ISCTM Autumn Conference

Options and methods to improve cognitive assessment in clinical trials of AD and its precursors

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Disclaimer

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Outline

- **Considerations on primary clinical endpoints and meaningful clinical benefits**
- **New Guidance for Industry on early AD**
- **Answers to your questions**

Primary Efficacy Endpoint

- Must establish clinical benefit, i.e., a favorable effect in how a patient feels, functions, or survives
  - Feel = a patient's physical sensation or perceived mental state related to health within typical 'daily' life, e.g., pain, mood
  - Function = A patient's ability to perform an activity that is a meaningful part of typical 'daily' life

Endpoint Relationship to Treatment Benefit

- Direct (e.g., Rankin, Barthel)
- Indirect: concept being measured is not how a patient feels or functions, e.g., cognitive scale in AD, measure of strength or sensation after stroke
  - need additional evidence about the relationship between the indirect concept and how a patient feels or functions

Meaningful Clinical Benefit

- Primary endpoint must establish that the drug makes a meaningful difference for the patient
- Ideally, primary endpoint has that concept "built in" (e.g., "direct" measures) and is designed in such a way that a score change reflects a meaningful change for the patient (e.g., 1-point change in Rankin score, or 5-point change in Barthel index)

Meaningful Clinical Benefit

- If primary endpoint, by itself, does not establish meaningful clinical benefit, available paths include:
  - Use a responder definition, based on prior evidence showing that a certain degree of improvement with the selected scale represents a meaningful improvement
  - Use a “co-primary” functional or global endpoint

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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, 5630 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.

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AD Progression Model

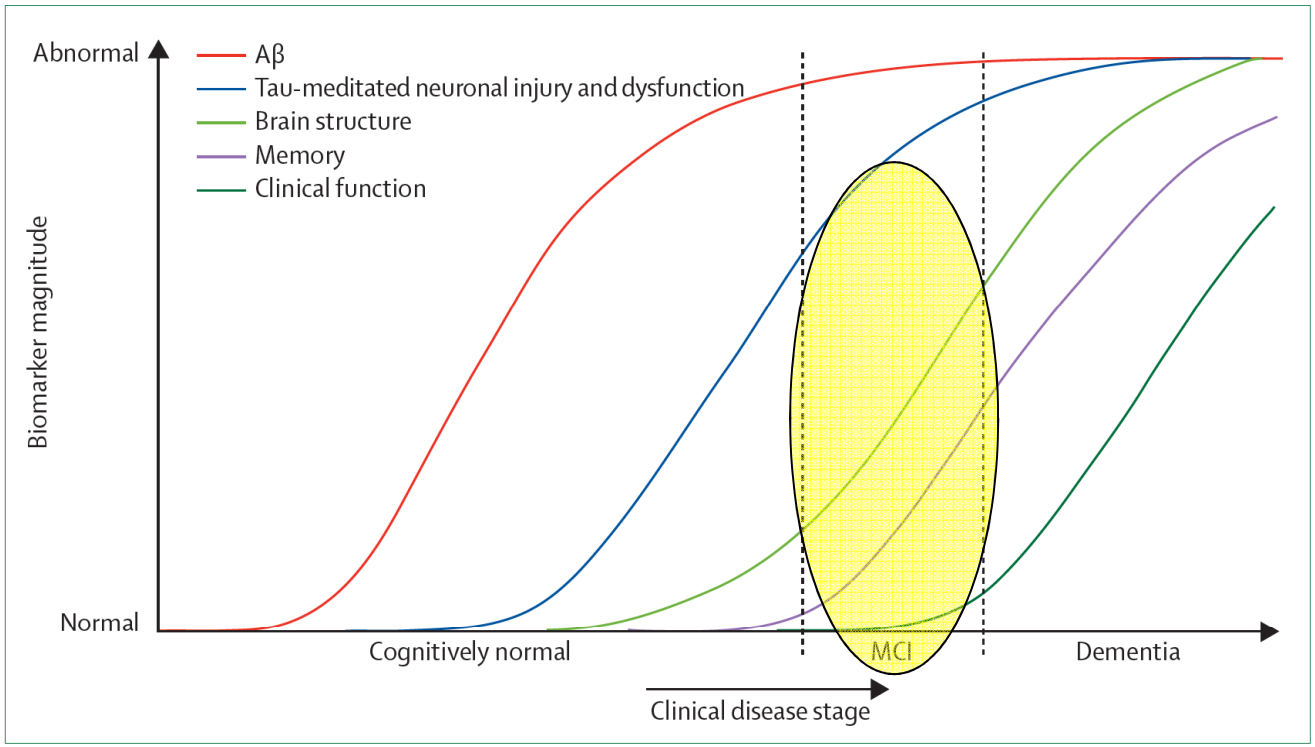


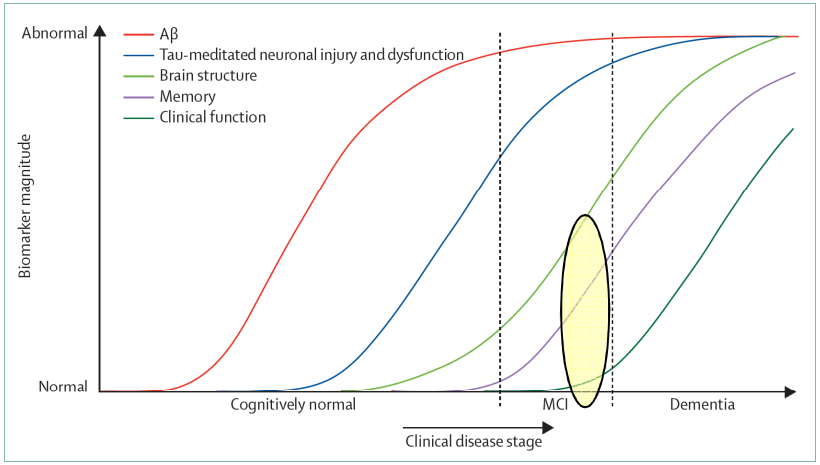
Figure 2: **Dynamic biomarkers of the Alzheimer's pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

AD Clinical Endpoints

- Dementia Trials
  - Co-primary outcome measures
    - Cognition
    - Function or Global Rating
- Early AD Trials
  - Co-primary approach impractical, because of limited or absent functional deficit
  - Alternative approaches proposed in the guidance

Early AD – Closer to dementia

- Detectable functional deficit
- No validated functional scales



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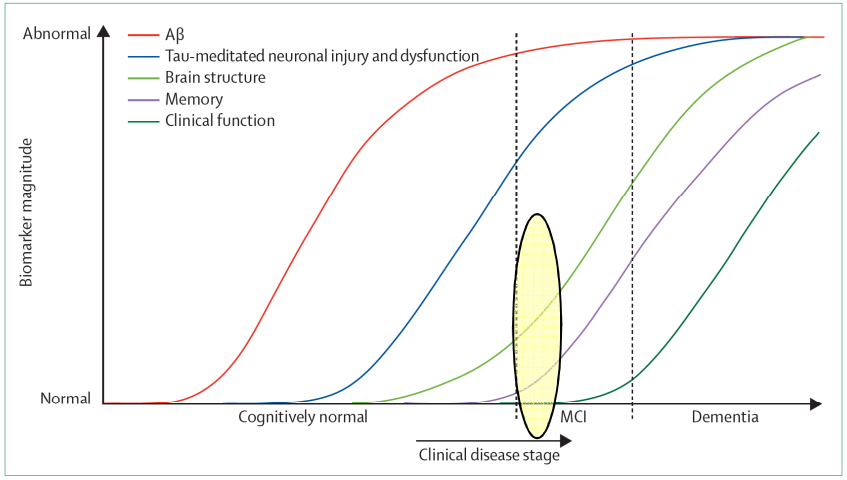
Clinical Endpoints in early AD – closer to dementia

- Single primary outcome measure acceptable
  - Must assess and establish a treatment effect on both cognition and function
    - Cognitive effect alone not sufficient
    - Example: Clinical Dementia Rating – Sum of Boxes (CDR-SB)

Early AD "Earlier Phase"

- Subtle cognitive deficits
- No detectable functional deficit



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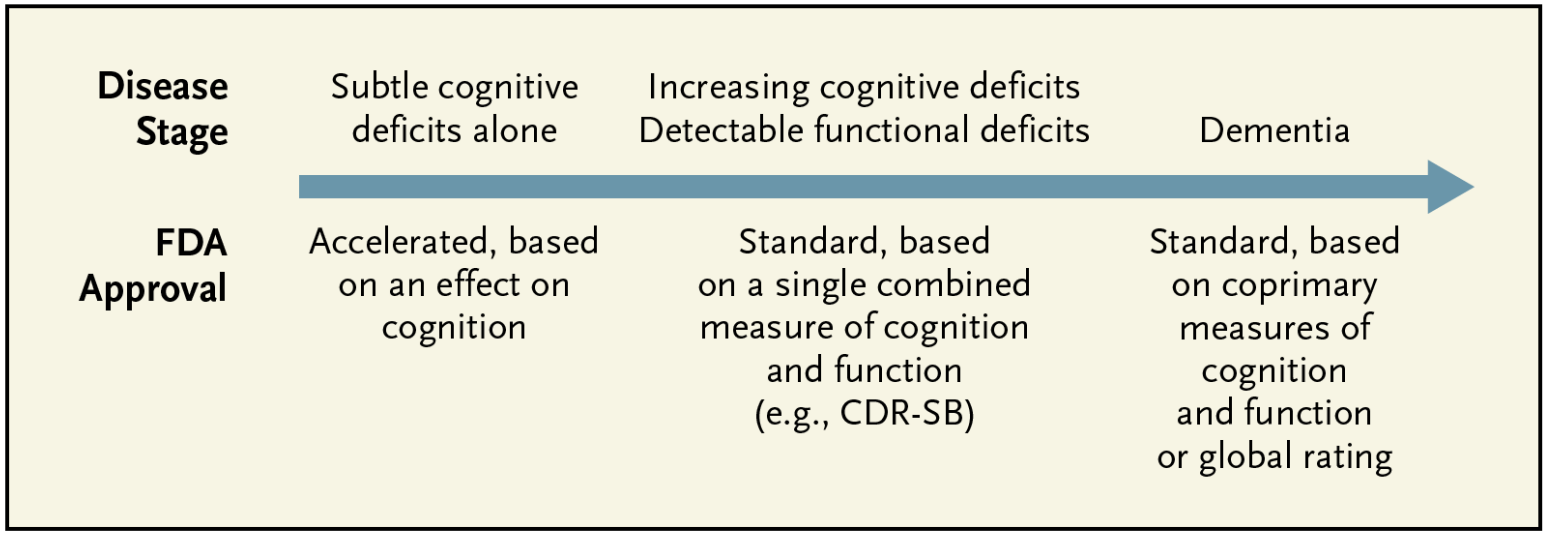
Clinical Endpoints in Early AD – "Earlier Phase"

- Assessment of function not doable
- Isolated cognitive measure considered for possible accelerated approval (subpart H)
  - Effect on an intermediate clinical endpoint that is reasonably likely to predict ultimate clinical benefit (*i.e.,* an effect on functional abilities)
  - Requires confirmatory post-marketing study to establish clinical benefit

Clinical Endpoints



Potential Regulatory Pathways in Early Alzheimer's Disease.

Answers to Your Questions

Is it reasonable to work with FDA to identify an endpoint that will be sufficient as a basis for approval for the drugs currently under development, while concurrently evaluating other approaches for a better primary endpoint in the long term?

- The Neurology Division (DNP) routinely entertains novel endpoints for drugs under IND development (interacting with drug Sponsor)
- Individual Sponsors can work with DNP to gain acceptance of their proposed endpoint for their drug under development
- DNP, however, does not validate or qualify novel endpoints, and does not guide the development of new endpoints, outside of the normal IND process

Is a composite endpoint of traditional scales potentially sufficient for an approval?

- Possibly, but composite endpoint must demonstrate contribution of both cognitive and functional elements in overall endpoint effect
- Overall effect can be "driven" by any component of the composite scale, and an overall win does not ensure effect on all individual components of the scale
  - e.g., a scale combining cognition and function could have "movement" based on cognition alone, which would be problematic to support a traditional approval

If an intervention could significantly separate from placebo solely based on imaging and biological biomarkers, would this be sufficient for an approval?

- Imaging and biological markers are not validated surrogates → standard approval not an option
- Relationship between biomarkers and clinical outcomes not well understood (e.g., recent phase 3 studies with effects on biomarkers but not on clinical outcomes) → Subpart H approval not an option

After a chemical entity has been granted approval for AD or a prodromal syndrome based on cognitive and/or functional primary outcomes and it was also shown that biomarkers significantly separated, could subsequent application for a new drug (of the similar or different mechanism) be approved solely based on the biomarker endpoint?

- Possibly, but only after the biomarker(s) are considered to be fully validated surrogate endpoints
- This requires demonstration of a consistently reliable relationship between a drug effect on a clinical endpoint and a drug effect on the surrogate biomarker, in multiple studies with drugs of different mechanisms of action

Do the individual items of neuropsychological tests need to be revalidated as part of the qualification process? Does the Division of Neurology think of neuropsychological tests in this manner?

- For the purpose of use as part of a primary endpoint in a trial reviewed by DNP, as long as scales measures clinically important elements, revalidation may not be required
  - Specifics should be discussed with the division
- Requirements for formal qualification are different

With regard to patient-reported outcomes, could or should performance-based functional tests substitute for informant ratings? Could they be the basis for approval if designated as the primary outcomes? If so, could this be the sole basis for approval?

- Performance based tests not required
- PROs less restrictive than performance-based tests
  - Ability to select functions to test relevant to a broad range of patients is critical; Semi-structured interviews more flexible
- PROs should have caregiver input (self-report concern)
- For standard approval, demonstration of a favorable effect on both cognition and functional abilities is required

Do outcomes measures need to be proven responsive to treatment before adoption, especially for a novel endpoint? If the answer is yes, does this not impose an excessive burden on the measure, because this ties drug effects and outcomes measures into a package?

- Answer is NO

For the pre-dementia stages of the disease, can improvement on a single cognitive measure be sufficient for approval or is improvement on a functional or global measure also required? If so, must that measure be a co-primary? Could a patient-reported outcome measure be used?

- Cognitive measure alone is insufficient for *standard* approval at any stage of the disease
- In the early phase of early AD, a cognitive measure alone could be considered for accelerated approval
- In the later phase of early AD, a scale combining cognition and function is recommended
- A PRO can be used to assess the functional abilities of patients (with caregiver input).

Considering the NEJM paper which appeared in March (Kozauer & Katz, 2013), could Dr. Bastings let us know more about the definition of a 'sensitive cognition measure' on which the accelerated-approval mechanism could be used to register a compound solely on the basis of this measure for an early stage of Alzheimer's, such as preclinical Alzheimer's disease, where no overt behavioral problems are being experienced.

- Cognitive test should assess relevant domains (e.g., memory, orientation, attention, reasoning, language, and praxis)
- Expectation that drug is disease-modifying (e.g., supported by effect on biomarker), and that benefit will grow over time

Also could he expand upon 'the stipulation that post-approval studies will be conducted to verify the clinical benefit'. For example over what period would such trials need to be conducted, could the endpoint be a prevention of further cognitive decline, or would it need to be a delay in the emergence of prodromal symptoms?

- Endpoint should relate to the emergence of a functional advantage; cognitive benefit should persist during that period
- Confirmatory study should be underway at the time of accelerated approval; confirmatory study would typically be an extension of the study that supported accelerated approval in which blinding to original treatment would be maintained

Acknowledgments

- Nick Kozauer, clinical team leader for Alzheimer's disease drug development
- Rusty Katz