“Enhancing Translational Research and Clinical Development in Alzheimer’s Disease and other Dementia: The Way Forward”

11-12 November 2014, Lausanne

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AC Immune
CEO

New insights into Alzheimer’s disease and future therapeutic options
1. AD – Where we stand
2. AD - What’s new
3. AD - Emerging topics
What needs to be done to have a successful AD treatment in 2025?
AD is a complex disease affecting multiple targets. Abeta and Tau pathways are very promising targets.
- Slowing of cognitive decline is possible

**Crenezumab** ABBY phase 2
Change in ADAS-cog 12 in mild patients (MMSE 22-26)

- Solanezumab Expedition 1 and 2 phase 3 - pooled
Change in ADAS-cog 14 in mild patients (MMSE 20-26)

Ref: Cummings, AAIC 2014

Ref: Siemers, Eli Lilly conference call 2012
Protection from AD by Iceland gene mutation

Early onset Alzheimer’s in people with genetic predisposition (examples)
- Columbia family clan: Paisa mutation (E280A PS1) leads to Abeta accumulation
- People with Down syndrome: Triple copy of APP gene leads to Abeta accumulation

Ref: Nature 2012
| **Clinical trial** | AD prevention trial in cognitively healthy individuals who will develop AD because of their genetic predisposition  
Test the amyloid hypothesis  
Phase II study of 300 subjects, double-blind, placebo-controlled |
| **Study partners** | Banner Alzheimer Institute, Arizona USA  
US National Institutes of Health (NIH)  
University of Antiochia, Colombia  
Genentech – developer of Crenezumab  
AC Immune – discoverer of Crenezumab |
| **Participant characteristics** | 30 years and older being in a preclinical phase of AD  
No cognitive impairment |
| **Study objectives** | Change on the “API composite cognitive test battery” total score  
Safety, biomarkers, time to MCI or dementia due to AD |
| **Study timelines** | First patients received dose in Dec. 2013  
Interim analysis after 2 years of treatment  
2020: Study completion |
### Session 2: Biomedical Research, Diagnostics and Regulatory Science

A path to the future – example of prevention of AD in DS population

| Clinical trial | World first clinical trial for vaccine targeting Alzheimer’s disease in people with Down syndrome  
|                | Test the amyloid hypothesis  
|                | Phase I clinical study, double-blind, placebo-controlled |
| Study partners | AC Immune  
|                | University of San Diego’s Down Syndrome Center for Research and Treatment  
|                | US National Institutes of Health (NIH)  
|                | LuMind Foundation and Research Down Syndrome |
| Participant characteristics | 35-45 years old people with Down syndrome |
| Study objectives | Safety and tolerability  
|                  | Effect on induction of anti-Abeta antibodies  
|                  | Clinical and cognitive measures  
|                  | Biomarkers to study Abeta brain and CSF load |
| Study timelines | Recruitment of patients planned to start early 2015  
<p>|                  | 6 months treatment + 12 months safety follow up |</p>
<table>
<thead>
<tr>
<th>Study population</th>
<th>API ADAD Trial</th>
<th>DIAN Trial</th>
<th>A4 Trial</th>
<th>API ApoE4 Trial</th>
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<td>Population</td>
<td>300 volunteers from kindred with PSEN1 mutation</td>
<td>240 volunteers from families with FAD mutation</td>
<td>1100 volunteers over 70 years old with amyloid in brain</td>
<td>1300 volunteers, age 60-75 with two copies of ApoE4</td>
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<td>Time to onset</td>
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<td>NIA US AD Association Roche Eli Lilly</td>
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- Tau pathology spreads through the brain

- Tau pathology correlates well with disease severity

Ref: Shah et al, JNM 2014
Ref: Okamura et al, Brain 2014
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**A step closer to the future – first anti-Tau agents in clinical trials**

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<th>Timeline</th>
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Ref: Alzforum, October 2014
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Where do we need to go

Current

Symptomatic treatments

Future

Disease prevention based on risk factors and targets from genetics

Disease modification based on pathophysiology

Emerging

Treatments of psychiatric consequences

Combination therapies

Biomarkers

Adapted from US academy of Science
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Emerging strategies – combination therapy

- Prevention therapy
- Symptomatic treatment
- Disease modifying combination therapy
- Disease modifying monotherapy
Symptomatic combination therapies

- Memantine plus Donepezil in moderate to severe AD
- Alpha7 nicotinic acetylcholine receptor activators plus BACE-inhibitors (University of Maryland, preclinical)

Combination therapy targeting Abeta pathway (preclinical)

- Anti-Abeta antibody plus BACE-inhibitor LY 2811376 (Eli Lilly)
- Gantenerumab plus BACE-inhibitor (Roche)

Abeta and Tau
Emerging strategies – new hot targets discussed in academia and industry

- Neuroinflammation
- Mitochondrial dysfunctions
- Epigenetics: HDAC inhibitors, miRNA modulators
- Neurogenesis
- Stem cells
- Neurotrophins
- Endoplasmatic reticulum stress
- Unfolded protein response
- Cell cycle dysfunctions
Potential approaches to accelerate clinical development of disease modifying therapies in AD

- Phase I
- Phase IIA
- Phase IIB
- Phase III

Phase I/IIA Tolerability and biomarker effects

Phase IIIB

Phase III

Phase I/IIA Tolerability and biomarker effects in patients

Phase IIIB/III, +/- adaptive design

Confirmatory study

Conditional approval

Ref: White paper, CEOi
Support development and implementation of surrogate markers in clinical trials

Allow early access to new medicines with highly positive Phase II/III results through conditional approval / adaptive licensing / Treatment IND

Support approval of drugs based on a single (cognitive) endpoint in early disease

Accelerate development of combination therapy through regulatory acceptance of appropriate preclinical and clinical safety data

Encourage industry through longer market exclusivity

Harmonize regulatory guidance for AD development
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Key needs to find a cure for AD before 2025

- Partnerships between industry, regulatory bodies and other stakeholders and new financing models
- Focus on early stages of disease
- Abeta and Tau remain major targets – new targets and concepts need attention
- Consideration of combination therapy
- Global registries, data sharing and analyses
- Different endpoints, tools and strategies for symptomatic and disease modifying treatments