Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based on New Analysis of Larger Dataset from Phase 3 Studies

October 22, 2019

New analysis of larger dataset showed that aducanumab reduced clinical decline in patients with early Alzheimer's disease as measured by the pre-specified primary and secondary endpoints

Based on discussions with the FDA, the Company plans to submit a Biologics License Application in early 2020

Biogen aims to offer aducanumab to eligible patients previously enrolled in clinical studies

The positive results of this new analysis were driven primarily by greater exposure to high dose aducanumab in the larger dataset as compared to data available at the time of the futility analysis

CAMBRIDGE, Mass. and TOKYO, Oct. 22, 2019 (GLOBE NEWSWIRE) -- Biogen (Nasdaq: BIIB) and Eisai, Co., Ltd. (Tokyo, Japan) today announced that, after consulting with the U.S. Food and Drug Administration (FDA), Biogen plans to pursue regulatory approval for aducanumab, an investigational treatment for early Alzheimer's disease (AD). The Phase 3 EMERGE Study met its primary endpoint showing a significant reduction in clinical decline, and Biogen believes that results from a subset of patients in the Phase 3 ENGAGE Study who received sufficient exposure to high dose aducanumab support the findings from EMERGE. Patients who received aducanumab experienced significant benefits on measures of cognition and function such as memory, orientation, and language. Patients also experienced benefits on activities of daily living including conducting personal finances, performing household chores such as cleaning, shopping, and doing laundry, and independently traveling out of the home. If approved, aducanumab would become the first therapy to reduce the clinical decline of Alzheimer's disease and would also be the first therapy to demonstrate that removing amyloid beta resulted in better clinical outcomes.

The decision to file is based on a new analysis, conducted by Biogen in consultation with the FDA, of a larger dataset from the Phase 3 clinical studies that were discontinued in March 2019 following a futility analysis. This new analysis of a larger dataset that includes additional data that became available after the pre-specified futility analysis shows that aducanumab is pharmacologically and clinically active as determined by dose-dependent effects in reducing brain amyloid and in reducing clinical decline as assessed by the pre-specified primary endpoint Clinical Dementia Rating-Sum of Boxes (CDR-SB). In both studies, the safety and tolerability profile of aducanumab was consistent with prior studies of aducanumab.

"With such a devastating disease that affects tens of millions worldwide, today's announcement is truly heartening in the fight against Alzheimer's. This is the result of groundbreaking research and is a testament to Biogen's steadfast determination to follow the science and do the right thing for patients," said Michel Vounatsos, Chief Executive Officer at Biogen. "We are hopeful about the prospect of offering patients the first therapy to reduce the clinical decline of Alzheimer's disease and the potential implication of these results for similar approaches targeting amyloid beta."

Based on discussions with the FDA, the Company plans to file a Biologics License Application (BLA) in early 2020 and will continue dialogue with regulatory authorities in international markets including Europe and Japan. The BLA submission will include data from the Phase 1/1b studies as well as the complete set of data from the Phase 3 studies.

The Company aims to offer access to aducanumab to eligible patients previously enrolled in the Phase 3 studies, the long-term extension study for the Phase 1b PRIME study, and the EVOLVE safety study. Biogen will work towards this goal with regulatory authorities and principal investigators with a sense of urgency.

Study Results
EMERGE (1,638 patients) and ENGAGE (1,647 patients) were Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies designed to evaluate the efficacy and safety of two dosing regimens of aducanumab. These studies were discontinued on March 21, 2019, following the results of a pre-specified futility analysis which relied on an earlier and smaller dataset. The futility analysis was based on data available as of December 26, 2018, from 1,748 patients who had the opportunity to complete the 18-month study period and predicted that both studies were unlikely to meet their primary endpoint upon completion. Futility analyses are common in large clinical studies and use statistical modeling to attempt to predict the outcome of the studies based on a number of pre-specified assumptions and criteria.

Following the discontinuation of EMERGE and ENGAGE, additional data from these studies became available resulting in a larger dataset, which included a total of 3,285 patients, 2,066 of whom had the opportunity to complete the full 18 months of treatment. A new extensive analysis of this larger dataset showed a different outcome than the outcome predicted by the futility analysis. Specifically, the new analysis of this larger dataset showed EMERGE to be statistically significant on the pre-specified primary endpoint (P=0.01). Biogen believes that data from a subset of ENGAGE support the findings from EMERGE, though ENGAGE did not meet its primary endpoint. Biogen consulted with external advisors and the FDA on these different results and their implications.

"This large dataset represents the first time a Phase 3 study has demonstrated that clearance of aggregated amyloid beta can reduce the clinical decline of Alzheimer's disease, providing new hope for the medical community, the patients, and their families," said Dr. Anton Porsteinsson, William B. and Sheila Konar Professor of Psychiatry, Neurology and Neuroscience, director of the University of Rochester Alzheimer's Disease Care, Research and Education Program (AD-CARE), and principal investigator. "There is tremendous unmet medical need, and the Alzheimer's disease community has been waiting for this moment. I commend Biogen, the FDA, the medical community, and the patients and their study partners for their persistence in working to make today's announcement a reality."

In EMERGE, which met its pre-specified primary endpoint in the new analysis, patients treated with high dose aducanumab showed a significant reduction of clinical decline from baseline in CDR-SB scores at 78 weeks (23% versus placebo, P=0.01). In EMERGE, patients treated with high dose aducanumab also showed a consistent reduction of clinical decline as measured by the pre-specified secondary endpoints: the Mini-Mental State Examination (MMSE; 15% versus placebo, P=0.06), the AD Assessment Scale-Cognitive Subscale 13 Items (ADAS-Cog 13; 27% versus placebo, P=0.01), and the AD Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version (ADCS-ADL-MCI; 40% versus placebo, P=0.001). Imaging of amyloid plaque deposition in EMERGE demonstrated that amyloid plaque burden was reduced with low and high dose aducanumab compared to placebo at 26 and 78 weeks (P<0.001). Additional biomarker data of tau levels in the cerebrospinal fluid supported these

clinical findings. Biogen believes that data from patients in ENGAGE who achieved sufficient exposure to high dose aducanumab supported the findings of EMERGE.

In both studies, the most commonly reported adverse events were amyloid-related imaging abnormalities-edema (ARIA-E) and headache. The majority of patients with ARIA-E did not experience symptoms during the ARIA-E episode, and ARIA-E episodes generally resolved within 4 to 16 weeks, typically without long-term clinical sequelae. Biogen plans to present further detail on the new analysis of the larger dataset from EMERGE and ENGAGE at the Clinical Trials on Alzheimer's Disease (CTAD) meeting in December 2019.

After reviewing the data in consultation with the FDA, Biogen believes that the difference between the results of the new analysis of the larger dataset and the outcome predicted by the futility analysis was largely due to patients' greater exposure to high dose aducanumab. Multiple factors contributed to the greater exposure to aducanumab in the new analysis of the larger dataset, including data on a greater number of patients, a longer average duration of exposure to high dose, the timing of protocol amendments that allowed a greater proportion of patients to receive high dose, and the timing and pre-specified criteria of the futility analysis.

Biogen Conference Call and Webcast
On October 22, 2019, at 8:00 a.m. ET, Biogen will host its third quarter 2019 earnings conference call, which will include a discussion of the new analysis of the larger dataset from the Phase 3 studies of aducanumab. This conference call will be broadcast via the internet and will be accessible through the Investors section of Biogen's website, www.biogen.com. Following the live webcast, an archived version of the call will be available on the website. Supplemental information in the form of a slide presentation is also accessible at the same location on the internet and will be subsequently available on the website for at least one month.

About Aducanumab
Aducanumab (BIIB037) is an investigational human monoclonal antibody studied for the treatment of early Alzheimer's disease. Biogen licensed aducanumab from Neurimmune under a collaborative development and license agreement. Since October 2017 Biogen and Eisai have collaborated on the development and commercialization of aducanumab globally.

EMERGE and ENGAGE were Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group studies designed to evaluate the efficacy and safety of aducanumab. The primary objective of the studies was to evaluate the efficacy of monthly doses of aducanumab as compared with placebo in reducing cognitive and functional impairment as measured by changes in the CDR-SB score. Secondary objectives were to assess the effect of monthly doses of aducanumab as compared to placebo on clinical decline as measured by MMSE, ADAS-Cog 13, and ADCS-ADL-MCI.

About Biogen
At Biogen, our mission is clear: we are pioneers in neuroscience. Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological and neurodegenerative diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Kenneth Murray, and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today Biogen has the leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, commercializes biosimilars of advanced biologics, and is focused on advancing research programs in multiple sclerosis and neuroimmunology, neuromuscular disorders, movement disorders, Alzheimer's disease and dementia, ophthalmology, immunology, neurocognitive disorders, acute neurology, and pain.

We routinely post information that may be important to investors on our website at www.biogen.com. To learn more, please visit www.biogen.com and follow us on social media – Twitter, LinkedIn, Facebook, YouTube.

About Eisai Co., Ltd.
Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. Eisai's corporate philosophy is to give first thought to patients and their families, and to increase the benefits that health care provides to them. Under this philosophy, the company endeavors to become a *human health care (hhc)* company. With approximately 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our hhc philosophy by delivering innovative products to address unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

Leveraging the experience gained from the development and marketing of Aricept®, a treatment for Alzheimer's disease and dementia with Lewy bodies, Eisai has been working to establish a social environment that involves patients in each community in cooperation with various stakeholders including the government, healthcare professionals and care workers, and is estimated to have held over ten thousand dementia awareness events worldwide. As a pioneer in the field of dementia treatment, Eisai is striving to not only develop next generation treatments but also to develop diagnosis methods and provide solutions.

For more information about Eisai Co., Ltd., please visit www.eisai.com.

Biogen Safe Harbor
This news release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, about additional results from the Phase 3 clinical studies of aducanumab; the potential clinical effects of aducanumab; the potential benefits, safety, and efficacy of aducanumab; potential regulatory discussions, submissions, and approvals and the timing thereof; clinical development programs, clinical trials, data readouts, and presentations related to aducanumab; the enrollment of any future clinical studies of aducanumab; the treatment of AD; the potential of Biogen's commercial business and pipeline programs, including aducanumab; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai; and risks and uncertainties associated with drug development and commercialization. These statements may be identified by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "possible," "potential," "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 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 without limitation actual timing and content of submissions to and decisions made by the regulatory authorities regarding aducanumab; regulatory submissions may take longer or be more difficult to complete than expected; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including aducanumab; actual timing and enrollment of future studies of aducanumab; the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis; risks of unexpected costs or delays; the risks of other unexpected hurdles; uncertainty of success in the development and potential commercialization of aducanumab; failure to protect and enforce Biogen's data, intellectual property, and other proprietary rights and uncertainties relating to intellectual property claims and challenges; risks relating to the potential launch of aducanumab, including preparedness of healthcare providers to treat patients, the ability to obtain and maintain adequate reimbursement for aducanumab, and other unexpected difficulties or hurdles; product liability claims; and third party collaboration risks. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement, as well as the risk factors identified in Biogen's

most recent annual or quarterly report and in other reports it has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this news release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

Contacts

MEDIA CONTACT:
Biogen Inc.
David Caouette
+ 617 679 4945
public.affairs@biogen.com

INVESTOR CONTACT:
Biogen Inc.
Joe Mara
+781 464 2442
IR@biogen.com

MEDIA CONTACT:
Eisai Co., Ltd.
Public Relations Department
TEL: +81-(0)3-3817-5120
Eisai Inc.
Public Relations Department
TEL: +1-551-262-2686

INVESTOR CONTACT:
Eisai Co., Ltd.
Investor Relations Department
TEL: +81-(0)3-3817-5327