Biogen: A multi-faceted approach to Alzheimer's disease

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Discovery and Development
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Organize for Long-term Success

Focus areas

Specialty medicines
- Multiple Sclerosis
- Inflammatory Bowel Disease (IBD)

Neurodegeneration
- Alzheimer’s Disease
- Parkinson’s
- ALS
- Neuroimmunology

Rare diseases
- Hemophilia
- Spinal Muscular Atrophy (SMA)
- Neuropathic Pain
Neurology Disease Area Focus

Unmet Need

Core Competency

Validated Targets

Development Feasibility

Adjacencies
- Ophthalmology
- Neuropathic pain

MS
AD
PD
ALS
Drug Development: How to Increase Probability of Success

1. Clinical Observations, Genetics, Exploratory Research
2. Drug Discovery
3. Pharmacology, Early Clinical Development
4. Late Clinical Development
Alzheimer’s: An Opportunity to Change the Disease

• Terrible disease with modest treatment options
• ~7 year lifespan after diagnosis
• 6th leading cause of death (US)
• ~5.4M patients diagnosed (US); expected 13.8M by 2050#
• ~200k pts under age 65 (US)#
• Estimated $200B+ cost (US)#
• ~44M people affected worldwide*

**Biogen Alzheimer’s Disease R&D Strategy**

**Vision:** A global leader, establishing aducanumab as a foundational therapy and building a portfolio of differentiated complementary therapies

**Establish foundation**
- Advance aducanumab
- Enable more patients to access treatment
  - Prevention
  - Diagnosis

**Advance our programs**
- Support BAN2401 and E2609
- Implement biomarkers to enable clinical decisions

**Broaden impact**
- Advance Tau programs
- Investigate new MOAs

Continue to evaluate external opportunities
# Alzheimer’s Disease Development Efforts

<table>
<thead>
<tr>
<th>MOA</th>
<th>Discovery</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Filing</th>
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<tbody>
<tr>
<td>Aducanumab* (Anti-amyloid β mAb)</td>
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<td>BAN2401† (Anti-amyloid β mAb)</td>
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<td>E2609† (BACE inhibitor)</td>
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<td>BIIB076* (Anti-Tau mAb)</td>
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<td>BIIB080‡ (Tau ASO)</td>
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<td>Additional MOAs</td>
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* Collaboration programs with Neurimmune
† Collaboration programs with Eisai
‡ Collaboration program with IONIS
Key Evidence that β-amyloid Dysregulation is Central to Disease

Human Genetics
Dominantly inherited (APP, PS1, PS2) involved in processing of amyloid

Pathology
Pathological hallmarks
Amyloid-β (Aβ) plaques

Proof of Concept
Emerging clinical signals
(aducanumab, solanezumab, crenezumab)

APP: amyloid precursor protein; PS1/PS2: presenilin-1/presenilin-2
Potential to Disrupt the Disease Cascade

- Soluble Aβ40
- Aβ peptide
- Aβ42
- Aducanumab*
- BAN2401*
- E2609*
- tau agents
- tau tangles
- cytotoxicity
- synaptic impairment
- dementia

* Collaboration program
Alzheimer’s Starts Many Years Prior to Onset of Symptoms

Biomarkers – Enabling our Pipeline

Use of biomarkers in Alzheimer’s:

- In early clinical studies, to demonstrate *target engagement*
- To select *the right patients*
- To demonstrate *effect on disease* pathophysiology
Aducanumab Drug Development
Phase Ib Interim Results: Primary endpoint, safety

- ARIA-E was the main safety and tolerability finding
- Dose and ApoE ε4 carriage dependent
- Majority of events are asymptomatic. Symptoms, when present
  - Mostly rated as mild to moderate
  - Generally transient and self-resolving
  - Include headache, confusion, visual disturbances
- Monitorable and Manageable
  - 56% of subjects who develop ARIA-E able to resume dosing without ARIA-E recurrence
Phase Ib Interim Results: Secondary endpoint, amyloid PET Imaging

**Phase Ib Interim Results: Secondary endpoint, amyloid PET Imaging**

- **Secondary endpoint, amyloid PET Imaging**
  - Composite SUVR
  - Adjusted mean change from baseline

- **Aducanumab (mg/kg)**
  - Placebo (n=30)
  - 1 (n=21)
  - 3 (n=26)
  - 6 (n=23)
  - 10 (n=27)

- **Aducanumab (mg/kg)**
  - Placebo (n=34)
  - 1 (n=26)
  - 3 (n=27)
  - 6 (n=27)
  - 10 (n=27)

**Week 26**
- **P<0.01; ***P<0.001** vs placebo

**Week 54**
- *******

Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter. 1. Ostrowitzki et al. Arch Neurol 2012; 2. Clark et al. Lancet Neurol 2012
Phase Ib Interim Results: Exploratory endpoint, CDR-sb

CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.
Phase Ib Interim Results: Exploratory endpoint, MMSE

MMSE is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized subjects who received at least one dose of study medication and had at least one post-baseline questionnaire assessment.
Aducanumab Ph1b Interim Results Indicate

- Statistically significant, dose- and time-dependent amyloid plaque reduction at 6 months and 1 year
- Statistically significant, dose-dependent slowing of decline on MMSE and CDR-SB at 1 year
- ARIA-E was the main safety/tolerability finding

ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MMSE, Mini-Mental State Examination
Selecting a Phase 3 Early AD Population based on a Ph1b subpopulation

- We selected a subpopulation from PRIME for the Phase 3 study: Early AD population

<table>
<thead>
<tr>
<th>Phase 3 Early AD Population</th>
<th>PRIME Subpopulation</th>
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<tr>
<td>CDR Global Score 0.5</td>
<td>✓</td>
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<tr>
<td>MMSE score ≥24</td>
<td>✓</td>
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<tr>
<td>RBANS score ≤85</td>
<td>✓</td>
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<tr>
<td>CDR memory domain score ≥0.5</td>
<td>✓</td>
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<tr>
<td>Positive amyloid PET scan (visual read)</td>
<td>✓</td>
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- Of 165 patients randomized and dosed in PRIME, 92 met the Phase 3 criteria for Early AD: 26 with mild AD and 66 with prodromal AD

MCI, mild cognitive impairment; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.
Amyloid Plaque Reduction with Aducanumab in the Early AD Subpopulation: Post-hoc Analysis

Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.
# Aducanumab Phase 3 Overview

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<th>Phase 3 Design</th>
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<td><strong>Studies</strong></td>
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<td><strong>Population</strong></td>
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<td><strong>ApoE ε4 genotype</strong></td>
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<td><strong>Dosing</strong></td>
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<td><strong>Duration</strong></td>
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<td><strong>Primary endpoint</strong></td>
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<td><strong>Other key endpoints</strong></td>
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<td><strong>Sample size</strong></td>
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ADAS-Cog 13, Alzheimer’s Disease Assessment Scale-Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer’s Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); ASL-MRI, arterial spin labelling MRI; fMRI, functional MRI; MCI, mild cognitive impairment; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; vMRI, volumetric MRI
Alzheimer’s Disease is a Continuum Starting Prior to Symptoms

10-15%\(^\text{I}\) Conversion/year

Amyloid positive, cognition normal

At risk Population

Subjective memory decline

MCI due to AD / Prodromal

Cognitive and functional decline fulfilling dementia

Early AD

27%* of over 65’s - US at risk population

~13M

~8%\(^\#\) of over 65’s - US amnestic MCI pop.

~3.8M

5.3 M - Diagnosed with Alzheimer’s disease in the US

Mild

~1.4M

Moderate

~1.6M

Severe

~2.3M


# Challenges for a Disease-modifying Therapy in Early Alzheimer’s Disease

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<tr>
<th>Patient journey</th>
<th>Primary areas of concern that could limit access and uptake if unaddressed</th>
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| **Screening**   | Social stigma  
Lack of early disease acceptance due to perceived poor outcomes and caregiver burden | Payor concerns  
Large patient population creates new direct costs and lack of consensus on determining value |
|                 | Limited capacity  
- Brain imaging  
- Infusion  
- AD-focused HCPs  
- Education of PCPs | Few technology solutions  
Need for development and standardization of imaging tools or biomarkers for identification, response or safety |
|                 | Lack of alignment on measures  
Lack of consensus on measures for diagnosis, patient population, clinical response or treatment goals |
| **Diagnosis**   | ✔️ | ✔️ | ✔️ | ✔️ | ✔️ |
| **Treatment**   | ✔️ | ✔️ | ✔️ | ✔️ | ✔️ |
| **Follow up and monitoring** | ✔️ | ✔️ | ✔️ | ✔️ | ✔️ |
Alzheimer’s Disease at Biogen

• Multi-pronged portfolio approach with amyloid and tau
• Aducanumab demonstrated proof of biology and concept in Ph1b & has now begun enrolling subjects with early AD in two pivotal Phase 3 studies (ENGAGE & EMERGE)
• Aducanumab has the potential to fundamentally change treatment paradigm of AD by slowing the course of the disease
• We recognize the challenges of this disease area and are organizing to address and prepare for them