Forward-looking statements

This presentation and the discussions during this conference call contain forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our strategy and plans; potential of, and expectations for, our commercial business and pipeline programs; capital allocation and investment strategy; clinical development programs, clinical trials, and data readouts and presentations; risks and uncertainties associated with drug development and commercialization; regulatory discussions, submissions, filings, and approvals and the timing thereof; the potential benefits, safety, and efficacy of our and our collaboration partners’ products and investigational therapies; the anticipated benefits and potential of investments, collaborations, and business development activities; our future financial and operating results; 2021 financial guidance; plans relating to share repurchases. These forward-looking statements may be accompanied by such words as “aim,” “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “plan,” “potential,” “possible,” “prospect,” “will,” “would,” and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs will result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our dependence on sales from our products; uncertainty of long-term success in developing, licensing, or acquiring other product candidates or additional indications for existing products; failure to compete effectively due to significant product competition in the markets for our products; failure to successfully execute or realize the anticipated benefits of our strategic and growth initiatives; difficulties in obtaining and maintaining adequate coverage, pricing, and reimbursement for our products; our dependence on collaborators, joint venture partners, and other third parties for the development, regulatory approval, and commercialization of products and other aspects of our business, which are outside of our full control; risks associated with current and potential future healthcare reforms; risks related to commercialization of biosimilars; failure to obtain, protect, and enforce our data, intellectual property, and other proprietary rights and the risks and uncertainties relating to intellectual property claims and challenges; the risk that positive results in a clinical trial may not be replicated in subsequent or confirmatory trials or success in early stage clinical trials may not be predictive of results in later stage or large scale clinical trials or trials in other potential indications; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events, restrictions on use with our products, or product liability claims; risks relating to the distribution and sale by third parties of counterfeit or unfit versions of our products; risks relating to the use of social media for our business; risks relating to technology failures or breaches; risks relating to management and key personnel changes, including attracting and retaining key personnel; failure to comply with legal and regulatory requirements; the risks of doing business internationally, including currency exchange rate fluctuations; risks relating to investment in our manufacturing capacity; problems with our manufacturing processes; fluctuations in our effective tax rate; the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations, and financial condition; fluctuations in our operating results; risks related to investment in properties; the market, interest, and credit risks associated with our investment portfolio; risks relating to share repurchase programs; risks relating to access to capital and credit markets; risks related to indebtedness; change in control provisions in certain of our collaboration agreements; environmental risks; and any other risks and uncertainties that are described in other reports we have filed with the U.S. Securities and Exchange Commission (SEC).

These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.
Investor R&D Day Agenda

- **Introduction**
  - Michael Hencke
  - Investor Relations

- **Opening Remarks**
  - Michel Vounatsos
  - Chief Executive Officer

- **Biogen R&D Strategy**
  - Alfred Sandrock, Jr., M.D., Ph.D.
  - Head of Research & Development

- **A Leading Alzheimer’s Disease Clinical Portfolio**
  - Samantha Budd Haeberlein, Ph.D.
  - Head of Neurodegeneration Development
  - Lynn Kramer, M.D.
  - Chief Clinical Officer, Neurology Business Group at Eisai Co., Ltd.

- **New Innovations for Neuropsychiatric Diseases**
  - Mona Kotecha, M.D.
  - Senior Medical Director
  - Jim Doherty, Ph.D.
  - Chief Research Officer, Sage Therapeutics

- **Building an ALS Portfolio**
  - Toby Ferguson, M.D., Ph.D.
  - Head of Neuromuscular Development

- **Novel Therapeutic Approaches for Stroke**
  - Josh Bell, M.D., Ph.D.
  - Medical Director

- **Advancing a Late-stage Lupus Pipeline**
  - Nathalie Franchimont, M.D., Ph.D.
  - Head of MS & Immunology Development

- **Closing Remarks**
  - Alfred Sandrock, Jr., M.D., Ph.D.
  - Head of Research & Development
<table>
<thead>
<tr>
<th>Topic</th>
<th>Head/Principal</th>
</tr>
</thead>
</table>
| Research: Building the Pipeline of the Future | Chris Henderson, Ph.D.  
Head of Research |
| Alzheimer’s Disease Research Portfolio | Dominic Walsh, Ph.D.  
Head of the Neurodegeneration Research Unit |
| MS Portfolio                  | Jerome Hanna, MB BCh  
Senior Medical Director |
| Human Genetics                | Sally John, Ph.D.  
Head of Translational Biology |
| Biogen Gene Therapy           | Junghae Suh, Ph.D.  
Head of Gene Therapy Accelerator Unit |
| Biomarkers                    | John Beaver, Ph.D.  
Head of Biomarkers |
| Biogen Digital Health (BDH)   | Martin Dubuc  
Head of Biogen Digital Health |
| Movement Disorders at Biogen  | Tien Dam, M.D.  
Head of Movement Disorders |
| Biotherapeutics and Medicinal Sciences at Biogen | Anabella Villalobos, Ph.D.  
Head of Biotherapeutic and Medicinal Sciences |
| Biogen Digital Health Sciences | Shibeshih Belachew, M.D., Ph.D.  
Head of Biogen Digital Health Sciences |
| Biogen Digital Health External Innovation & Alliances | James Williams, Ph.D.  
Head of Biogen Digital Health External Innovation & Alliances |
| Carole Ho, M.D.               | Chief Medical Officer & Head of Development, Denali Therapeutics |
Opening Remarks

Michel Vounatsos
Chief Executive Officer
Tremendous unmet needs impacting millions of patients

Alzheimer's Disease
- #1 neurodegenerative disease
- > 30M patients worldwide

Amyotrophic Lateral Sclerosis
- < 5 years average life expectancy

Parkinson's Disease
- #2 neurodegenerative disease
- ~10M patients worldwide

Multiple Sclerosis
- >1M treated patients, but no ability to completely halt or reverse disease progression

Neuropsychiatry
- ~260M depression patients worldwide
- >700,000 suicides annually

Neuropathic Pain
- 5–10% of adults have chronic pain with neuropathic features

Lupus
- ~4M people with SLE and ~2M with CLE worldwide; disproportionately impacts people of color

Neurodevelopmental Disorders
- Orphan diseases with no treatment and lifetime disability

Spinal Muscular Atrophy
- A leading genetic cause of infant mortality

Stroke
- 5th leading cause of death in the U.S.

Ophthalmology
- Up to 200,000 patients with inherited retinal disorder in the U.S.

Parkinson's Disease
- #2 neurodegenerative disease
- ~10M patients worldwide

Biosimilars
- Enabling and improving access to advanced care for >100 million of patients with auto-immune and ophthalmology disorders treatable with biologics

Source: Lancet Neurology, 2017; World Health Organization; The ALS Association; American Heart Association; Biogen, data on file.
Biogen data on file; SLE = systemic lupus erythematosus; CLE = cutaneous lupus erythematosus
Key highlights

1. Neuroscience is an area with significant unmet needs, representing a compelling value creation opportunity

2. Biogen is the leader in neuroscience with a robust and diversified portfolio across disease areas and therapeutic modalities

3. The science is breaking, potentially de-risking neuroscience and providing an opportunity for early and targeted treatments towards prevention

4. Biogen’s strong talent and specialized expertise in neuroscience enable us to leverage the interconnectivity and shared biology across diseases

5. Biogen's pipeline has matured with multiple near and mid-term opportunities to deliver new therapies
Neuroscience is at an inflection point

Biomarker Advances
Global market for neurological biomarkers is projected to nearly double by mid-2020s

Clinical Development Productivity
~30% projected relative increase in Neurology clinical development productivity (2018-2023)

Targeted Therapeutics
~1,700 neurological monogenic diseases present a significant opportunity for genetically targeted modalities

Capital Inflows
2020: Record-breaking funding (~$7.5B) and upfront partnering (~$4B) payments in Neuro

Pre-screened Patient Pools
Improved patient segmentation via 'omics gives potential to precision medicine in complex neurological disorders

Delivery Technologies
Advance of blood brain barrier crossing technologies increases ability to direct drug to target in CNS

Digital / Data
Generation of massive clinical datasets with AI technologies unlocking deeper insights with greater efficiency

Biogen is a pioneer in neuroscience

Patient focus

World-class talent & expertise with pioneering mindset

Shared biology & interconnectivity across disease states

Multi-target, multi-modality approach

Multiple Sclerosis
Alzheimer's Disease
Spinal Muscular Atrophy
Biogen Digital Health
Leading in neuroscience with a robust and diversified portfolio

Progress since 2017

33 Clinical programs

25 New clinical programs

12 Programs in Phase 3 or filed, including aducanumab in E.U. and Japan

27 Business development deals

MS and Neuroimmunology

Alzheimer’s Disease and Dementia

Neuromuscular Disorders including SMA and ALS

Parkinson’s disease and movement disorders

Ophthalmology

Neuropsychiatry

Immunology

Neurovascular

Neuropathic Pain

Biosimilars

MS = multiple sclerosis; SMA = spinal muscular atrophy; ALS = amyotrophic lateral sclerosis
## 2021 - a transformational year with multiple milestones

### Life-Cycle Management
- Positive Phase 3b NOVA study for six-week dosing with natalizumab IV
- TYSABRI™ subcutaneous administration approved in the EU
- PLEGRIDY™ intramuscular administration approved in the US
- TECFIDERA approved in China
- Initiated RESPOND trial evaluating benefits of SPINRAZA™ in patients treated with ZOLGENSMA®
- Initiated ASCEND trial evaluating benefit of higher-dose SPINRAZA™ in patients treated with EVRYSDI®
- TYSABRI™ subcutaneous administration not approved in US

### Regulatory
- ADUHELM (aducanumab) approved in the U.S. for Alzheimer’s
- BYOOVIZ™, a biosimilar candidate referencing Lucentis® (ranibizumab), approved in US and EU
- Positive CHMP opinion for VUMERITY in the EU

### Phase 3
- Positive Phase 3 study of zuranolone in major depressive disorder
- Positive Phase 3 study of BAT1806, a proposed biosimilar referencing ACTEMRA®/RoACTEMRA® (tocilizumab)
- Initiated Phase 3 study of BIIB059 in Systemic Lupus Erythematosus
- Phase 3 BIIB111/AAV2-REP1 in Choroideremia – primary endpoint not met
- Expected Phase 3 Readout in Q4 2021 - zuranolone in MDD (CORAL)
- Expected Phase 3 Readout in fall 2021 - tofersen in SOD-1 ALS (VALOR)

### Phase 2
- Positive Phase 2 study of BIIB131 (TMS-007) in acute ischemic stroke - Asset acquired from TMS
- Positive Phase 2 study of BIIB124 (SAGE-324) in essential tremor
- Phase 2 readout of vixotrigine in small fiber neuropathy
- Phase 2/3 BIIB112 in X-linked retinitis pigmentosa – primary endpoint not met
- Phase 2 study of gosuranemab in Alzheimer’s – primary endpoint not met
- Phase 2 study of cinpanemab (BIIB054) in Parkinson’s - primary endpoint net met

### Phase 1
- Phase 1b study of BIIB080 in Alzheimer’s disease
- 2 additional potential study initiations expected in 2021

### Preclinical
- 3 research to development transitions
- 4 additional potential transitions anticipated in 2021
Continuing to build a multi-franchise portfolio

Expected 2021 Data Readout

- **TODAY**
  - Alzheimer’s
  - SMA
  - Multiple Sclerosis
  - Biologics

- **EARLY-MID 2020s**
  - Essential Tremor
  - Lupus
  - Stroke
  - Depression
  - Alzheimer’s
  - Neuromuscular (SMA + ALS)
  - Multiple Sclerosis
  - Biologics

- **OUR VISION**
  - Ophthalmology
  - Neuropathic Pain
  - Movement Disorders
  - Immunology
  - Neurovascular
  - Neuropsychiatry
  - Dementia
  - Neuromuscular
  - Multiple Sclerosis
  - Biologics

Expected 2021 Data Readout
6 key readouts expected by end of 2022 across a diversified neuroscience portfolio

<table>
<thead>
<tr>
<th>Pivotal Readouts</th>
<th>Data Readout</th>
<th>Expected By</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD1-ALS</td>
<td>Phase 3 data for tofersen</td>
<td>Fall 2021</td>
</tr>
<tr>
<td>MDD</td>
<td>Phase 3 data for zuranolone*</td>
<td>Late 2021#</td>
</tr>
<tr>
<td>PPD</td>
<td>Phase 3 data for zuranolone*</td>
<td>Mid-2022</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>Phase 3 data for lecanemab*</td>
<td>H2 2022</td>
</tr>
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<thead>
<tr>
<th>Proof-of-concept Readouts</th>
<th>Data Readout</th>
<th>Expected By</th>
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<tbody>
<tr>
<td>CIAS</td>
<td>Phase 2 data for BIIB104</td>
<td>Mid-2022</td>
</tr>
<tr>
<td>C9orf72-ALS</td>
<td>Phase 1 data for BIIB078*</td>
<td>H1 2022</td>
</tr>
</tbody>
</table>

* Collaboration program; # Data from the CORAL Study for rapid response therapy in MDD when co-initiated with standard antidepressant therapy; ALS = amyotrophic lateral sclerosis; MDD = major depressive disorder; PPD = postpartum depression; CIAS = cognitive impairment associated with schizophrenia.
Biogen R&D Strategy

Alfred Sandrock, M.D., Ph.D.
Head of R&D

R&D Day
September 21, 2021
Why neuroscience? Why now?

There is no greater unmet need

The time is ripe for advances

Disease Understanding
New Modalities
Improved Measurement
Patient Selection
Enhanced Regulatory Science
How we mitigate the risk of neuroscience drug development

**THE WHAT**

Choosing the right discovery & development programs

**THE HOW**

Improving the drug development methodology
Choosing the right discovery / development programs:

THE WHAT

Serious, life threatening
Incidence / Prevalence
Treatment Availability

Human Genetics
Molecular Pathophysiology
Clinical Observations
Clinical Trial Data

Unmet Need
Core Competency
Target Validation
Development Feasibility

Molecular Pathophysiology
Modality
Pharmacology
Clinical Development
Biomarkers Development
Partnership Excellence

Drug Development Tools
(e.g., Biomarkers, Digital Devices)
Clinical Measurement
Regulatory Science
## Multiple strategic partnerships and M&A to bolster our portfolio and capabilities

**Marketed assets**
- **IONIS**
  - SMA
- **Alkermes**
  - Multiple Sclerosis
- **Eisai**
  - Alzheimer’s Disease
- **neurimmune**
  - Alzheimer’s Disease
- **SAMSUNG BIOEPIS**
  - Biosimilars – Immunology
- **Genentech**
  - Immunology and Oncology

**Clinical programs**

<table>
<thead>
<tr>
<th>Company</th>
<th>Disease Area</th>
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<tbody>
<tr>
<td><strong>IONIS</strong></td>
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<tr>
<td><strong>Eisai</strong></td>
<td>Alzheimer’s Disease</td>
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<tr>
<td><strong>neurimmune</strong></td>
<td>Multiple Sclerosis</td>
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<tr>
<td><strong>SAMSUNG BIOEPIS</strong></td>
<td>Biosimilars – Ophthalmology</td>
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<tr>
<td><strong>Genentech</strong></td>
<td>Multiple disease areas</td>
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<td><strong>IONIS</strong></td>
<td>Ophthalmology</td>
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<tr>
<td><strong>neurimmune</strong></td>
<td>Neuropathic Pain</td>
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</table>

**Preclinical programs**

<table>
<thead>
<tr>
<th>Program</th>
<th>Disease Area</th>
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<tbody>
<tr>
<td>Neuromuscular (SMA), Multiple Sclerosis</td>
<td>Alzheimer’s Disease, Parkinson’s Disease, Neuromuscular, other indications</td>
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<tr>
<td>Neurological diseases</td>
<td>Neuromuscular (SMA)</td>
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<tr>
<td>Huntington’s Disease</td>
<td>Huntington’s Disease</td>
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<td>Ophthalmology</td>
<td>Ophthalmology</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>Multiple disease areas</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Enhanced AAV production for GT manufacturing</td>
</tr>
</tbody>
</table>

**Platform capabilities**
- **mirNA scaffolds**
- **CRISPR / Cas – gene editing cargo tech**
- **High yield producer cell lines for GT manufacturing**
- **Novel AAV capsids**
- **Enhanced AAV production for GT manufacturing**

*Not an exhaustive list*
Includes strategic partnerships and M&A executed between 1995 – August 2021
Improving the drug development methodology

THE HOW

How we used to do it

Biology → Drug → Disease

“Efficacy” in an “animal model”

Drug → Disease

“Translation”

Drug → Disease

In Humans
Improving the drug development methodology

THE HOW

Biogen’s approach

Diagram:
- Drug (1)
- Biology (2)
- Disease (3)
- Biogen’s approach cycle (4)
The example of aducanumab in Alzheimer’s disease

“Reverse Translational Medicine” (Neurimmune, Inc.)

1. Human Genetics
2. Human Pathology
3. Longitudinal Observations (Imaging, biomarkers)

Aducanumab

Amyloid Hypothesis

Alzheimer’s Disease

Tg2576 transgenic mouse studies
Amyloid PET imaging in humans
Study 103

CDR-sb, MMSE, ADAS-Cog13, ADCS-ADL-MCI
Studies 103, 301, 302

Studies 103, 301, 302
World class expertise

Biotherapeutics & Medicinal Sciences | Anabella Villalobos, PhD, Head of Biotherapeutic and Medicinal Sciences | On Demand

Gene Therapy | Junghae Suh, PhD, Head of Gene Therapy Accelerator Unit | On Demand

Research at Biogen | Chris Henderson, PhD, Head of Research | On Demand

Alzheimer’s Disease Research | Dominic Walsh, PhD, Head of the Neurodegeneration Research Unit | On Demand

Human Genetics | Sally John, PhD, Head of Translational Biology | On Demand
World class expertise

Drug Biology Disease

Biomarkers | John Beaver, PhD | Head of Biomarkers | On Demand
Biogen Digital Health | Martin Dubuc, Head of Biogen Digital Health | On Demand

Alzheimer’s Disease | Samantha Budd Haeberlein, PhD, Head of Neurodegeneration Development Unit and Lynn Kramer, MD, Chief Clinical Officer at Eisai | Live
Neuropsychiatry | Mona Kotecha, MD, Sr. Medical Director and Jim Doherty, PhD, Chief Research Officer at Sage Therapeutics | Live
ALS | Toby Ferguson, MD, Head of Neuromuscular Development Unit | Live
Stroke | Josh Bell, MD, PhD, Medical Director | Live
Lupus | Nathalie Franchimont, MD, PhD, Head of MS and Immunology Development Unit | Live
Movement Disorders | Tien Dam, MD, Senior Medical Director and Carole Ho, MD, Chief Medical Officer at Denali Therapeutics | On Demand
Multiple Sclerosis | Jerome Hanna, MD, Senior Medical Development | On Demand
Recruiting top talent to drive the discovery & development process

**THE WHO**

**Recent recruits:**

**From Academia:**
- Kip Connor, PhD, MEEI
- Rick Livesey, MD, PhD, UCL
- Junghae Suh, PhD, Baylor
- Dominic Walsh, PhD, Harvard

**From Industry:**
- Stuart Bailey, D.Phil, Novartis
- Siân Smethurst, PhD, Pfizer
- Sophie Parmentier-Batteur, PharmD, PhD, Merck
- Diane Rocco, MSc, MBA, Pfizer
Biogen’s four pillared R&D strategy

The What

The How

The Focus

The People
Future of therapeutics in neurology: Targeted therapies

Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference

Future of therapeutics in neurology: Treating before symptoms

Genetics + Precision Phenotyping → Prevention

- We envision a world where most diseases of the nervous system will be preventable
- We will move from treating patients to treating people
Biogen is building unparalleled R&D capabilities to help shape the future of therapeutics in neurology

Molecular pathophysiology of disease, enabled by human genetics

Multiple modalities

Novel drug development tools

Improved measurements

Targeted therapeutics

Enable disease prevention
A Leading Alzheimer's Disease Clinical Portfolio

Samantha Budd Haeberlein, Ph.D., Head of the Neurodegeneration Development Unit

Lynn Kramer, M.D., Chief Clinical Officer, Neurology Business Group at Eisai Co., Ltd.

R&D Day
September 21, 2021
Alzheimer’s disease clinical portfolio

Anti-Abeta Antibodies – Aducanumab and Lecanemab

- Reduce amyloid beta plaque significantly by 18 months
- Reduction in amyloid beta plaque is associated with a reduction in clinical decline
- Lecanemab off treatment / return to treatment data:
  - Initiation of treatment later in disease, patients do not catch up clinically
  - Amyloid beta plaque, once lowered, was stable for approximately 2 years off treatment
  - Blood biomarker data suggests disease biology starts to rebound after stopping at 18 months
- Additional data needed to inform optimal duration of treatment

Tau mechanisms

- So far, extracellular Anti-Tau antibodies have not impacted pathology or disease progression
- Lowering of Tau protein, which is designed to reduce all forms of toxic tau, has been achieved in Alzheimer’s disease patients with BIIB080

Biogen has capabilities, experience and a rich portfolio as we work to address Alzheimer’s disease
## Biogen has an industry leading Alzheimer’s disease portfolio

<table>
<thead>
<tr>
<th>Target</th>
<th>Program</th>
<th>Modality</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<td>Amyloid-β</td>
<td>Aducanumab (ADUHELM™)*</td>
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<td>Lecanemab/BAN2401*</td>
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<td>ATV-Amyloid-β**</td>
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<tr>
<td>Tau</td>
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<td>AAV-ZFP-MAPT^</td>
<td>GTx</td>
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</tbody>
</table>

*collaboration with Eisai  
**collaboration with Denali  
#collaboration with Ionis  
##collaboration with Neurimmune  
^collaboration with Sangamo
The two pathological hallmarks of Alzheimer’s disease in the brain are β-amyloid plaques and neurofibrillar tangles.

1) Amyloid beta peptides are released extraneuronally as monomers.

2) Aggregation of Aβ

3) Intraneuronal tau phosphorylation and aggregation

4) Synaptic dysfunction, inflammation and neuronal death

Aβ = amyloid beta; APP = amyloid precursor protein
**1st generation Anti-amyloid agents did not lower amyloid beta plaque**

**Bapineuzumab**

**Amyloid-β ^11^C-PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials**

*Neurology 2015;85:692-700.*

**Crenezumab**

**Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE)**

Stephen Lipton a, b, c, Lee A. Varghese a, b, c, William Choi d, Michael Knopf a, c, Michael LeWitter e, Patrick S. Brown a, b, c, Josephine Grunwald d, Jason Chau e, tropical and Mediterranean e, Janice Rotenberg e, Andrew S. Schmidt e, Eric A. Haughey e, Andrew C. Grady e, Steve M. Sherrill e, and Myron Fuld e

**Solaneuzumab**

**Phase 3 solaneuzumab trials: Secondary outcomes in mild Alzheimer’s disease patients**

Eric S. Siemers a, b, c, Karen L. Sendel d, Christopher Carlson e, Michael Casey e, Gopal N. Sehgal e, Hong Liu-Seifert e, Sherie A. Dowsett e, Michael J. Ponce-corvo e, Robert A. Dean f, Ronald Demattos e

*US Life and Company, Indianapolis, IN, USA; 2*nd BiogenIdec, Philadelphia, PA, USA

**Alzheimer’s & Dementia 2016; 12:110-120**

**Trials also studied patients at later stages of Alzheimer’s disease & included individuals without evidence of Aβ pathology (i.e., patients without Alzheimer’s disease)**
Alzheimer’s disease has a continuously progressive underlying pathophysiology

Biogen’s portfolio focuses on therapies for stages 3 & 4 with potential to expand to earlier and later stages

- Amyloid-β deposition increases throughout the pre-clinical stage and precedes clinical symptoms by decades [Vermunt 2019]

- Subsequent markers of tau pathology and neurodegeneration, which closely correlate with cognitive impairment, increase continuously throughout disease progression [Villemagne 2013]

- Symptomatic Alzheimer’s disease represents the latter stage of a larger disease continuum, reflective of continuous pathophysiologic processes [Bateman 2012]

- Early clinical signs correspond to an already advanced pathologic disease state [Villemagne 2013]
Biogen continues to build a robust portfolio and capabilities aimed at treating Alzheimer’s disease

Accelerate clinical development optimizing the use of BIOMARKERS (blood, digital, imaging)

Maximize the potential of the clinical portfolio through acceleration of TAU PROGRAMS and COMBINATION/ADD-ON approaches

Increase understanding of Alzheimer’s disease PATHOPHYSIOLOGY and ATN biomarker profile in humans to inform future treatment paradigm

Ensure sustainability of the research portfolio maximizing the MULTIMODALITY/MULTITARGET approach

Strategic imperatives to advance Biogen’s portfolio and R&D capabilities
Aducanumab (ADUHELM™) anti-amyloid monoclonal antibody

ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer’s disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).
**Aducanumab: Mechanism of action and binding selectivity**

### β-Amyloid Aggregation Pathway

- **Monomer** → **Oligomer** → **Protofibril** → **Fibril**

- **Formation of oligomers on the fibril surface** (“Secondary Nucleation”)

- **Binding of Aducanumab to fibrils** interferes with aggregation process and reduces formation of neurotoxic Aβ oligomers [Linse 2020]

- Shallow and compact epitope of Aducanumab contributes to its selectivity for Aβ aggregates [Arndt 2018]

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Aducanumab: Reduction in amyloid beta plaque in a dose- and time-dependent manner

Table 4: Biomarker Results of ADUHELM in Study 1

<table>
<thead>
<tr>
<th>Biomarker Endpoint at Week 78</th>
<th>ADUHELM High dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Beta PET Composite SUVR</td>
<td>N=170</td>
<td>N=159</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>1.383</td>
<td>1.375</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.264</td>
<td>0.014</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-0.278, p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Amyloid Beta PET Centiloid</td>
<td>N=170</td>
<td>N=159</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>85.3</td>
<td>83.5</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td>-60.5 (-71%)</td>
<td>3.4</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-64.3, p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*P-values were not statistically controlled for multiple comparisons.

Table 5: Biomarker Results of ADUHELM in Study 2

<table>
<thead>
<tr>
<th>Biomarker Endpoint at Week 78</th>
<th>ADUHELM High dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Beta PET Composite SUVR</td>
<td>N=183</td>
<td>N=204</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>1.497</td>
<td>1.376</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.235</td>
<td>-0.003</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-0.232, p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Amyloid Beta PET Centiloid</td>
<td>N=183</td>
<td>N=204</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>90.8</td>
<td>83.8</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td>-54.0 (-59%)</td>
<td>-0.5</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-53.5, p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*P-values were not statistically controlled for multiple comparisons.

Table 6: Biomarker Results of ADUHELM in Study 3

<table>
<thead>
<tr>
<th>Biomarker Endpoint at Week 54</th>
<th>ADUHELM 10 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Beta PET Composite SUVR</td>
<td>N=28</td>
<td>N=42</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>1.44</td>
<td>1.44</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.263</td>
<td>0.014</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-0.277, p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Amyloid Beta PET Centiloid</td>
<td>N=28</td>
<td>N=42</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>94.5</td>
<td>96.5</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td>-58.0 (-61%)</td>
<td>-61.1, p&lt;0.0001</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-53.5, p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*P-values were not statistically controlled for multiple comparisons.

US Prescribing Information, 2021
Aducanumab: Continued reduction in amyloid beta plaque

Among those dosed with ADUHELM during the placebo-controlled period in Study 3, amyloid beta plaque levels in the brain continued to decline in a time- and dose dependent manner in the long-term extension period through Week 222*.
Aducanumab: Clinical

**Table 5: Clinical Results of ADUHELM in Study 1**

<table>
<thead>
<tr>
<th>Clinical Endpoint at Week 78</th>
<th>ADUHELM High dose (N=547)</th>
<th>Placebo (N=548)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDR-SB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>2.51</td>
<td>2.47</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.55</td>
<td>1.74</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>-0.19 (-22%)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0120</td>
<td></td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>26.3</td>
<td>26.4</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.7</td>
<td>-3.3</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>0.6 (-18%)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0493</td>
<td></td>
</tr>
<tr>
<td><strong>ADAS-Cog 13</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>22.746</td>
<td>21.867</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>3.763</td>
<td>5.162</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>-1.400 (-27%)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0097</td>
<td></td>
</tr>
<tr>
<td><strong>ADCS-ADL-MCI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>42.5</td>
<td>42.6</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.5</td>
<td>-4.3</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>1.7 (-40%)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td><strong>NPI-10</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>4.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Difference from placebo (%)</td>
<td>-1.3 (-87%)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0215</td>
<td></td>
</tr>
</tbody>
</table>

*P-value was not statistically controlled for multiple comparisons.

**Emerge**

The primary efficacy endpoint was the change from baseline on the CDR-Sum of Boxes (CDR-SB) at Week 78. In Study 1, treatment with ADUHELM high dose demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.39 [-22%], p = 0.0120).

**Engage**

No statistically significant differences were observed between the ADUHELM-treated and placebo-treated patients on the primary efficacy endpoint, the change from baseline in CDR-SB score at 78 weeks.

**Prime**

Clinical assessments in Study 3 were exploratory. Results for clinical assessments were directionally aligned with the findings from Study 1, with less change from baseline in CDR-SB and MMSE scores at 1 year in the ADUHELM 10 mg/kg fixed-dose group than in patients on placebo (CDR-SB: -1.26, 95% CI [-2.356, -0.163]; MMSE: 1.9, 95% CI [0.06, 3.75]).
Aducanumab: Reduction in amyloid beta plaque and clinical decline

*Exposure-Response Relationships*

Model based exposure-response analyses for Studies 1 and 2 demonstrated that higher exposures to ADUHELM were associated with greater reduction in clinical decline on CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI.

In addition, higher exposures to ADUHELM were associated with greater reduction in amyloid beta plaque in Studies 1 and 2.

An association between reduction in amyloid beta plaque and clinical decline on CDR-SB was also observed.

Biogen Data on File, *US Prescribing Information, 2021
Aducanumab: Reduction in amyloid beta plaque and clinical decline – poster presented at AAIC (P57499)

Analysis of clinical decline by Aβ status at follow-up (Table 1)

A numerically smaller magnitude of decline across key clinical measures in all 3 studies was observed in participants in whom Aβ plaque levels were lowered to levels considered to be amyloid negative (SUVR ≤1.10) relative to those who did not reach this threshold (SUVR >1.10).

<table>
<thead>
<tr>
<th>Table 1. Clinical decline by Aβ PET status at follow-up in clinical studies of aducanumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 3 studies (by Aβ PET status at Week 78)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>CDR-SB, median/mean</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change at Week 50</td>
</tr>
<tr>
<td>Change at Week 78</td>
</tr>
<tr>
<td><strong>MMSE, median/mean</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change at Week 50</td>
</tr>
<tr>
<td>Change at Week 78</td>
</tr>
<tr>
<td><strong>ADAS-Cog 13, median/mean</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change at Week 50</td>
</tr>
<tr>
<td>Change at Week 78</td>
</tr>
<tr>
<td><strong>ADCS-ADL-MCI, median/mean</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change at Week 50</td>
</tr>
<tr>
<td>Change at Week 78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Phase 1b PRIME study (by Aβ PET status at Week 54)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>CDR-SB, median/mean</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change at Week 26</td>
</tr>
<tr>
<td>Change at Week 54</td>
</tr>
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<td><strong>MMSE, median/mean</strong></td>
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</tr>
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<td>Change at Week 54</td>
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</table>

Rajagovindan et al., Reductions in Biomarkers of Alzheimer’s Disease Pathophysiology Following Treatment With Aducanumab Were Associated With Slowing in Clinical Decline. Poster AAIC, 2021
Aducanumab: Safety

- The safety of ADUHELM has been evaluated in 3,078 patients who received at least one dose of ADUHELM.

- Adverse reactions that were reported in at least 2% of patients treated with ADUHELM and at least 2% more frequently than in patients on placebo:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADUHELM 10 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>ARIA-H microhemorrhage</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>ARIA-H superficial siderosis</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Fall</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Confusion/Delirium/Altered Mental Status/Disorientation</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
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<td>15</td>
<td>2</td>
</tr>
<tr>
<td><strong>Fall</strong></td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td><strong>Confusion/Delirium/Altered Mental Status/Disorientation</strong></td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

*Headache includes the adverse reaction related terms headache, head discomfort, migraine, migraine with aura, and occipital neuralgia.

*Diarrhea includes the adverse reaction related terms diarrhea and infectious diarrhea.

*Confusion/Delirium/Altered Mental Status/Disorientation includes the adverse reaction related terms confusional state, delirium, altered state of consciousness, disorientation, depressed level of consciousness, disturbance in attention, mental impairment, mental status changes, postoperative confusion, and somnolence.

US Prescribing Information, 2021
Aducanumab: ARIA

- In Emerge and Engage, ARIA (-E and/or -H) was observed in 41% of patients treated with ADUHELM with a planned dose of 10 mg/kg (454 out of 1105), compared to 10% of patients on placebo (111 out of 1087).

- ARIA-E was observed in 35% of patients treated with ADUHELM 10 mg/kg, compared to 3% of patients on placebo.

- The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) carriers than in ApoE ε4 non-carriers (42% and 20%, respectively).

- Clinical symptoms were present in 24% of patients treated with ADUHELM 10 mg/kg who had an observation of ARIA (-E and/or -H), compared to 5% of patients on placebo.

- The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time.
Aducanumab: What’s next

Confirmatory Trial (FDA requirement)

Study elements are under discussion based on:
- Insights from feasibility assessments (operational and KME consultations)
- New analyses pertinent to informing the study design
- Engagements with regulatory agencies (initially FDA, subsequently others)
- Other aducanumab program objectives/considerations

EMBARK Study

Phase 3b Open-Label, Multicenter, Safety Study of Aducanumab in Subjects With Alzheimer’s Disease Who Had Previously Participated in the Aducanumab Studies

To evaluate the long-term safety and tolerability of aducanumab after a wash-out period imposed by the discontinuation of the feeder studies in participants who had previously received aducanumab or placebo.

iCARE AD Study

International Collaboration for Real-World Evidence in Alzheimer’s Disease (ICARE AD) – A Prospective Real-World Observational Study of Aducanumab in Patients with Alzheimer’s Disease in the US
- Evaluate long-term clinical and quality of life outcomes in the real-world setting
- Provide insight into the health care resource utilization
- Assess long-term safety of aducanumab

Continue regulatory reviews and submissions

Subcutaneous formulation under development
BIIB080 (IONIS MAPT$_{Rx}$) MAPT (Tau protein) ASO
BIIB080 (IONIS MAPT$_{Rx}$) – Tau ASO reduction of Tau protein is applicable to multiple tauopathies

- BIIB080 reduces de novo production of all 6 human splice isoforms of tau, therefore should reduce all post-translationally modified forms of tau including aggregates and other toxic species
- Targets intracellular tau directly – reduces both intracellular and extracellular tau

**Ongoing trial:**
- Placebo-controlled multiple ascending dose study of lumbar intrathecal bolus (ITB) administration of BIIB080 in patients with mild Alzheimer’s disease
- Placebo-controlled period is complete, and the open-label long term extension (LTE) is ongoing
- All subjects (N=46) completed the treatment evaluation period
BIIB080 (IONIS MAPT<sub>Rx</sub>): the first clinical demonstration of antisense-mediated suppression of CSF tau protein in patients with Alzheimer’s disease

- BIIB080 treatment resulted in a time and dose-dependent reduction in the concentration of CSF t-tau and phospho-tau
- Mild and moderate AEs were reported in MAD Part 1 following ITB administrations of the BIIB080 every 4 or 12 weeks (total of 4 and 2 doses, respectively) to adults with mild Alzheimer’s disease
- Based on Phase 1 efficacy/safety, BIIB080 will be evaluated in Phase 2 for Alzheimer’s disease
Evaluation of Anti-amyloid add-on treatments to potentially further inhibit disease pathology

<table>
<thead>
<tr>
<th></th>
<th>1. Amyloid beta peptides are released extraneuronally as monomers</th>
<th>2. Aggregation of Aβ</th>
<th>3. Intraneuronal tau phosphorylation and aggregation</th>
<th>4. Synaptic dysfunction, inflammation and neuronal death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 Aβ Inhibition + Anti-Tau</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2 and 4 Aβ Inhibition + Anti-inflammatory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 Aβ Inhibition + Anti-Tau + Anti-inflammatory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aβ=amyloid beta; APP=amyloid precursor protein.
Lecanemab (BAN2401)  
anti-amyloid monoclonal antibody  

In collaboration with Eisai Co., Ltd.

Lynn Kramer, M.D.  
Chief Clinical Officer, Neurology Business Group at Eisai Co., Ltd.

The statements included in this presentation belong to Eisai and do not necessarily reflect those of Biogen or any other party.
Phase II Lecanemab (BAN2401) treatment suggests fast, deep and sustained clearance of Aβ plaques and acceptable tolerability

- No titration is required, allowing patients to receive the highest dose (10mg/kg biweekly) from the beginning of the treatment
- Aβ plaque reduction was observed at 3 months in Study 201-OLE (fast clearance). In both Study 201 Core and Study 201-OLE, brain amyloid was reduced to negative levels in ≥80% subjects* (deep clearance)
- Aβ plaque level differences from subjects who received placebo in Study 201 Core were maintained during Gap period

The incidence of ARIA-E was 0.8% in placebo arm and not more than 10% in any of the treatment arms in Study 201 Core

Approximately 60% of ARIA-E occurred within first 3 months of treatment and MRI findings were typically resolved within 4–12 weeks

For subjects who received 10mg/kg biweekly during 201 Core, the incidence of ARIA-E was 8.9%, consistent with the rate observed during the 201 Core study

Favorable safety profile in the highest dose

The incidence of ARIA-E was 9.9% for the group at the highest treatment dose (10mg/kg biweekly) in Study 201 Core

- The incidence of ARIA-E was 0.8% in placebo arm and not more than 10% in any of the treatment arms in Study 201 Core
- Approximately 60% of ARIA-E occurred within first 3 months of treatment and MRI findings were typically resolved within 4–12 weeks

Lecanemab is an investigational antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen

*Estimated from baseline value with a negative Composite SUVr threshold of 1.10
ARIA-E = amyloid-related imaging abnormality-edema; OLE = open label extension; SUVr = positron emission tomography standard uptake value ratio
New era of plasma biomarkers to potentially track disease progression and treatment effect with Lecanemab (BAN2401) in Phase II

**Plasma Aβ42/40 ratio demonstrates relationship to amyloid PET and disease progression**

- Increase in plasma Aβ42/40 ratio during lecanemab treatment correlated with PET SUVr and clinical outcomes during lecanemab treatment phases in Study 201 Core and Study 201-OLE while losing correlation in untreated Gap period
- Discontinuing treatment allows plasma Aβ42/40 ratio to start decreasing again, which is an early indicator of brain Aβ plaque accumulation and is associated with clinical decline observed after treatment discontinuation. These findings suggest that continued treatment may be beneficial for patients while still in the Early AD Stage
- These results suggest potential to use plasma Aβ42/40 ratio to monitor drug effects in individual subjects/patients

*Presented at The Alzheimer’s Association International Conference (AAIC) 2021. Oral presentation No.57780 and Poster presentation No.57760

**PET = positron emission tomography**
Phase II clinical effects of treatment interruption and long-term dosing to generate insights into optimal Lecanemab (BAN2401) regimen

New data\(^1\) on ADCOMS\(^2\) from Study 201-OLE suggested potential long-term clinical effect of continued treatment

- For subjects with early AD at Study 201-OLE baseline, while off-treatment during the gap in the treatment period, subjects who received 10 mg/kg biweekly of lecanemab administration in the Core phase continued to perform better than those who received placebo on ADCOMS. This may suggest a potential disease-modifying effect of lecanemab\(^3\). (Figure 1)

- Reduction in clinical decline relative to natural disease progression was seen in subjects who received placebo during the Core phase\(^4\) and were treated for the first time with lecanemab 10 mg/kg biweekly during the OLE phase, and in subjects who were treated with lecanemab 10mg/kg biweekly both during the Core phase\(^4\) and during the OLE phase (reference similar population from ADNI). This may support the concept of increased long-term clinical effect of continued treatment with lecanemab when initiated in the early AD stage\(^3\). (Figure 2)

1. Similar results were observed for Clinical Dementia Rating Sum of Boxes (CDR-SB) and Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); 2. Alzheimer’s Disease Composite Score. Evaluated between scores of 0.00~1.97. Higher scores suggests worsening of clinical decline; 3. The Alzheimer’s Association International Conference (AAIC) 2021 Oral presentation No.57780; 4. Subjects with early AD at the OLE baseline; 5. Partially modified based on the data presented at The Alzheimer’s Association International Conference (AAIC) 2021: Oral presentation No.57780; Subject number in Core: placebo/ADNI/ Core: 10mg/kg biweekly are Core baseline: 20/145/17, Core 3 months: 20/-/16, Core 6 months: 19/143/17, Core 9 months: 20/-/17, Core 12 months: 20/142/16, Core 18 months: 20/78/17, 3 months follow-up after Core: 20/-/16, Gap period (off lecanemab): -/139/-, OLE baseline: 20/-/17, OLE 6 months: 19/81/16, OLE 12 months: 19/-/14, OLE 18 months: 20/49/17; ADNI = Alzheimer’s Disease Neuroimaging Initiative

Figure 1. Study 201 Core ~ Gap period ADCOMS\(^3\)

Figure 2. Study 201-OLE ADCOMS\(^5\)
Lecanemab (BAN2401) Phase III Study design in early Alzheimer’s Disease (clarity AD)

**Clarity AD, 18-month Phase III study in early AD**

**Inclusion population:**
- Early AD (MCI or mild AD)
- Amyloid positive

**Treatments:** 1:1 randomization 10mg/kg biweekly vs. placebo

**Strata:**
- ApoE4 status (ApoE4 carriers or non-carriers)
- Clinical staging
- Concurrent AD Medication Use – presence or absence of ongoing approved AD treatment
- Geographical Region

**Enrollment:**
- 1,795 subjects randomized completed March 2021
- LPO expected September 2022
- Primary Endpoint: CDR:SB

**FDA granted Breakthrough Therapy designation (BTD) for lecanemab for the treatment of Alzheimer’s disease (AD) in June 2021**

Basis of BTD was recently published results of Phase IIb study (Study 201) in early AD (MCI due to AD and mild AD)

- Lecanemab showed consistent reduction of decline across several clinical and biomarker endpoints at the highest doses (10 mg/kg biweekly)
- Communication with the FDA to seek the most optimal regulatory pathway has been initiated
Lecanemab (BAN2401) Phase III Study design and preliminary screening data in preclinical Alzheimer’s Disease

AHEAD 3-45\(^1\) Phase III study in preclinical AD preliminary screening data\(^2\)

- Early results of PET eligibility across the two trials of AHEAD 3-45 Study are consistent with projections based on existing observational data (ADNI and HABS)
- Experience to date with screening and randomization suggests feasibility to identify participants across the continuum of preclinical Alzheimer’s disease i.e., those at-risk for amyloid accumulation and cognitive decline
- Approximately 80 sites have been activated globally, and over 100 participants were randomized.

Clinical study for subcutaneous formulation is under preparation

- SC formulation should increase convenience for the patients
- IND to be amended for development of subcutaneous formulation in Q2 with initiation of Phase I study to evaluate its pharmacodynamics and bioavailability in 2021
- Device for subcutaneous formulation is concurrently under development

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HABS = Harvard Aging Brain Study
Alzheimer’s disease clinical portfolio

Anti-Abeta Antibodies – Aducanumab and Lecanemab

- Reduce amyloid beta plaque significantly by 18 months
- Reduction in amyloid beta plaque is associated with a reduction in clinical decline
- Lecanemab off treatment / return to treatment data:
  - Initiation of treatment later in disease, patients do not catch up clinically
  - Amyloid beta plaque, once lowered, was stable for approximately 2 years off treatment
  - Blood biomarker data suggests disease biology starts to rebound after stopping at 18 months
- Additional data needed to inform optimal duration of treatment

Tau mechanisms

- So far, extracellular Anti-Tau antibodies have not impacted pathology or disease progression
- Lowering of Tau protein, which is designed to reduce all forms of toxic tau, has been achieved in Alzheimer’s disease patients with BIIB080

Biogen has capabilities, experience and a rich portfolio as we work to address Alzheimer’s disease
New Innovations for Neuropsychiatric Diseases

Mona Kotecha, M.D., Senior Medical Director, Biogen
Jim Doherty, Ph.D., Chief Research Officer, Sage Therapeutics

R&D Day
September 21, 2021
Biogen neuropsychiatry pipeline aims to address critical unmet needs in depression and schizophrenia

~284 million people worldwide suffer from depression or schizophrenia

~52 million US adults experience mental illness, and ~13 million, serious mental illness

Estimated 2017 global prevalence counts of mental disorders > 970 million people

Schizophrenia and depressive disorders account for >55 million years lived with disability (a measure of overall impact of illness)

~19 million people with major depressive disorder (MDD) in US

Standard of care antidepressants have modest efficacy, slow onset of action, and require chronic administration

Approximately one-third of patients are treatment-resistant (failed two or more antidepressants)

~1.5 million people in US with schizophrenia

Pharmacotherapy in schizophrenia primarily addresses positive symptoms only

Unaddressed needs include:
- Management of negative symptoms
- Improvement of cognition

Psychiatric manifestations (depression, altered cognition) are common manifestations of Biogen core disease areas

**Multiple Sclerosis (MS)**
- 53% of surveyed patients with MS experienced depression as a major symptom of disease\(^1\)
- Based on meta-analysis, depression is the most prevalent MS comorbid condition\(^2\)

**Alzheimer’s Disease/Dementia**
- ~40% of people with Alzheimer’s disease (AD) suffer from significant depression\(^5\)
- Over a third of caregivers of dementia patients reported six or more symptoms of depression\(^6\)
- Agitation occurs frequently with AD; AD might have concomitant psychosis\(^7\)

**Movement Disorders**
- Clinically significant depressive symptoms are common in Parkinson’s disease (~ 35% prevalence)\(^3\)
- Psychiatric manifestations may also include psychosis, anhedonia\(^4\)

**Spinal Muscular Atrophy (SMA)**
- ~60% of all SMA caregivers experienced depression\(^8\)
- ~70% of Type 3 SMA caregivers experienced depression\(^8\)

---

Future portfolio growth is anchored on late-stage assets in depression and schizophrenia.

- Revolutionize Depression Treatment by Addressing Unmet Needs
- Accelerate Neuropsychiatry Disease Expansion
- Establish Neuropsychiatry Innovation Engine

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Filed</th>
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<tbody>
<tr>
<td>zuranolone (GABA&lt;sub&gt;A&lt;/sub&gt; PAM)- PPD</td>
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<tr>
<td>zuranolone (GABA&lt;sub&gt;A&lt;/sub&gt; PAM)- MDD</td>
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<tr>
<td>BIIB104 (AMPA-PAM) - CIAS</td>
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</tbody>
</table>
Zuranolone (SAGE-217)  
Investigational Therapeutic for the treatment of PPD and MDD

In collaboration with Sage Therapeutics

Jim Doherty, Ph.D.  
Chief Research Officer, Sage Therapeutics

The statements included in this presentation belong to Sage Therapeutics and do not necessarily reflect those of Biogen or any other party.
Safe Harbor Statement

The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “can,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity,” “goal,” “potential,” “target,” or “continue,” and other similar expressions.

Forward-looking statements in this presentation include statements regarding: the planned timing for reporting of data from ongoing clinical trials; the potential profile and benefit of zuranolone in MDD and PPD; regulatory filing plans and potential regulatory pathways; the potential for future regulatory filing and approval of zuranolone; future opportunities for zuranolone development; our estimates as to the number of people who might benefit from zuranolone in the future and other statements regarding plans and expectations with respect to zuranolone. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:

- Ongoing clinical trials of zuranolone may not meet their primary endpoints or key secondary endpoints. Success in prior clinical trials may not be repeated or observed in ongoing, planned or future studies. Final results of studies where we reported interim results may not be consistent with the interim results. Non-clinical and clinical results from ongoing or future trials may not support regulatory approval on the timelines we expect or at all or may require additional clinical trials or nonclinical studies.

- We may experience slower than expected enrollment in our ongoing clinical trials or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities.

- We may encounter unexpected safety or tolerability issues with respect to zuranolone;

- The FDA and other regulatory authorities may ultimately decide that the design or results of our completed, ongoing or planned clinical trials, even if positive, are not sufficient to file for or obtain regulatory approval of zuranolone in the indications that are the focus of our development plans despite prior regulatory advice. At any stage, regulatory authorities may ask for additional clinical trials, nonclinical studies or other data in order for us to proceed further in development or to file for or obtain regulatory approval.

- We may never pursue development of zuranolone in additional indications.

- The actual market for zuranolone, if successfully developed and approved, may be smaller than our current estimates; or we may not achieve market acceptance or reimbursement at acceptable levels.

- We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for zuranolone, or to defend our patent portfolio against challenges from third parties.

- We may face competition from others developing products for similar uses as those for which zuranolone is being developed.

- We may not be able to establish and maintain key business relationships with third parties or we may encounter technical and other unexpected hurdles in the manufacture and development of zuranolone.

- Any of the foregoing or other factors may negatively impact our ability to achieve our goals, mission, opportunities, plans or expectations for our business.

For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the “Risk Factors” section of our most recent Quarterly Report on Form 10-Q, and in our other public filings, with the Securities and Exchange Commission, available on the SEC’s website at http://www.sec.gov. Any forward-looking statement represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.
Unique target profile has the potential to revolutionize the care of depression

Novel Approach/MOA
- Selectively modulates GABA<sub>A</sub> receptors<sup>1,2</sup>
- May help neuronal networks rebalance<sup>3-5</sup>

Short Course
- Oral
- 2-week treatment, with sustained effect

Rapid Onset, Durable, As-Needed
- Rapid response – within days<sup>6,7</sup>
- Sustained efficacy, as needed therapy<sup>6,8</sup>

Well-Tolerated
- Favorable tolerability profile<sup>7-9</sup>
- Differentiated side effect profile

Zuranolone
Neuroactive Steroid (NAS)
Target Profile

Neuroactive steroids modulate phasic and tonic GABAergic inhibition

Phasic and Tonic GABAergic inhibition play different roles in regulating brain circuitry

Figures adapted from Jacob et al.\(^1\) and Reddy et al.\(^2\)

Zuranolone enhances GABA$_A$ receptor function

- Zuranolone is a synthetic NAS GABA$_A$ receptor PAM with a pharmacological profile similar to brexanolone
- Zuranolone enhances both phasic and tonic inhibition
- Zuranolone has nanomolar potency at enhancing inhibitory GABA$_A$ receptor currents in:
  - a set of recombinant human GABA$_A$ receptor configurations in vitro
  - neurons from rodent brain slices

<table>
<thead>
<tr>
<th>Receptor</th>
<th>EC$_{50}$ (nM)</th>
<th>$E_{\text{max}}$ (%)</th>
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<td>$\alpha_1\beta_2\gamma_2$</td>
<td>374</td>
<td>1041</td>
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<tr>
<td>$\alpha_4\beta_3\delta$</td>
<td>163</td>
<td>640</td>
</tr>
</tbody>
</table>

NAS = neuroactive steroid; PAM = positive allosteric modulator

Althaus et al. Neuropharm. 2020;181, 108333
## Zuranolone clinical development program

### Mono-therapy

<table>
<thead>
<tr>
<th>STUDY #</th>
<th>Indication</th>
<th>Phase</th>
<th>Design</th>
<th>Primary objectives</th>
<th>Primary endpoint</th>
<th>Population</th>
<th>Status</th>
<th>Met primary endpoint</th>
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<tbody>
<tr>
<td>201B</td>
<td>MDD</td>
<td>Phase 3</td>
<td>RCT</td>
<td>Efficacy: 30 mg vs placebo</td>
<td>HAM-D17 total score at Day 15</td>
<td>HAM-D17 ≥22 MADRS ≥32</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td>301</td>
<td>MDD</td>
<td>Phase 3</td>
<td>RCT</td>
<td>Efficacy: 30 mg vs placebo</td>
<td>HAM-D17 total score at Day 15</td>
<td>HAM-D17 ≥24 MADRS ≥28</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td>201A</td>
<td>MDD</td>
<td>Phase 3</td>
<td>RCT</td>
<td>Efficacy: 30 mg vs placebo</td>
<td>HAM-D17 total score at Day 15</td>
<td>HAM-D17 ≥20 MADRS ≥28</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td>301B</td>
<td>MDD</td>
<td>Phase 3</td>
<td>RCT</td>
<td>Efficacy: 30 mg vs placebo</td>
<td>HAM-D17 total score at Day 15</td>
<td>HAM-D17 ≥24 MADRS ≥28</td>
<td>Completed</td>
<td>Ongoing</td>
</tr>
<tr>
<td>301</td>
<td>MDD</td>
<td>Phase 3</td>
<td>OL</td>
<td>Long-term safety: 1-year follow-up (30 and 50 mg)†</td>
<td>Safety/tolerability at Week 52</td>
<td>HAM-D17 total score at Day 15</td>
<td>Completed</td>
<td>Ongoing</td>
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</table>

### Simultaneous start with ADT

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>STUDY</th>
<th>Phase</th>
<th>Design</th>
<th>Primary objectives</th>
<th>Primary endpoint</th>
<th>Population</th>
<th>Status</th>
<th>Met primary endpoint</th>
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</thead>
<tbody>
<tr>
<td>MDD-305</td>
<td>MDD</td>
<td>Phase 3</td>
<td>RCT</td>
<td>Efficacy as rapid-response therapy in MDD</td>
<td>HAM-D17 total score at Day 15</td>
<td>HAM-D17 ≥24 MADRS ≥28</td>
<td>Ongoing</td>
<td>Enrolling</td>
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</tbody>
</table>

†The SHORELINE trial initially enrolled patients using zuranolone 30 mg; the protocol was amended to allow then enrolled patients to receive retreatment with zuranolone 50 mg and a new cohort was initiated with zuranolone 50 mg initial dose with zuranolone 50 mg retreatment.
201B Study: Rapid and sustained reduction in symptoms of depression

Change from baseline in HAM-D17

HAM-D17 = 17-Item Hamilton Depression Rating Scale
ROBIN Study: Rapid and sustained reduction in symptoms of depression

Change from baseline in HAM-D17

**Primary Endpoint (Day 15)**
- Placebo: -13.6
- Zuranolone: -17.8
  - p = 0.003

Deligiannidis et al. *AMA psychiatry* 2021; 78, 951-959
WATERFALL Study: Rapid and sustained reduction in symptoms of depression

Change from baseline in HAM-D17

**Primary endpoint**
LS mean (SE) CFB in HAM-D total score on Day 15:
-14.1 (0.51) in zuranolone group and -12.3 (0.50) in placebo group; favors zuranolone over placebo of -1.7 points; 95% CI (-3.1, -0.3), \( p=0.0141 \)

HAMD-17 = 17-item Hamilton Rating Scale for Depression; LS = least squares; SE = standard error. Data on file.

*p<0.05. Other than Day 15, p values are nominal and not adjusted for multiple comparisons.

\( * \) indicates significance compared to placebo.
MOUNTAIN Study: Supportive evidence for zuranolone

Change from baseline in HAM-D17 score

- Primary endpoint, reduction of HAM-D at day 15, **not met** in full analysis set.
- Significant improvement in HAM-D scores at days 3, 8, and 12 in full analysis set.

*Primary endpoint, reduction of HAM-D at day 15, **not met** in full analysis set.
*Significant improvement in HAM-D scores at days 3, 8, and 12 in full analysis set.

*<0.05.
HAM-D17 = 17-item Hamilton Rating Scale for Depression; LS = least squares.
Mittal A et al. Poster presented at: the American Academy of Neurology Annual Meeting (Poster #010); 2020; virtual/Toronto, Canada.
SHORELINE Study: 12-month retreatment (30 mg Cohort)

Approximately 70% of participants with positive response to the initial 2-week course of zuranolone required one or two courses of treatment during the 12-month study.

Courses of Treatment over 12 months:

- One (42.9%) n= 210
- Two (25.6%) n= 125
- Three (11.9%) n= 58
- Five (8.8%) n= 43

Subjects were required by protocol to achieve response to continue into the naturalistic follow-up period.

*The SHORELINE trial initially enrolled patients using zuranolone 30 mg; the protocol was amended to allow then enrolled patients to receive retreatment with zuranolone 50 mg and a new cohort was initiated with zuranolone 50 mg initial dose with zuranolone 50 mg retreatment.
The profile of zuranolone is consistent across LANDSCAPE and NEST

**Measures of Efficacy**
- **Investigator Reported**
  - HAM-D
  - HAM-A
  - MADRS
  - Response/Remission
- **Patient Reported**
  - SF-36
  - PHQ-9

**Measures of Tolerability**
- Adverse Event Profile
- Discontinuations
- NNH

HAM-A = Hamilton anxiety rating scale; MADRS = Montgomery-Asberg depression rating scale; SF-36 = 36-item short form survey; PHQ-9 = Patient health questionnaire-9; NNH = number needed to harm
Consistent tolerability profile of zuranolone

- Safety data has been collected from more than 3,000 subjects treated with zuranolone in clinical trials to date\(^1\)-\(^4\)
  - Most AEs associated with zuranolone occurred during the 2-week treatment period
  - Among patients with MDD treated with zuranolone in randomized phase 2 and 3 clinical trials to date, <5% discontinued treatment due to AEs\(^1\)-\(^4\)
  - In the naturalistic, open-label, SHORELINE study, 6.5% of patients in the 50-mg arm discontinued treatment due to AEs\(^4\)

- AEs of nausea and diarrhea are frequently associated with use of standard-of-care antidepressants (sometimes occurring in >20% of patients)\(^5\)
- All SSRIs along with SNRIs have been shown to have significant sexual side effects; prevalence of sexual side effects can be as high as 50% to 70% among individuals taking SSRIs\(^6\)

- Nausea and diarrhea occurred in <12% of patients with MDD receiving zuranolone in phase 2 and phase 3 studies\(^1\)-\(^4\)
- There were no signals for increased suicidal ideation/behavior, as assessed by the C-SSRS and no evidence of withdrawal symptoms after discontinuation of zuranolone as assessed by the PWC-20\(^6\)
- Data from the MOUNTAIN study suggest that treatment with zuranolone 30 mg is not associated with treatment-emergent sexual dysfunction as assessed by a post-hoc analysis of CSFQ-14 total score\(^7\)

**Most Common (≥5%) AEs Across Phase 2 and 3 Trials\(^1\)-\(^4\)**

<table>
<thead>
<tr>
<th>AEs</th>
<th>% Patients (min–max)</th>
<th>AEs</th>
<th>% Patients (min–max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6%–18%</td>
<td>URTI</td>
<td>1%–8%(^\dagger)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6%–15%</td>
<td>Diarrhea</td>
<td>2%–7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%–15%</td>
<td>Fatigue</td>
<td>2%–7%(^\dagger)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%–11%</td>
<td>Dry mouth</td>
<td>4%–6%</td>
</tr>
<tr>
<td>Sedation</td>
<td>4%–9%</td>
<td>Insomnia</td>
<td>5%(^\dagger)</td>
</tr>
</tbody>
</table>

**Serious AEs Across Phase 2 and 3 Trials**

<table>
<thead>
<tr>
<th>Study, % Patients</th>
<th>Serious AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=503)</td>
</tr>
<tr>
<td>MDD-201B(^1)</td>
<td>0</td>
</tr>
<tr>
<td>MOUNTAIN(^2)</td>
<td>0.5%</td>
</tr>
<tr>
<td>WATERFALL(^3)</td>
<td>0.7%</td>
</tr>
<tr>
<td>SHORELINE(^4)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Note:** Trial designs differ; indirect comparison for discussion purposes only

AE = adverse event; CSFQ-14 = Changes in Sexual Functioning Questionnaire-14 (CSFQ-14); C-SSRS = Columbia-Suicide Severity Rating Scale; MDD = major depressive disorder; PWC = 20-item Physician Withdrawal Checklist; SNRI = serotonin noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; URTI = upper respiratory tract infection.

Based on MOUNTAIN study. \(^1\)Based on SHORELINE study. \(^\dagger\)During the initial 28-day treatment cycle—November 2020 data cut. \(^\dagger\)Based on interim analysis of patients who received up to 5 treatments of zuranolone over 12 months.

Integrated analysis from placebo-controlled trials in LANDSCAPE and NEST

Low discontinuation rate

<table>
<thead>
<tr>
<th>Discontinuation due to side effects rates</th>
<th>Placebo</th>
<th>Sage 217 (30mg and 50mg)</th>
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</thead>
<tbody>
<tr>
<td>217 MDD-201B</td>
<td>0.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Robin</td>
<td>0.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>217-MDD-301A</td>
<td>3.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>217-MDD 301B</td>
<td>1.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Weighted average (by n)</td>
<td>1.7%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

Discontinuation due to side effects is commonly utilized as a metric of harm: side effects that hinder ability to remain compliant to medication has implications for real-world clinical practice in MDD.

Number Needed to Harm (NNH) = 1/(%Discontinuation_{217} – %Discontinuation_{PBO})

NNH = 1/(0.02765799 - 0.0174489) = 98

Number Needed to Harm (NNH) = 1/(%Discontinuation_{217} – %Discontinuation_{PBO})

NNH = 1/(0.02765799 - 0.0174489) = 98

*Integrated analyses include 201B, 301A(Mountain) >=24 HAMD subgroup, 301B, Robin
1. Citrome J Affective Disorders 2016
Zuranolone has the potential to impact millions globally

Companies believe efficacy data to date are sufficient to support NDA filing, additional supplemental data may support life cycle management opportunities

Composition of Matter Patent through 2034, subject to potential extensions

<table>
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<tr>
<th>2021</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
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<tbody>
<tr>
<td><strong>DEPRESSION FRANCHISE</strong></td>
<td></td>
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<tr>
<td>Zuranolone (Sage-217)</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✔️</td>
<td>Report topline data from WATERFALL Study in major depressive disorder (1H21)</td>
<td></td>
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<tr>
<td>✔️</td>
<td>Report full data from SHORELINE Study 30 mg cohort in major depressive disorder</td>
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<tr>
<td></td>
<td>Report topline data from CORAL Study in major depressive disorder for rapid response treatment when co-initiated with new antidepressant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Report topline data cut from SHORELINE Study 50 mg cohort in major depressive disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Early:Q1-Q2; Mid:Q2-Q3; Late: Q3-Q4

PPD = postpartum depression, MDD = major depressive disorder, TRD = treatment resistant depression, GAD = generalized anxiety disorder, BPD = bipolar depression
BIIB104 in Cognitive Impairment Associated with Schizophrenia (CIAS)
Improving cognition in schizophrenia treatment is a high priority to psychiatrists.

### Treatment priority in stabilized schizophrenia patients

*% of surveyed psychiatrists who consider a given treatment goal a top three priority*%

- Improve negative symptoms
- Improve social integration/functioning
- Improve cognition
- Improve daily living skills

### Factors influencing choice of drug therapy to improve patient’s social functioning

*% of respondents noting the goal is ‘very important’ or ‘important’ *

- Efficacy (symptom control)
- Good tolerability
- Potential to preserve/improve cognition
- Improved level of adherence

---

The FOCUS international survey on psychiatrists’ opinions on cognition in schizophrenia conducted among 2,975 psychiatrists in 21 countries in North America, Europe, Australia, and New Zealand¹

Survey conducted among 4,163 psychiatrists treating patients with schizophrenia from 42 countries in Europe, the Middle East, and Africa²

---


FOCIS = Focus on Cognition in Schizophrenia

*select treatment goals & factors shown
**BIIB104 is a high-impact AMPAR positive allosteric modulator (PAM)**

NMDA receptor (NMDAR) hypofunction may underlie cognitive impairment in schizophrenia

- **Synaptic plasticity** is hypothesized to underlie cognitive processes such as memory
- AMPA and NMDA receptors play an important role in regulating synaptic plasticity and function
- **NMDAR hypofunction** may contribute to CIAS
- Increased AMPA receptor (AMPAR) activity can augment NMDAR activity and synaptic function
- A key mechanism of NMDAR-regulated increases in synaptic activity is AMPAR insertion into the synapse

---

**By potentiating AMPAR activity, BIIB104 may enhance NMDAR function and potentially improve CIAS**

---

AMP, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, cyclic adenosine monophosphate; CIAS, cognitive impairment associated with schizophrenia; NMDA, N-methyl-D-aspartate

Clinical effects of BIIB104 in stable schizophrenia

Promising early results demonstrated; ongoing Phase 2 trial with anticipated readout in 2022

Phase 1b (completed)¹

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement from Baseline at Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-1.5</td>
</tr>
<tr>
<td>PF-04958242 0.25 mg</td>
<td>1.3</td>
</tr>
<tr>
<td>PF-04958242 0.475 mg</td>
<td>3.9</td>
</tr>
</tbody>
</table>

LS Improvement on MCCB Working Memory Domain T-Score (p = 0.0143); Exposure-response relationship at Day 14 (p <0.05) slope = 0.872 (CI: 0.154 – 1.604)

Phase 2 (ongoing)

- **Population**: participants with a diagnosis of schizophrenia for at least 2 years; on background antipsychotics
- **12-week treatment period**: cognitive and functional testing at baseline and Week 12
- **Primary endpoint**: Change from baseline in MATRICS* Consensus Cognitive Battery (MCCB) working memory domain score at week 12
- Additional assessments of cognition, functioning, and psychiatric symptoms conducted

Results expected in 2022

https://clinicaltrials.gov/ct2/show/NCT03745820

*MATRICS – Measurement and Treatment Research to Improve Cognition in Schizophrenia


LS = least squares; MCCB WM = MATRICS Consensus Cognitive Battery Working Memory; MMRM = mixed effect model repeated measures
BIIB104 and zuranolone: Potential to transform schizophrenia and depression

- Depression and schizophrenia are estimated to affect more than 284 million people worldwide and significant unmet needs remain for both conditions\(^1\)

- Despite available treatments, depression continues to rank in the top 5 causes of global disability for men and women\(^2\)

- There are no approved treatments for CIAS, which leads to significant interference in day-to-day functioning, independent living skills, employment and social interactions\(^3\); and existing antidepressants have limitations

- Zuranolone and BIIB104 may address important unmet needs and may offer potential hope to change the reality of living with these disorders

---

Building an ALS Portfolio

Toby Ferguson, M.D., Ph.D.
Head of Neuromuscular Development

R&D Day
September 21, 2021
# Industry leading neuromuscular portfolio

<table>
<thead>
<tr>
<th>Program</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>LCM</th>
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<tbody>
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<tr>
<td>C9orf72 ASO (BIIB078)***</td>
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<td>XPO1 Inhibitor (BIIB 100)</td>
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<tr>
<td>Ataxin-2 ASO (BIIB 105)***</td>
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<td>Anti-C9orf72 (BIIB 106) Asset~~~</td>
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<td>SOD1 Asset</td>
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<td>sALS Asset</td>
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<td>Ataxin 2 Asset</td>
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<td>C9orf72 Asset</td>
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<td>SPINRAZA~</td>
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<td>ActRIIA/B ligand trap (BIIB110)</td>
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<td>SMA Asset****</td>
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<td>DM1 Asset^^^</td>
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**Advance Industry-Leading ALS Pipeline**

**Sustain Leadership in SMA**

**Pioneer Clinically Meaningful Treatments in Rare Muscle Disease**

ALS = amyotrophic lateral sclerosis; ASO = antisense oligonucleotide; DMD = Duchenne muscular dystrophy; LCM = lifecycle management; SMA = spinal muscular atrophy
DISEASE OVERVIEW
Rare, fatal, disease characterized by motor neuron loss in the brain and spinal cord - Average survival after diagnosis of 3-5 years

Global Epidemiology:
- Prevalence*: 168k
  - Genetic ALS ~ 14k
  - SOD1 ALS ~ 3.8k

CURRENT THERAPIES
Currently approved treatments provide a modest effect on motor function and survival
- Riluzole and edaravone are the approved treatments for ALS in the U.S.
- Critical unmet need for effective treatment options

*Estimated using the same approach as Brown et al. SOD1 and C9orf72 Genetics Variant Neuroepidemiology 2021
Learnings from previous failures reshaped our approach to ALS

**Dexpramipexole: A case study in ALS drug development**

Despite lack of clear mechanistic rationale, dexpramipexole demonstrated encouraging early clinical results.

Learnings from rich dataset in over 800 patients reshaped Biogen’s approach to clinical development in ALS

**Key Learnings from previous ALS trials**

Identify and evaluate genetically validated targets in defined patient populations

Pursue the most appropriate modality for each target and include multiple outcome measures to capture totality of disease (vital capacity, strength, appropriate PROs)

Implement biomarkers of target engagement, disease activity, and treatment response in early-stage studies

**Biomarkers**

<table>
<thead>
<tr>
<th>Drug exposure</th>
<th>Target engagement biomarker</th>
<th>Surrogate marker of efficacy</th>
<th>Clinical efficacy</th>
</tr>
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<tbody>
<tr>
<td>Cudcowicz et al., 2013</td>
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</table>
Neurofilament as a biomarker of neuronal degeneration and recovery in neuromuscular disease

Adapted from Verde et al., 2021

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunoassay; NFL = neurofilament light; ECL Simoa = electrochemiluminescence single-molecule array digital immunoassay
Neurofilament as a biomarker of neuronal degeneration and recovery in neuromuscular disease

EMPOWER ALS patients with higher levels of plasma NFL show more rapid decline

Neurofilament level is decreased following SPINRAZA treatment in SMA¹

¹ Adapted from Darras et al. Ann Clin Transl Neurol, 2019

Biogen data on file
Genetic forms of ALS continue to be underdiagnosed

Approximately 10% of ALS patients have known genetic mutations, including C9orf72, SOD1, TARDBP and FUS\(^2\)

- Among those patients, \(~72\%\) of patients do not have a known family history of ALS\(^1\)
- Among patients with SOD1 mutation, \(~61\%\) of patients do not have a known family history of ALS\(^1\)

### Prevalence of Known Genetic Mutations in ALS\(^1,2\)

- Unknown: 90%
- Known genetic mutation: 10%
  - C9orf72: 7%
  - TARDBP: 1%
  - FUS: 0%
  - SOD1: 1.9%

### Patients with known family history

- Only 50% are genetically tested in the US

### Patients with unknown family history

- Only 20% are genetically tested in the US

---

Increasing awareness of genetic ALS and providing access to genetic tests are critical to identify patients with mutations responsible for the disease.

**Biogen** and **Invitae** have partnered on a no-charge genetic testing program called **ALS Identified™**.

**Access** to Genetic Tests and **Education** on Genetic ALS

**Launched in the US.**

**Geographic expansion** is under assessment

**De-identified data** will be relayed to ClinVar – help advance scientific research on ALS
Mutations in *SOD1* were the first identified genetic cause of ALS

*SOD1* gene encodes a ubiquitously expressed enzyme called *superoxide dismutase 1*

**Mutated SOD1 is prone to misfold** and can interfere in multiple cellular processes

*SOD1* ALS cases are characterized by cytoplasmic inclusions of aggregated *SOD1* protein selectively in motor neurons

Data indicate that **toxicity of mutant SOD1 is derived from a gain-of-function mechanism**

Robberecht and Philips, 2013
Tofersen* is a gapmer ASO that selectively targets SOD1 mRNA

Tofersen mediates RNase H-dependent degradation of SOD1 mRNA to reduce the synthesis of SOD1 protein

*Discovered by Ionis Pharmaceuticals

mRNA = messenger RNA; RNase = ribonuclease;

Dose-dependent decrease in SOD1 concentrations

Reduction in NF levels was observed with tofersen

All missing data were imputed with the use of a mixed model for repeated measures. BL = baseline; CI = confidence interval; CSF = cerebrospinal fluid; PD = pharmacodynamic; SOD1 = superoxide dismutase 1.

2. In the combined placebo group, there was one anomaly for the CSF sample at Day 15; the result was below the limit of quantitation and was noted as missing data.

Geometric mean ratios were calculated using the least squares method. Post-baseline missing values were imputed using a mixed model for repeated measures.

3. Participants in the fast-progressing disease subgroup had a SOD1 mutation characterized as having a fast-progressing disease course (A4V, A4T, G41S, H43R, L84V, G93A, R115G, L106V, L38V, V148G with an average disease duration ≤ 3 years) and pre-randomization ALS-FRS-R slope decline of ≥ 0.2 points per month.

BL = baseline; CI = confidence interval; FP = fast-progressing disease subgroup.
Exploratory clinical measures

Tofersen-treated patients appeared to experience a slowing of decline compared with placebo-treated patients across clinical outcome measures.

Clinical function: total ALS-FRS-R score

Respiratory function: Predicted SVC (%)

Muscle strength: HHD megascore

1. Means were calculated using the least squares method. Post-baseline missing values were imputed using a mixed model for repeated measures.
2. Raw means presented. Post-baseline missing values were imputed using the last observation carried forward method.

ALS-FRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CI = confidence interval; HHD = handheld dynamometry; LS = least squares; SD = standard deviation; SVC = slow vital capacity.

Randomized, double-blind, placebo-controlled, phase 3 study of tofersen administered to adult participants (N ≈ 99) with ALS and a confirmed SOD1 mutation

**Key:**
- ▲: Dose
- 🌾: Follow-up visit

**Loading dose period**
- Study day 1

**Maintenance dose period**
- Study day 57
- Study day 85
- Study day 113
- Study day 141
- Study day 169
- Study day 197

**Follow-up**

**Treatment arms:** tofersen 100 mg versus placebo, 15 ml intrathecal bolus over 1–3 minutes of treatment

**Primary endpoint (efficacy)**
- Change from baseline to Week 28 in the ALSFRS-R total score

**Key secondary endpoints (PD and efficacy)**
- Change from baseline in total CSF SOD1 and plasma NfL concentrations
- Change from baseline in SVC
- Change from baseline in HHD
- Overall and ventilation-assistance-free survival

**LTE** = long-term extension; PD = pharmacodynamic; pNf-H = phosphorylated neurofilament heavy chain

3. Defined as ≥ 22 hours of mechanical ventilation (invasive or noninvasive) per day for ≥ 21 consecutive days.

**VALOR is expected to read out in the Fall of 2021**
Neurofilament elevations precede clinical symptoms thus enabling a presymptomatic trial

Elevations in NF observed prior to clinical evidence of ALS in participants rapidly progressive SOD1 mutations

Benatar M, Turner M, Wuu J; ALS FTD; 2019

ATLAS study overview

Part A: Natural history run-in (with monthly NfL screen), n ~ 150
- No intervention

Part B: Placebo-controlled, n ~ 28
- Tofersen 100 mg or placebo
- Proceed to Part B if:
  - NfL ≥ 44 pg/mL and Δ from baseline ≥ 10 pg/mL
  - Still presymptomatic

Part C: Open-label
- Tofersen 100 mg
- Proceed to Part C upon: Emergence of clinically manifest ALS

Part D: Placebo-controlled
- Tofersen 100 mg or placebo
- Proceed to Part D upon: Emergence of clinically manifest ALS (prior to detection of elevation in neurofilament)
- Up to 2 years in duration

Study screening and enrollment

Study objective
To evaluate whether presymptomatic initiation of tofersen can delay emergence of clinically manifest ALS and/or slow decline in function after emergence of clinically manifest ALS

Primary endpoint
Proportion of participants with emergence of clinically manifest ALS within 12 months of randomization

2. Assuming other eligibility criteria are met.
BIIB078* is an intrathecally administered ASO being investigated for the treatment of C9ORF72 ALS

BIIB078 selectively targets RNA transcripts from the repeat-containing portion of the human C9ORF2 gene, reducing repeat-associated RNA-mediated toxicity and dipeptide protein toxicity.

BIIB078 reduces dipeptide repeats in CNS of transgenic mice.

BIIB078 Studies

Phase 1

Phase 2

Phase 3

Phase 4


*Discovered by Ionis Pharmaceuticals

CNS = central nervous system.
Nearly all ALS patients (~97%) have TDP-43 aggregates in their brains and spinal cords

- TDP-43 aggregation found in ~97% of ALS patients
- Mutations in TDP-43 cause ALS and increase TDP-43 aggregation
- TDP-43 inclusion pathology is correlated with motor neuron death

**Cytoplasmic aggregation of TDP-43 may lead to both toxic gain- and loss-of-function phenotypes**
BIIB105* is an intrathecally administered ASO being investigated for the treatment of broad ALS

Reduction of ATXN2 may improve TDP-43 toxicity and clinical outcomes in ALS

Preclinical observations

Wildtype Atxn2 reduction increases survival and functionality and reduces TDP-43 pathology in yeast, fly, and mouse models

Human genetic evidence

Intermediate repeat PolyQ expansion (30–33) in ATXN2 results in 7x increased risk of ALS and is associated with a more aggressive phenotype

BIIB105 Studies

Phase 1
Phase 2
Phase 3
Phase 4

* Discovered by Ionis Pharmaceuticals
ALS, amyotrophic lateral sclerosis.
Utilize genetic analysis and functional genomics for target selection and prioritization

- Access to unique GWAS databases
- Access to clinical endpoints to ask genetic questions related to ALS progression
- Integrate data from human biology hub and single-nucleus RNA-seq

Build better discovery tools to model human disease by focusing translatability to validate novel targets

- Human disease vs control
- In-vivo model
- In-vitro model
- Target Validation
- Mechanism of Action
- Screening

Extend our internal research to the exploration of novel targets by using Biogen Discovery Engine and proprietary knowledge

Select targets and pathways de-risked with genetic validation and relevant biology.
Learnings from our genetic programs will inform therapy development for broader ALS populations

Trial design and conduct learnings are transferrable across the portfolio

Biomarker (i.e., neurofilament) development will enable early decisions

Patient ID efforts will accelerate trial enrollment and expand treatable population (for genetic targets)

Presymptomatic trial will define the early ALS disease spectrum and accelerate time to diagnosis

SOD1 ALS
Tofersen
C9ORF72 ALS
BIIB078 (C9 ASO)

Broad ALS Population
BIIB105 (Ataxin-2 ASO)
BIIB100 (XPO1 inhibitor)

ALS Population

Biomarker (i.e., neurofilament) development will enable early decisions

C9orf72 7%
SOD1 2%
TDP43 1%
FUS <1%

Broad ALS: 90% of all ALS cases
Novel Therapeutic Approaches for Stroke

Josh Bell, M.D., Ph.D.
Medical Director

Biogen Investor R&D Day
September 2021
Stroke overview & review of current Biogen clinical programs
Two programs lead Biogen’s innovative drug development in the neurovascular portfolio

- **BIIB131 (TMS-007)** – recently acquired following a positive Phase 2a study, is a potential best-in-class thrombolytic drug candidate
- **BIIB093** – Agent in Phase 3 using a novel approach to target edema complicating one of the most severe forms of ischemic stroke
Stroke is a devastating condition in great need of improved therapeutic approaches

<table>
<thead>
<tr>
<th>Acute Ischemic Stroke (AIS)</th>
<th>85% of all stroke cases are AIS</th>
<th>5th leading cause of mortality in US</th>
<th>Affects 1 in 6 people in their lifetime</th>
<th>Avg. age: 65 yrs.; risk doubles each decade after 55</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Incidence (2020)</th>
<th>U.S.</th>
<th>China</th>
<th>EU</th>
<th>JP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS</td>
<td>~620 K</td>
<td>~2M</td>
<td>~400 K</td>
<td>~125k</td>
</tr>
</tbody>
</table>

- ~10-15% of AIS cases are LHI
- Associated with occlusion of the middle cerebral artery
- Risk of severe edema, herniation
- Avg. age: ~10 yrs. younger (~55 yrs)
- 40-80% mortality with high risk of severe disability
Biogen is developing stroke programs competitively positioned to address significant needs in Acute Ischemic Stroke (AIS).

BIIB131 may have potential to show improved safety profile and later and longer therapeutic window from 4.5 to 24 hours beyond currently approved thrombolytic therapy administration.

EVT = Endovascular Thrombectomy; LVO = Large vessel occlusion; tPA = tissue Plasminogen Activator

BIIB131 may have potential to show improved safety profile and later and longer therapeutic window from 4.5 to 24 hours beyond currently approved thrombolytic therapy administration.
BIIB131: recently acquired, potential best-in-class therapeutic for Acute Ischemic Stroke

Hypothesized Dual Mechanisms of Action

1. BIIB131 changes conformation of plasminogen to increase fibrin binding and facilitate activation from endogenous tissue Plasminogen Activator (tPA). It does not directly convert plasminogen to plasmin, thereby limiting systemic effects.

2. Inhibits soluble epoxide hydrolase, reducing production of pro-inflammatory mediators of vasoconstriction and breakdown of the blood brain barrier.

Potential best-in-class thrombolytic investigational agent with extended therapeutic window and favorable safety profile.

DHET = dihydroxyeicosatrienoic acids; EET = epoxyeicosatrienoic acids; EH = epoxide hydrolase; PA = plasminogen activator
BIIB131 phase 2a controlled study design

Primary Endpoint:
The incidence of symptomatic intracranial hemorrhage with clinical deterioration (≥4 points in NIHSS at 24 hours)

Key Secondary Efficacy Endpoints:
- Modified Rankin Scale (mRS) score at Day 90
- Recanalization rate on Magnetic Resonance Angiogram (MRA) at 24 hours

Patients with AIS Ineligible for tPA or thrombectomy
NIHSS 6~23 Age: ≤ 88
Primary endpoint: safety

Table 14.3.1.1 Summary of Symptomatological Intracranial Hemorrhage with Exacerbation of NIHSS 4 or Higher up to 24 hours after Administration of TMS-007_SAF

<table>
<thead>
<tr>
<th>Item</th>
<th>Treatment</th>
<th>N</th>
<th>Subjects</th>
<th>Percent (%)</th>
<th>95% CI for Incidence</th>
<th>Comparison with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatological Intracranial Hemorrhage*1</td>
<td>1 mg/kg</td>
<td>6</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>39.3</td>
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<tr>
<td></td>
<td>3 mg/kg</td>
<td>18</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>15.3</td>
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<tr>
<td></td>
<td>6 mg/kg</td>
<td>28</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>10.1</td>
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<tr>
<td></td>
<td>Pooled TMS-007</td>
<td>52</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>38</td>
<td>1</td>
<td>2.6</td>
<td>0.1</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*1: Symptomatological intracranial hemorrhage with exacerbation of NIHSS 4 or higher up to 24 hours after administration (type 1 or type 2 parenchymal hemorrhage)

*2: Fisher's exact test

---: Not applicable

Favorable safety profile based on primary endpoint

- Symptomatic intracranial hemorrhage with worsening of NIHSS ≥4 points: Zero (0%) in BIIB131 groups and one (2.6%) in the placebo group
BIIB131 showed statistically significant improvement on mRS, registrational endpoint of functional independence.
MRA illustrates impact on vessel recanalization

• Illustrative case of 78-year-old male with occlusion of right middle cerebral branch artery, NIHSS score of 9, randomized to BIIB131, 3 mg/kg cohort.
• Time to treatment: 8.5 hours post-stroke

MRA at baseline

MRA at 24 hours

90-day outcome

mRS of 1

No significant disability, despite symptoms; able to perform all usual duties and activities
Robust effects on visible vessel recanalization

Full or Partial Opening

<table>
<thead>
<tr>
<th></th>
<th>Placebo Pooled</th>
<th>TMS Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>15 (100)</td>
<td>24 (100)</td>
</tr>
<tr>
<td>Number of participants with recanalization n (%)</td>
<td>4 (26.7)</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>Estimate of odds ratio (TMS vs placebo)</td>
<td></td>
<td>4.23</td>
</tr>
<tr>
<td>95% CI for the odds ratio</td>
<td></td>
<td>0.99, 18.07</td>
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</table>

In patients with full or partial visible vessel occlusion, the percentage of subjects receiving BIIB131 achieving recanalization was greater than those treated with placebo.
Phase 2a study of BIIB131 in Acute Ischemic Stroke demonstrated positive impacts on blood vessel reopening and patient functional recovery¹

- **Treatment:** 52 Patients were treated with BIIB131 up to 12 hours after the onset of stroke symptoms - average time to treatment was 9.5 hours vs. 9.3 hours for placebo

- **Safety:** No incidence of symptomatic intracranial hemorrhage

- **Recanalization:** Improved recanalization rate in patients with a visible occlusion – 58.3% for BIIB131 vs. 26.7% for placebo

- **Functional Recovery:** Significant improvement in patient functional recovery as measured by modified Rankin Scale, a measure of independence in daily living

BIIB131 is a thrombolytic with potentially improved efficacy & safety profile

Team is actively designing further clinical studies to confirm the safety and efficacy

¹) Phase 2a: N = 90: 52-BIIB131, 38-Placebo
BIIB093 (IV glibenclamide) inhibits the SUR1-TRPM4 ion channel, a key regulator of cerebral edema

- Positive Ph 2 data in secondary/tertiary endpoints for mortality, midline shift, and positive trend for functional outcome (day 90 mRS shift)

- Well established safety profile with oral glyburide; Hypoglycemia is the only identified safety risk and can be mitigated by clinical management. Observational studies of sulfonylureas safe and beneficial in diabetic stroke patients

SUR1 up-regulated in focal cerebral ischemia

SOC = standard of care

SUR1-TRPM4 = sulfonylurea receptor 1-transient receptor potential melastatin 4
BIIB093 administration was associated with reduced disability and reduced midline shift in phase 2 trial

Reduction in mortality at 30 days and positive effect on midline shift

**Primary endpoint:** mRS score of 0–4 at 90 days without decompressive craniectomy

OR = 1.91; p = 0.12

IV glibenclamide is also referred to as glyburide
BIIB093 phase 3 study is designed to evaluate short- and long-term functional outcomes in LHI patients

Part 1

Randomization 1:1

Total BIIB093 IV 3-stage infusion over 72 hours

Placebo

Administration ≤10 hours from symptom onset

Subjects with LHI measured by diffusion-weighted MRI imaging or CT scan (n= 768)

Subjects may also receive standard of care treatment

Primary endpoint:

- Modified Rankin Scale score at Day 90

Additional secondary efficacy endpoints:

- Overall survival at Day 90
- Functional outcome at Day 90
- Midline shift

Part 2

12 Month Follow-up

FDA

- Special Protocol Assessment agreement obtained
- US Orphan Drug designation and Fast Track status granted
Biogen is entering the neurovascular space with potentially transformative compounds

• Neurovascular disorders are significant cause of disability and mortality worldwide

• Innovative approaches to improve outcomes and address unmet needs are needed

• Biogen’s neurovascular portfolio aims to address both the interruption of blood flow and the accompanying brain edema that impact patient outcomes in stroke

• BIIB093 and BIIB131 are two novel late-stage agents to anchor growth into a future neurovascular portfolio
Advancing a Late-stage Lupus Pipeline

Nathalie Franchimont, M.D., Ph.D.
Head of Multiple Sclerosis and Immunology Development

R&D Day
September 21, 2021
Immunology as a therapeutic area to Biogen

**Immunology as a Franchise**

**Neurology as a Franchise**

**Neuro-immuno MS pipeline**

**Immunology Expertise as a Tool**

**Leadership in Lupus**

- Foundation to 2015
- 2020
- Present

**Biogen**
Biogen Lupus portfolio has multiple Phase 3 assets

<table>
<thead>
<tr>
<th></th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapirolizumab-Pegol* (anti-CD40L mAb)-SLE</td>
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<tr>
<td>BIIB059 (anti-BDCA2 mAb)-SLE</td>
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<tr>
<td>BIIB059 (anti-BDCA2 mAb)-CLE</td>
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<tr>
<td>SM-SLE</td>
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</table>

SLE: Systemic Lupus Erythematosus
CLE: Cutaneous Lupus Erythematosus

*Dapirolizumab Pegol – collaboration with UCB
BDCA2 = blood dendritic cell antigen 2; mAb = monoclonal antibody; SM = small molecule
Perspectives: We believe we can lead in Lupus

**Execute**
- Phase 3 assets Dapirolizumab Pegol and BIIB059 represent potential first in class molecules anchored on genetic and/or human validation in early clinical development
- Increased prevalence and severity of lupus in underserved populations provides a unique opportunity to demonstrate our commitment to improving health equity

**Maximize**
- Potential new assets leveraging our expertise in key biological pathways:
  - Type-I Interferon (IFN)/plasmacytoid dendritic cells (pDC) directed
  - B-cell directed

**Potential for Life Cycle Management (LCM) and growth**
- Advances in genetics + Artificial Intelligence (AI) tools = match of mechanism to disease
- Translational biomarkers to establish Proof of Biology (POB) + efficient Proof of Concept (POC) study design = higher Probability of Success (POS) opportunities for LCM in autoimmune diseases with high unmet need
Cutaneous Lupus Erythematosus (CLE) and Systemic Lupus Erythematosus (SLE): Chronic autoimmune diseases with high unmet needs

CLE: Skin-based form of lupus

- Genetic predisposition, ultraviolet irradiation, and certain pharmaceutical agents may trigger immune responses in CLE
- Symptoms including photosensitivity, rash, pain, and pruritis (itch)
- Skin damage, including scarring and skin atrophy, occurs in some chronic forms
- Most subjects with CLE may not develop systemic manifestations

SLE: Lupus impacting multiple organs

- Genetic predisposition and environmental factors contribute to the development of SLE
- Impacts ~4M people worldwide; 90% women and most prevalent during child-bearing years
- More common and severe among non-Caucasians
- Increased risk of premature death (including infections and thrombotic/renal events)
- Multiple, varied organs and symptoms, including in:
  - Skin
  - Heart
  - Brain
  - Lungs
  - Joints
  - Kidneys

Acknowledgement: DermNet New Zealand

CLE = acute cutaneous lupus erythematosus; CLE = cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus;

BIIB assets have distinct MOA as compared to approved therapies in SLE

- **Systemic Lupus Erythematosus (SLE)**
  - Anifrolumab (Saphnelo®): mAb anti-IFNR (Approved 2021)
  - Belimumab (Benlysta®): mAb anti-BLyS (Approved 2011)
  - Dapirolizumab Pegol: polyethylene glycol (PEG)-conjugated antigen-binding (Fab') fragment anti-CD40L (NCT04294667)
  - BIIB059: mAb anti-BDCA2 (NCT04895241)

- **Lupus Nephritis (LN)**
  - Voclosporin (Lupkynis®): SM calcineurin inhibitor (Approved 2020)
  - Belimumab (Benlysta®): mAb anti-BLyS (Approved 2020)

Figure: adapted from Vukelic at al. 2018: Front. Immunol., 16 November 2018 | https://doi.org/10.3389/fimmu.2018.02658
BIIB059: Anti-BDCA2 Antibody, has a potentially differentiated mechanism of action which is distinct from Anifrolumab

- BIIB059 is a humanized monoclonal antibody against human BDCA2, engineered as IgG1 with full effector function
- BIIB059 leads to BDCA2 internalization and inhibition of all Type I IFN and pDC-derived pro-inflammatory mediators that are implicated in SLE/CLE
- BIIB059 inhibits pDC-derived Type I IFNs by pDCs at site of disease while preserving the protective Type I IFN response to viruses in all other cells

The binding of BIIB059 to BDCA2 leads to rapid internalization of BDCA2 from the cell surface of pDCs, thereby inhibiting the production of pDC-derived IFN-Is, IFN-I, cytokines, and chemokines.1

De-risking approach to BIIB059 pathway: supporting genetic evidence and early Proof of Biology/Proof of Concept (POB/POC)

Genetics (Type I IFN/IRF5)

IRF5 is the top non-HLA risk gene for Lupus

Risk allele increases expression of IRF5 and increase risk by ~50% per allele (all ancestries)

Proof of Biology in Phase 1

- BIIB059 normalizes MxA expression and reduces cellular infiltration in skin lesions

Link Proof of Biology to Early Proof of Concept

- Correlation plot of change in MxA expression from baseline and percentage change of CLASI-A score from baseline for all patients (placebo treated, triangles; BIIB059 treated, circles)

BIIB059 Clinical Development suggests promising efficacy in skin in Phase 1

First in Human (FIH) Study

- 230LE101 SAD-MAD in HV and 1 cohort SLE with active skin manifestation (NCT02106897)¹
  - PK/PD correlation established
  - Single dose of BIIB059 in SLE patients dampened expression of interferon responsive genes in the blood and interferon responsive proteins (MxA) in the skin = Proof of Biology
  - Early signs of efficacy
  - Acceptable safety


**BIIB059**

- Early signs of efficacy
- Acceptable safety

1 of 4 placebo-treated patients showed a response as denoted by 4-point reduction, due to initiation of corticosteroid therapy

6 out of 8 BIIB059-treated subjects show reduced MxA expression in skin and reduced CLASI-A Score

CLASI Response is defined as a ≥4-point reduction from baseline in CLASI-A at Week 4 or Week 12

¹HV = Healthy Volunteers; MAD = multiple-ascending-dose, PK = pharmacokinetic, PD = pharmacodynamic, SAD = single-ascending-dose
BIIB059 clinical development suggests promising efficacy in skin and joint manifestation in Phase 2

Phase 2 Study

- 230LE201 – LILAC Study: A 2-Part RCT in SLE (Part A) and CLE (Part B) Populations (NCT02847598) achieved primary endpoints in Part A (change in total active joint count) in SLE and Part B (change in CLASI-dose response) in CLE

- BIIB059 demonstrated a favorable safety profile

Absolute change in total active joint count-
Part A (SLE)
(sum of the tender joint count and swollen joint count )

Percent change in CLASI-A Score from baseline-
Part B (CLE)


CLE: Cutaneous Lupus Erythematosus; SLE: Systemic Lupus Erythematosus
LS: Least Squares, SE: Standard Error
BIIB059 Phase 2 data demonstrated reduction in disease activity in SLE on registration endpoint (secondary endpoint Phase 2)

Phase 2 secondary endpoint: Proportion of subjects with a SLE Responder Index (SRI) of ≥4 (SRI-4) (Part A- SLE)

<table>
<thead>
<tr>
<th>Week</th>
<th>LS mean diff (95% CI)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 16</td>
<td>16.2 (-0.7, 33.1)</td>
<td>2.15 (0.96, 4.83)</td>
<td>0.063</td>
</tr>
<tr>
<td>Week 20</td>
<td>23.8 (6.9, 40.6)</td>
<td>3.06 (1.34, 6.99)</td>
<td>0.008</td>
</tr>
<tr>
<td>Week 24</td>
<td>26.35 (9.46, 43.24)</td>
<td>3.49 (1.55, 7.84)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

LS = least squares; diff = difference from placebo; OR = odds ratio

BIIB059 today and tomorrow

Topaz Phase 3 SLE studies

- A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of BIIB059 in Adult Participants With Active Systemic Lupus Erythematosus Receiving Background Nonbiologic Lupus Standard of Care
- 2 doses of BIIB059 or Placebo
- Primary Efficacy evaluated at Week 52: SRI-4
- Secondary endpoints will also assess organ-specific outcomes

Ongoing and future activities

- FPI in Topaz 1 (NCT04895241) June 2021
- FPI in Topaz 2 (NCT04961567), twin Phase 3 study, August 2021
- CLE planned
- Potential to conduct Life Cycle Management (LCM) in diseases where pDC/Type I IFN play a critical role
CD40/CD40L is a Cardinal Pathway in Autoimmunity

- Considerable pharmacological evidence developed over >20 years suggests that blockade of the pathway is efficacious in inflammatory and autoimmune conditions
- Dapirolizumab Pegol (DZP) has been studied in multiple pre-clinical models including lupus models with proof of concept being demonstrated
- No evidence of platelet activation in human or rhesus macaque platelets and no evidence of increased thromboembolic events in the development program at present

DZP Demonstrated POB on anti-dsDNA Level

- Anti-double stranded DNA (Anti-dsDNA) demonstrated improvement across all DZP groups at Week 24 vs placebo. Following DZP withdrawal, anti-dsDNA generally worsened and returned to baseline

**Anti-dsDNA: anti double stranded DNA; PBO: placebo; SOC: standard of care.**

*Furie et al., Rheumatology 2021 May 6;keab381. doi: 10.1093/rheumatology/keab381; NCT02804763*
Results of Dapirolizumab Pegol Phase 2 Lupus study on BICLA

A multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study Followed by an Observational Period to Evaluate the Efficacy and Safety of Dapirolizumab Pegol in Subjects With Moderately to Severely Active Systemic Lupus Erythematosus

Double Blind period

Observational period (no treatment)

BICLA = British Isles Lupus Assessment Group Disease Activity Index 2004

The primary analysis for BICLA response used Multiple Comparison Procedure–Modeling (MCP-Mod) methodology to identify the best candidate dose-response model: BICLA responder rates did not fit pre-specified dose-response models (best-fitting model [Emax]: p=0.07).

Furie et al., Rheumatology 2021 May 6;keab381. doi: 10.1093/rheumatology/keab381; NCT02804763
DZP today and tomorrow

PHOENYCS GO Phase 3 Study

- Phase 3 double-blind, multi-center, randomized, placebo-controlled, parallel group, global study, to evaluate the efficacy and safety of DZP in patients (N=450) with moderately to severely active SLE despite standard of care treatment (NCT04294667)
- Primary endpoint is achievement of BICLA response at week 48

Ongoing and Future Activities

- PHOENYCS GLIDE Open Label Extension (OLE, NCT04976322) initiated
- Scientific relevance of the pathway in multiple autoimmune diseases are under assessment for additional indications
We believe Biogen has great potential in Lupus

Biogen’s deep and well-established areas of R&D expertise positions us to be a leader in Lupus and other potential autoimmune diseases of high unmet medical need

<table>
<thead>
<tr>
<th>Expertise and History in Immunology</th>
<th>Potential to Launch the First Portfolio in Lupus with DZP and BIIB059</th>
<th>Future Opportunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Utilizing decades of knowledge in immunological pathways</td>
<td>• Two assets with human validation</td>
<td>• Capitalizing on pDC and B-cell biology for assets in Lupus</td>
</tr>
<tr>
<td>• Expertise in multiple modalities targeting immune cells</td>
<td>• Strong development expertise in Lupus and MS</td>
<td>• Life Cycle Management (LCM) opportunities for lead assets</td>
</tr>
</tbody>
</table>