Aducanumab: Hype, or Headway for the Alzheimer’s Amyloid Hypothesis?

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April 13, 2015

DefinedHealth
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March 2016
New York City
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BioEurope Spring
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Stockholm, Sweden
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Is Biogen/Neurimmune’s Aducanumab Hype, or Headway for the Alzheimer’s Amyloid Hypothesis?

**Biogen Alzheimer’s Drug Exceeds Expectations**

**Biogen Reports Its Alzheimer’s Drug Sharply Slowed Cognitive Decline**

**Biogen Drug Could Inspire New Hope For Alzheimer’s Treatments**

**Biogen Soars as Alzheimer’s Drug Slows Disease In Trial**

Biogen Stock Performance (since Nov-2014)

- **20-March-2015:** Positive interim results from P1b trial presented at 2015 AD/PD Conference
- **02-Dec-2014:** Positive interim analysis of P1b PRIME study reported (reduced brain amyloid levels)
- **29-Jan-2015:** Announced intent to go from P1b to P3

Google Finance, headlines – various news sources

Alzheimer’s Insight Briefing © Defined Health
The Tauists Fight Back: A Mayo Study Published Last Month Suggests That “Tau Wins the ‘Bad Guy' Award”

Four days after Biogen presented the PRIME data, Mayo Clinic researchers published a study in *Brain* that found tau pathology predicted cognitive decline and memory loss better than amyloid pathology. According to lead author:

- “When you account for the severity of tau pathology, however, the relationship between amyloid and cognition disappears—which indicates tau is the driver of Alzheimer's”

David Knopman, Mayo Clinic – a co-author of the paper, was quoted in the March 20 BioCentury edition as saying tauopathies and amyloid likely act in parallel to put people at risk for neurodegeneration.
Alzheimer’s disease (AD) is a progressive neurodegenerative disease that gradually worsens over time and markedly interferes with social and occupational functioning.

AD afflicts ~5.2 million people in the US and over 15 million people worldwide.

By 2050, the number of people age 65 and older with AD may nearly triple.

In addition to the devastating effect on patients’ and caregivers’ function and quality of life, direct medical and indirect costs for AD are estimated at US $600 billion a year worldwide.
The AD Treatment Armamentarium Currently Consists Only of Symptomatic Therapies

- The only currently available AD treatments provide symptomatic relief, temporarily, but do not alter the underlying disease process.
- There are 5 symptomatic agents on the market in the US, four of which are acetylcholinesterase (AChE) inhibitors and one NMDA antagonist (Namenda).

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Drug Class</th>
<th>Patent Expiry Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aricept (donepezil)</td>
<td>Pfizer/Eisai</td>
<td>AChE inhibitor</td>
<td>Nov 2010</td>
<td>• Prior market leader, nearly all scripts converted to generics</td>
</tr>
<tr>
<td>Exelon (rivastigmine)</td>
<td>Novartis</td>
<td>AChE inhibitor</td>
<td>Aug 2012 (patch)</td>
<td>• Available as oral BID and transdermal patch – oral formulation rarely used</td>
</tr>
<tr>
<td>Razadyne ER (galantamine)</td>
<td>JNJ/Shire</td>
<td>AChE inhibitor</td>
<td>Aug 2008</td>
<td>• Never caught on in the market, GI side effects may have limited use</td>
</tr>
<tr>
<td>Cognex (tacrine)</td>
<td>Sciele</td>
<td>AChE inhibitor</td>
<td>Sept 2007</td>
<td>• First AChEI approved. • Liver enzyme monitoring severely limits use</td>
</tr>
<tr>
<td>Namenda (memantine)</td>
<td>Forest/Actavis</td>
<td>NMDA antagonist</td>
<td>Jan 2015</td>
<td>• IR version discontinued in Aug 2014 to be replaced by XR to defend against generics</td>
</tr>
</tbody>
</table>

SG Cowen Therapeutic Categories Outlook, March 2014; EvaluatePharma
The Branded AD Symptomatic Market Peaked at $3.6B in the US

♦ The US Alzheimer’s disease market rapidly expanded to a peak of $3.6B in 2009.
♦ Despite a growing patient population, the market has significantly retracted in recent years, as a result of generic erosion.
♦ There have been no novel AD products approved in the US since 2003.
Treatment Rates are Increasing as Intervention Moves to the Earliest Stages of the Disease

- The vast majority of patients with mild disease will be initiated on an acetylcholinesterase inhibitor (AChEI), unless they cannot tolerate the class of drugs.
- An increasing percentage of prodromal disease/MCI may also receive AChEI treatment.
- The NMDA antagonist, Namenda (memantine) is typically added at the moderate stage.

MMSE = Mini-Mental State Examination
Amyloid Plaques and Neurofibrillary Tangles (Tau) are Hallmark Pathologies of AD

Even in the earliest stages of AD, the brain may have a full load of amyloid which has been building over decades.
The primary event that induces the abnormal accumulation of Aβ is the dysregulated proteolytic processing by secretases of its parent molecule, the amyloid precursor protein (APP).

Dysregulated APP-processing results in the Aβ-peptide of predominantly 39 to 43 residues.

Further post-translational modifications result in a various number of N- and C-terminal variants of the Aβ-peptide, increasing heterogeneity and, thus, the number of possible targets.
Thus Far, Modulation of the Amyloid Beta Pathway Has Produced a “Conga-line of Clinical Disappointments”

- Amyloid-based passive immunotherapies that have failed to meet clinical endpoints in late-stage development.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Phase III:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bapineuzumab</td>
<td>N-terminus (aa 1-5)</td>
<td>trials were halted after completion of two trials demonstrated a failure to meet primary outcome measures of cognition and activities of daily living</td>
</tr>
<tr>
<td>3D6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solanezumab</td>
<td>central (aa 16-24), accessible only on soluble Aβ</td>
<td>Phase III: ongoing as preventive trial in familial AD (DIAN). Trials failed to meet their primary endpoints in cognition and activities of daily living. A subsequent analysis of mild AD patients pooled from both trials showed a significant effect on cognition.</td>
</tr>
<tr>
<td>m266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>N-terminal (aa 3-12) and C-terminus (aa 18-27)</td>
<td>Phase III: ongoing in prodromal AD patients (DIAN), amyloid reduction but also ARIAs were observed in Phase I.</td>
</tr>
<tr>
<td>full human mAb</td>
<td></td>
<td></td>
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</tbody>
</table>

Moreth et al. Immunity & Ageing 2013, 10:18i; https://neurogram.wordpress.com/2015/03/23/aducanumab-less-than-meets-the-eye/ (NeuroPerspective)²
Learnings from these so-called “failures” have advanced our understanding of the amyloid biology (e.g., understanding of epitopes) and trial design (e.g., earlier intervention, biomarkers to select for responders).
Hope for the Amyloid Approach Continues

♦ While about 20% of the AD pipeline is still amyloid focused, the competition is heating up – particularly in the early stage.

2010 AD Pipeline

2015 AD Pipeline

Agents in Development WW

Lancet, Adis R&D Insight, Cortellis

Alzheimer’s Insight Briefing
© Defined Health
Even if Statistically Significant, Will Amyloid Immunotherapies Prove to Be Clinically Relevant?

- Given the hopeful event that a disease modifying therapy passes the clinical and regulatory hurdles (whether amyloid-based or some other approach), the question still has to be asked: “Does the required statistical significance translates to clinical relevance?”
- Does the magnitude of effect and the benefit/risk ratio justify the cost to the patient/family and the healthcare system?
  - and for which specific patient population(s) (e.g., what stage of disease, what level of cognitive impairment)?
  - can these populations be definitively identified or diagnosed?
  - For what duration of effect/what magnitude of progression delay?

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Figure 5 Sensitivity of net benefits obtained through a hypothetical disease-modifying treatment to costing horizon, treatment effect and age of cohort. Panel A: results when costing over 5, 10 and 20 years; Panel B: result of increased and decreased treatment effect, as expressed in months delay in deterioration in MMSE score; Panel C: effect of mean cohort age at model start.

Barnett et al. BMC Neurology 2014, 14:101
Aducanumab: Hype, or Headway for the Alzheimer’s Amyloid Hypothesis?

Norman R. Relkin, MD, PhD
Associate Professor of Clinical Neurology, Weill Cornell Medical College

April 13, 2015
Lesson Learned from Initial Round of Passive Amyloid Immunotherapy Studies

- Comparison of passive amyloid immunotherapy studies that have reported statistically significant improvement on cognitive endpoints.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>mAb</td>
<td>Crenezumab</td>
<td>Solanezumab</td>
<td>Bapineuzumab</td>
</tr>
<tr>
<td>Study</td>
<td>Ph II ABBY; 73 wks; 431 patients</td>
<td>Ph III EXPEDITION 1; 80 wks; 1,012 patients</td>
<td>Phase II; 78 weeks; 234 patients</td>
</tr>
<tr>
<td>Population</td>
<td>Mild to moderate AD (baseline MMSE 18-26)</td>
<td>Mild to moderate AD (baseline MMSE 18-26; with positive florbetapir amyloid PET scan)</td>
<td>Mild to moderate AD (baseline MMSE 16-26)</td>
</tr>
<tr>
<td>Primary endpoint (result)</td>
<td>ADAS-Cog12 and CDR-SB (missed)</td>
<td>Change in brain amyloid load in florbetapir PET scan (missed)</td>
<td>ADAS-Cog11 and ADCS-ADL (missed)</td>
</tr>
<tr>
<td>Arms</td>
<td>High dose, all patients</td>
<td>High dose, very mild (baseline MMSE 22-26)</td>
<td>High dose, very mild (baseline MMSE 22-26)</td>
</tr>
<tr>
<td>MMSE change</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CDR-SB change</td>
<td>3.1% (p=0.85)</td>
<td>19.6% (p=0.42)</td>
<td>7.4% (p=0.84)</td>
</tr>
<tr>
<td>VE Apo E4</td>
<td>1 case of sulcal effusion</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>VE non-Apo E4</td>
<td>NA</td>
<td>0%</td>
<td>NA</td>
</tr>
</tbody>
</table>

BioCentury, Week of March 20, 2015
1st Generation AD Passive Immunotherapy Trials Employed Sequence-Specific anti-Ab Antibodies

**Bapineuzumab** *(AAB-001)*
- Humanized mouse monoclonal
- Binds first 5 a.a. of N-terminus
- Clears plaques and vascular Ab

**Solanezumab** *(LY2062430)*
- (Lilly-Humanized mouse Monoclonal)
- Binds to amino acids 14-28
- Binds soluble Ab

**PF-4360365**
- (Pfizer Failed 2011)
- Binds to C-terminus
- Deglycosylated to decrease Fc effects
- Clears plaques, less microglial action

**Sequence:**
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

1  5  10  15  20  25  30  35  40

N-terminus  Central Region  C-terminus

N Relkin 2015
The Amyloid Oligomer Hypothesis: Amyloid Oligomers are Neurotoxic

Aβ Monomer → Aβ Dimer → Aβ Oligomer → Spheric Oligomer

Oligomer or Protofibrils → Rough Fibrils → Smooth Fibrils

N Relkin 2015
Aducanumab: Epitope and Origin

✧ Neurimmune’s first antibody program derived from its Reverse Translational Medicine™ (RTM™) proprietary technology platform
  - RTM™ platform selectively targets misfolded, pathogenic forms of an aggregated target protein

✧ Novel, fully human IgG1 monoclonal antibody against beta amyloid (Aβ)
  - Derived using a reverse translational medicine methodology, using a template sourced from an endogenous anti-Aβ antibody from a patient who suffered from AD but had an unusually stable disease course
  - Targets insoluble fibrillar Aβ; preferentially parenchymal plaques over vascular forms
  - Preclinical data suggests activity through Fc-receptor mediated phagocytosis

✧ Partnered with Biogen in 2007
The Importance of Patient Population

♦ Intervention at the earliest stages of disease
♦ Biomarker confirmation of amyloid pathology
♦ ApoE status
Finding a Therapeutic Window

Anti-Amyloid Immunotherapy: What Can Go Wrong?

CD3 T-cell meningeal response to AN-1792

Vasogenic Brain Edema (ARIA-E)

Accelerated Brain Atrophy

Intra-cerebral Microhemorrhage (ARIA-H)

BAPENUZIMAB
Aducanumab First to Combine Significant Reduction of AB With Slowing of Clinical Impairment

- Even more detail on aducanumab data.

### Aducanumab 1b Trial Design

<table>
<thead>
<tr>
<th>Phase 1b Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifier</td>
</tr>
<tr>
<td>Design</td>
</tr>
<tr>
<td>Enrollment</td>
</tr>
</tbody>
</table>

**Dosing**
- IV doses administered -4 weeks apart over ~52 weeks (a total of 14 doses)
- Patients will receive low-dose #1, low-dose #2, mid-dose or high-dose BiIB 037 or matched placebo
- Qualifying participants can continue into the long term extension of a dose administered approximately 4 weeks apart for an additional 14 doses

**Key inclusion criteria**
- Subjects must meet criteria for Prodromal Alzheimer’s Disease (AD) or Mild Alzheimer’s Disease (AD):
  - a. Mini Mental State Examination (MMSE) score between 20-30,
  - b. Clinical Dementia Rating Scale (CDR) score of 0.5 or 1.0
- A free recall score of lesser or equal to 27 on the Free and Cued Selective Reminding Test (F-C-SRT) for prodromal Alzheimer’s Disease (AD)
- Subjects must have a positive florbetapir positron emission tomography (PET) amyloid scan

**Primary endpoint (result)**
- Number of Participants with Adverse Events (baseline to week 126)

### Aducanumab 1b Trial Interim Results

<table>
<thead>
<tr>
<th>Company</th>
<th>Biogen Inc. (NASDAQ: BIIB)/Neurimmune Holding AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb</td>
<td>Aducanumab</td>
</tr>
<tr>
<td>Study</td>
<td>Ph 1b PRIME; 54 wks; 166 patients</td>
</tr>
<tr>
<td>Population</td>
<td>Prodromal to mild AD (baseline MMSE 20-30) with positive florbetapir amyloid PET scan</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Safety (ongoing)</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pbo (n=40)</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg (n=31)</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg (n=33)</td>
</tr>
<tr>
<td></td>
<td>6 mg/kg (n=30)</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg (n=32)</td>
</tr>
<tr>
<td><strong>MMSE change (A)</strong></td>
<td>-3.14 (p&lt;0.05)</td>
</tr>
<tr>
<td><strong>CDR-SB change (A)</strong></td>
<td>2.04 (p&lt;0.05)</td>
</tr>
<tr>
<td><strong>VE Apo E4</strong></td>
<td>NA 5% 5% 43% 55%</td>
</tr>
<tr>
<td><strong>VE non-Apo E4</strong></td>
<td>NA 0% 9% 11% 17%</td>
</tr>
</tbody>
</table>

## Comparing Aducanumab to First Generation Amyloid Passive Immunotherapies

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>Cremenab</td>
<td>Solanezumab</td>
<td>Bapineuzumab</td>
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<td>Mild to moderate AD (baseline MMSE 18-26) with positive florbetapir amyloid PET scan</td>
<td>Mild to moderate AD (baseline MMSE 16-26)</td>
<td>Mild to moderate AD (baseline MMSE 16-26)</td>
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<tr>
<td><strong>Primary endpoint (result)</strong></td>
<td>Safety (ongoing)</td>
<td>ADAS-Cog12 and CDR-SB (missed)</td>
<td>ADAS-Cog11 and ADCS-ADL (missed)</td>
<td>ADAS-Cog11 and DAD (missed)</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>Pbo (n=40)</td>
<td>High dose, all patients</td>
<td>High dose, all patients</td>
<td>Pbo</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg (n=31)</td>
<td>High dose, very mild (baseline MMSE 22-26)</td>
<td>High dose, very mild (baseline MMSE 22-26)</td>
<td>Sola</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg (n=30)</td>
<td></td>
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<td></td>
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<td></td>
<td>6 mg/kg (n=30)</td>
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</tr>
<tr>
<td></td>
<td>10 mg/kg (n=32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MMSE change (A)</strong></td>
<td>-3.14</td>
<td>-0.58 (p&lt;0.05)</td>
<td>NA</td>
<td>-2.8 (p&lt;0.05)</td>
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<tr>
<td></td>
<td>-2.21 (p&lt;0.05)</td>
<td></td>
<td>NA</td>
<td>-2.1 (p=0.01)</td>
</tr>
<tr>
<td></td>
<td>-0.75</td>
<td></td>
<td>NA</td>
<td>-1.5 (p=0.087)</td>
</tr>
<tr>
<td></td>
<td>(p&lt;0.05)</td>
<td></td>
<td>NA</td>
<td>2.7 (p=0.043)</td>
</tr>
<tr>
<td><strong>CDR-SB change (A)</strong></td>
<td>2.04</td>
<td>19.6% (p=0.42)</td>
<td>7.4% (p=0.084)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>16% (p=0.51)</td>
<td>41.5% (p=0.044)</td>
<td></td>
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<tr>
<td></td>
<td>1.33</td>
<td></td>
<td>41.5% (p=0.044)</td>
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<tr>
<td></td>
<td>(p&lt;0.05)</td>
<td></td>
<td>(p=0.044)</td>
<td></td>
</tr>
<tr>
<td><strong>VE Apo E4</strong></td>
<td>NA</td>
<td>1 case of sulcal effusion</td>
<td>NA</td>
<td>Placebo 0.4%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td></td>
<td>0%</td>
<td>Solanezumab 0.9%</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>VE non-Apo E4</strong></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td></td>
<td>NA</td>
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</tr>
<tr>
<td></td>
<td>11%</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td></td>
<td>NA</td>
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</tbody>
</table>

BioCentury March 30 2015

Alzheimer’s Insight Briefing © Defined Health
Outstanding Questions about Aducanumab

♦ Does the P1b data suggest that aducanumab is clinically relevant?
♦ Is the drop-out-rate in the placebo group really higher than expected?
♦ So what about the 6mg/kg dose and other not-yet disclosed data?
♦ How should the 10mg/kg group data be interpreted, given the higher discontinuation rate and LOCF, last-observation-carried-forward (LOCF) methodology?
♦ What rates and severities of vasogenic edema are tolerable, and what efficacy would justify these risks?
♦ To what degree does aducanumab’s dose-responsiveness mitigate the limitations of a small study size?
  • Enough to go directly to P3?
♦ Thoughts on P3 trial design?

“Speaking of missing data: Where were the results from the other neuropsychological testing components (the NTB and FRCT) with their far more ‘granular’ assessment of cognitive functions? The similarity between the results obtained from the MMSE and CDR-SB is less validating than it might seem: Those two instruments overlap quite a bit…”

NeuroPerspective

https://neurogram.wordpress.com/2015/03/23/aducanumab-less-than-meets-the-eye/ (of NeuroPerspective)²
## Other Promising Agents and Trends

<table>
<thead>
<tr>
<th>Drug (Company)</th>
<th>Phase (Trial Name)</th>
<th>Target (RoA)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solanezumab (Eli Lilly)</strong></td>
<td>P3 (EXPEDITION 3) P2/3 DIAN-TU</td>
<td>anti-(\beta) mAB, (IV)</td>
<td>Pre-specified secondary analysis of pooled data from EXPEDITION 1 and 2 from patients with mild AD showed a slowing of cognitive decline ((p=0.001)) compared with placebo (ADAS-Cog14) ((34%) reduction in decline). EXPEDITION 3 only in mild patients and amyloid confirmed by Amyvid PET or CSF. DIAN-TU in patients with autosomal-dominant AD mutation.</td>
</tr>
<tr>
<td><strong>Crenezumab (Genentech, Roche)</strong></td>
<td>P2 (NCT01998841; GN28352)</td>
<td>anti-(\beta) mAB, (IV, SC)</td>
<td>In past ADAS-Cog12 and CDRSOB P2 studies, a significant change was observed in ADAS-Cog12 for patients in the milder AD subgroup (MMSE 22-26) treated with high dose. Currently evaluating agent for prevention in cognitively healthy participants with genetic predisposition.</td>
</tr>
<tr>
<td><strong>Gantenerumab (Roche)</strong></td>
<td>P3 (Marguerite RoAD); P2/3 DIAN-TU</td>
<td>SC, IV fully-human monoclonal antibody</td>
<td>Marguerite RoAD is evaluating agent in mild patients, with ADAS-Cog13 and ADCS-ADL as primary endpoints. DIAN-TU in patients with genetic mutation - autosomal-dominant AD.</td>
</tr>
<tr>
<td><strong>BAN2401 (Eisai)</strong></td>
<td>P2 (NCT01767311)</td>
<td>anti-(\beta) mAB, (IV)</td>
<td>Selectively targets (\beta) protofibrils, a soluble aggregate of amyloid beta-peptide; enrolled patients with early AD.</td>
</tr>
</tbody>
</table>

### Others
- BACE inhibitors: (JNJ-548691,E2609)
- Combination strategies: Lily’s P1 anti-\(\beta\) (plaque) mAB (LY3002813) with \(\beta\)-secretase inhibitor (LY 2811376).
- Advancements in trial methodologies
- Biomarkers
- Companion diagnostics
- Symptomatic therapies
- New, more sensitive cognitive measures
Defined Health is pleased to present:

**CANCER PROGRESS**

27th Annual Cancer Progress Conference  
March 2016  
New York City  
www.cancerprogressbyDH.com

**THERAPEUTIC INSIGHT**

BioEurope Spring  
April 4 – 6, 2016  
Stockholm, Sweden  
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

- **What's Hot & What's Not in Gene Therapies for Rare Disorders** | May 6, 2015 | Webinar | http://dfndhlth.com/rare-disorders
- **Texas Life Science Forum** | May 20, 2015 | Houston, TX | http://dfndhlth.com/TLS-2015
- **ASCO** | May 29 - June 2, 2015 | Chicago, IL | http://dfndhlth.com/ASCO-2015
- **BioPharm America** | September 15 - 17, 2015 | Boston, MA | http://dfndhlth.com/BPA-2015