of Early Stage
Disease

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Comments and suggestions regarding this draft document should be submitted within 60 days of
publication in the Federal Register of the notice announcing the availability of the draft
guidance. Submit electronic comments to http://www.regulations.gov. Submit written
comments to the Division of Dockets Management (HFA-305), Food and Drug Administration,
5650 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with
the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Nicholas Kozauer at 301-796-2250.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2013
Clinical/Medical

• Released – February 7th

• Comments until – April 9th

www.Regulations.gov
AD Progression Model

*Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade*

Aβ is identified by CSF Aβ42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.
AD Progression Model

- AD Dementia trials disappointing
- Move to Early AD trials
- Novel regulatory framework required

Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade
Aβ is identified by CSF Aβ42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.
**Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade**

Aβ is identified by CSF Aβ_{42} or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.
AD Progression Model

Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade
Aβ is identified by CSF Aβ42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.
AD Progression Model

**Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade**
Aβ is identified by CSF Aβ₄₀ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.
Goals

• Provide a framework for how drugs might be studied in Early AD trials

• Focus for continued discussion
Early AD Diagnosis

• Criteria under development:
  – National Institute on Aging – Alzheimer’s Association (NIA-AA)
  – International Working Group for New Research Criteria for the Diagnosis of AD

• Combine clinical/biomarker findings
  – Amyloid – PET
  – CSF levels of amyloid and/or tau
  – Brain volume (vMRI)
Early AD Diagnosis

• Guidance position:
  – Support trial enrichment
  – Respective criteria yet to be validated, Agency unable to formally endorse

• Critical point is that correct patients are identified
Clinical Endpoints

• Dementia Trials
  – Co-primary outcome measures
    • Cognition
    • Function or Global Rating

• Early AD Trials
  – Co-primary approach impractical
  – Should still apply in principle
Clinical Endpoints

• Closer to dementia
  – Detectable functional impairment
  – No well-validated functional scales
Clinical Endpoints

• Single primary outcome measure
  – Assesses both cognition and function
  – Example: Clinical Dementia Rating – Sum of Boxes (CDR-SB)
  – Open to other such scales
Clinical Endpoints

• Earliest Symptoms
  – Subtle cognitive deficits
  – No detectable functional impairment

Figure 2: Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF Aβ40, or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ-β-amyloid. MCI=mild cognitive impairment.
Clinical Endpoints

• Most to gain (potentially)

• Isolated cognitive measure
  – Several scales under development
  – Small effect sizes
  – Hard to interpret clinical meaningfulness
Clinical Endpoints

• Accelerated Approval (21 CFR 314.510)
  – Associated with an effect on a surrogate endpoint (e.g. viral load in HIV)
  – Effect on an intermediate clinical endpoint that is reasonably likely to predict ultimate clinical benefit (i.e., irreversible morbidity)
  – Requires further post-marketing evaluation to ensure the ultimate relationship to the ultimate clinical outcome
Clinical Endpoints

• Requires accurate identification of patients

• State of the science will be critical
  – e.g., Alzheimer’s Disease Neuroimaging Initiative (ADNI)
Clinical Endpoints

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Subtle cognitive deficits alone</th>
<th>Increasing cognitive deficits Detectable functional deficits</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approval</td>
<td>Accelerated, based on an effect on cognition</td>
<td>Standard, based on a single combined measure of cognition and function (e.g., CDR-SB)</td>
<td>Standard, based on coprimary measures of cognition and function or global rating</td>
</tr>
</tbody>
</table>

Potential Regulatory Pathways in Early Alzheimer’s Disease.
Biomarkers/Disease Modification

• Relates primarily to product labeling
• Desirable claim
• Divergence of slopes is problematic
Biomarkers/Disease Modification

• Correlation between AD biomarkers and clinical effect quite unclear

• Insufficient as single primary outcome measures (i.e., surrogates for Accelerated Approval)
Biomarkers/Disease Modification

• Potentially supportive of a disease modification claim
  – Combined with clinical endpoint

• Requires widespread evidence-based agreement
Alternative Trial Designs

RANDOMIZED START DESIGN
(Leber, 1997)

- Treatment initiation
  - Group 1

- Symptomatic Effect
  - Group 2 not only responds, but "catches up" with group 1

- Structural Effect
  - Group 2 responds, but loss, relative to group 1, is sustained.

Time

Performance

March 28, 2013
Summary

- AD is devastating and elusive
- Field moving to earlier trials
- Novel regulatory challenges
- Draft Guidance attempts to suggest pathways forward