DEVELOPING DRUGS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Disclaimer

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Outline

- Dementia stage Alzheimer's disease
- Early stage Alzheimer's disease (AD)
  - Early AD approaching onset of dementia
    - Prodromal AD or MCI due to AD
  - Very early AD
    - Preclinical AD

DEMENTIA STAGE ALZHEIMER'S DISEASE

Dementia Stage Alzheimer's Disease

- All drugs approved so far have been for patients at the dementia stage
  - Donepezil approved for all stages of AD
  - Galantamine and rivastigmine approved for mild to moderate AD
  - Memantine approved for moderate to severe AD

Dementia Stage Alzheimer's Disease

- Co-primary efficacy endpoints: cognitive measure and global or functional co-primary
  - Cognitive endpoint: ADAS-cog, Severe Impairment Battery (SIB)
  - Functional or Global measure: CIBIC-plus, ADCS-CGIC
- These endpoints do not represent "gold standards"
  - Other endpoints could be considered

EARLY STAGE ALZHEIMER'S DISEASE

Early Stage Alzheimer's Disease

- Area of considerable interest to FDA
  - Goal of intervening before major neuronal damage sets in is critically important
  - Effective disease-modifying interventions will likely have their most permanent impact before brain damage is too extensive

FDA Draft Guidance on Early AD (2013)

- Selection of patients with early AD closest to the onset of overt dementia (i.e., prodromal AD or MCI due to AD)
- Selection of patients who are determined to be at risk of developing AD (preclinical AD)
- Selection of endpoints for clinical trials in these populations

EARLY AD APPROACHING THE ONSET OF OVERT DEMENTIA

Primary Endpoint in Early Stage AD (approaching onset of dementia)

- Mild functional or global impairment difficult to detect before onset of overt dementia
- Assessment tools to assess global or functional impairment not suitable for that stage of the disease
- Composite scale assessing both cognition and function may be acceptable
  - Should not allow for overall finding of efficacy in the absence of functional benefit

Identifying the Right Patient Population

- Important to adequately enrich the patient population, both to keep drug risk acceptable and have trials of reasonable size and duration
  - CSF biomarkers
  - Amyloid imaging biomarkers

What Biomarkers Should Be Used to Select Patients?

- No FDA-endorsed set of diagnostic/inclusion criteria
- Variations in the selection of biomarkers and/or cognitive testing cutoff values may lead to the identification of patients who are at different stages of a progressive disease process

TRIALS IN PATIENTS WITH VERY EARLY ALZHEIMER'S DISEASE (PRECLINICAL)

Very Early AD

- Underlying anatomical and pathophysiologic changes in AD begin many years before clinical symptoms emerge
- Only subtle cognitive deficits at that stage
- Difficult to identify patients with very early AD
- Difficult to establish meaningfulness of drug effect

Very Early AD

- Primary endpoint: valid and reliable sensitive measure of cognitive performance
  - Possibility of Accelerated Approval pathway
- Following initial approval, requirement for demonstration that the observed effect translates into functional benefit (in new adequate and well-controlled studies or continuation of initial studies)


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