Amyloid, BACE and Beyond: Alzheimer’s Disease Research at Merck

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Goldman Sachs Alzheimer’s Symposium
April 11, 2016
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Merck’s BACE Inhibitor: Verubecestat (MK-8931)
The Amyloid Pathway

Adapted from Gandy, 2005
MK-8931 Reduces Aβ in CSF: A Multiple Dose CSF Study in AD Patients

• Study: indwelling CSF catheters in AD patients at steady state
• Results: dose-dependent reduction in CSF Aβ40 and sAPPβ
MK-8931 PK/PD For Dose Selection

- Objective: test maximally and sub-maximally A$\beta$ lowering doses
- Steady-state dose-response predicted from CSF with 90% confidence intervals
  - $>50\%$ CSF A$\beta$ reduction at 12 mg once daily
  - $>75\%$ reduction at doses 40 mg once daily
  - 60 mg daily dose in vanguard cohort for potential PK outliers and enriched safety
Pivotal Study Design Considerations

• Disease Severity
  – Safety
  – Methodology needs and availability

• Diagnostic
  – Imaging/CSF for symptomatic patients

• Regulatory
P017: Mild-Moderate AD Trial Design

- Randomized, placebo controlled, parallel-group, double blind trial
- 18 month duration of treatment
- MMSE 15-26 at study entry
- Two co-primaries: cognition (ADAS-Cog) and function (ADCS-ADL)
- Seamless phase 2/3 design with initial vanguard cohort

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MK-8931 60 mg
MK-8931 40 mg
MK-8931 12 mg
Placebo
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Vanguard Cohort

Extension
P017: Mild-Moderate AD Trial Design

- Randomized, placebo controlled, parallel-group, double blind trial
- 18 month duration of treatment
- MMSE 15-26 at study entry
- Two co-primaries: cognition (ADAS-Cog) and function (ADCS-ADL)
- Seamless phase 2/3 design including initial vanguard cohort

Primary Analysis Cohort

MK-8931 40 mg
MK-8931 12 mg
Placebo

Extension
P019: Prodromal Study

- Randomized, placebo controlled, parallel-group, double blind trial
- 24 month duration of treatment
- Subjects must have:
  - MMSE $\geq 24$
  - Threshold impairment on neuropsychological testing
  - Positive PET scan for amyloid
- Primary outcome measure: CDR-SB

24 Month Treatment Period

MK-8931 40 mg
MK-8931 12 mg
Placebo

Extension
Mild-Moderate Alzheimer’s Disease: Too Late for BACE Inhibition?
Mild-Moderate Initially, Then Prodromal

- Considerations that drove the decision to conduct protocol 17 in individuals with mild-moderate Alzheimer’s Disease
  - Medical need
  - Balancing benefit and risk for a novel mechanism vs. target population risk for disease progression
  - Appropriate and established tools
Mild-Moderate Initially, Then Prodromal

• Considerations that drove the decision to conduct protocol 17 in individuals with mild-moderate Alzheimer’s Disease
  – Medical need
  – Balancing benefit and risk for a novel mechanism vs. target population risk for disease progression
  – Appropriate and established tools

• Protocol 19 followed later in order to
  – Assess initial safety before treating healthier individuals
  – Work with regulators on methodologies and outcome measures
  – Establish a reliable distribution network for amyloid PET imaging
Mild-Moderate Initially, Then Prodromal

- Considerations that drove the decision to conduct protocol 17 in individuals with mild-moderate Alzheimer’s Disease
  - Medical need
  - Balancing benefit and risk for a novel mechanism vs. target population risk for disease progression
  - Appropriate and established tools
- Protocol 19 followed later in order to
  - Assess initial safety before treating healthier individuals
  - Work with regulators on methodologies and outcome measures
  - Establish a reliable distribution network for amyloid PET imaging
- But do these considerations ignore a (possibly) lower probability of success related to disease severity in protocol 17?
A Tentative Conclusion (While Awaiting Data)

- Alzheimer’s is a continuum along a severity spectrum
A Tentative Conclusion (While Awaiting Data)

• Alzheimer’s is a continuum along a severity spectrum
  – The impact of intervening successfully will be greater earlier than later...but
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**Diagram**

- Natural history
- Worsening Disease
- Time
- Intervention while presymptomatic
A Tentative Conclusion (While Awaiting Data)

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![Diagram showing natural history and intervention pathways]

- Natural history
- Intervention while presymptomatic
- Intervention early in disease course
- Intervention later in disease

Time

Worsening Disease
Beyond Amyloid: Next Generation Programs
For the foreseeable future there will be an ongoing need for a triad of better interventions.
New Clinical Development Programs

Slow/Halt Progression

Amyloid Targeted: BACE inhibition
Tau targeted: Inhibit aggregation
New Clinical Development Programs

Slow/Halt Progression

Amyloid Targeted: BACE inhibition
Tau targeted: Inhibit aggregation

Improve Function

Novel cholinergic and non-cholinergic targets to improve cognitive function
New Clinical Development Programs

Slow/Halt Progression → Amyloid Targeted: BACE inhibition
                           Tau targeted: Inhibit aggregation

Improve Function → Novel cholinergic and non-cholinergic
targets to improve cognitive function

Neuropsychiatric Signs and Symptoms → Sleep, agitation/psychosis