Eisai and Biogen Announce Detailed Results of Phase II Clinical Study of BAN2401 in Early Alzheimer's Disease at Alzheimer's Association International Conference (AAIC) 2018

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TOKYO and CAMBRIDGE, Mass., July 25, 2018 (GLOBE NEWSWIRE) -- Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq:BIIB) (Headquarters: Cambridge, Massachusetts, United States, CEO: Michel Vounatsos, "Biogen") announced detailed results from the Phase II study (Study 201) with BAN2401, an anti-amyloid beta (Aβ) protofibril antibody, in 856 patients with early Alzheimer's disease as part of Session DT-01 "Recent Developments in Therapeutics" (Presentation number: DT-01-07) at the Alzheimer's Association International Conference (AAIC) 2018 being held in Chicago, Illinois, United States on July 25. This abstract was accepted for Late Breaking oral presentation at AAIC.

Study 201 (ClinicalTrials.gov identifier NCT01767311) is a placebo-controlled, double-blind, parallel-group, randomized Phase II clinical study in 856 patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's dementia (collectively known as early Alzheimer's disease) with confirmed amyloid pathology in the brain. Patients were randomized to five dose regimens, 2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly and 10 mg/kg biweekly, or placebo. This study used a Bayesian Adaptive Randomization Design to automatically allocate newly enrolled patients into the study to treatment arms showing higher probability of efficacy based on the results of interim analyses.

The study assessed changes from baseline to 18 months in biomarkers measuring the underlying disease pathophysiology, including changes in amyloid accumulated in the brain as measured by amyloid PET (positron emission tomography). The clinical endpoints of Alzheimer's Disease Composite Score (ADCOMS), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) and Clinical Dementia Rating Sum of Boxes (CDR-SB) were also assessed from baseline to 18 months of treatment.

Through Bayesian interim analyses, the highest doses of 10 mg/kg monthly and 10 mg/kg biweekly were determined to be the treatment dosages with higher efficacy early in the trial, and as a result, the proportion of patients allocated to these treatment arms was greater (placebo: 247 patients, 2.5 mg/kg biweekly: 52 patients, 5 mg/kg monthly: 51 patients, 5 mg/kg biweekly: 92 patients, 10 mg/kg monthly: 253 patients, 10 mg/kg biweekly: 161 patients). Following a regulatory request (outside of the United States) in July 2014, the allocation of APOE4 carriers to the 10 mg/kg biweekly treatment arm was restricted, resulting in fewer APOE4 carriers in this arm and more patients being allocated to the 10 mg/kg monthly treatment arm.

BAN2401 demonstrated a dose-dependent reduction in amyloid plaques as measured by amyloid PET, and this reduction was statistically significant at all doses. At the highest dose of BAN2401 (10 mg/kg biweekly), an analysis of amyloid accumulated in the brain using standardized PET as measured on the Centiloid scale showed an observed mean at baseline of 74.5 and at 18 months of 5.5. Using a Mixed-effects Model with Repeated Measures (MMRM), the mean reduction in amyloid load was 70 units, which was statistically significant ($p<0.0001$). In amyloid PET image visual read, BAN2401 demonstrated a dose dependent conversion from amyloid positive to negative, and at the highest dose, 81% of patients converted from amyloid positive to negative at 18 months ($p<0.0001$).

Conventional statistical methods on predefined clinical endpoints at the 18 month final efficacy time point confirmed a dose-dependent slowing in cognitive decline from baseline on ADCOMS. The highest treatment dose of 10 mg/kg biweekly demonstrated a statistically significant slowing of clinical decline of 30% compared to placebo at 18 months ($p=0.034$). A statistically significant slowing of decline on ADCOMS was observed as early as 6 months ($p<0.05$) as well as at 12 months ($p<0.05$). Dose-dependent slowing in cognitive decline from baseline on ADAS-Cog was also observed for BAN2401, with the highest treatment dose of BAN2401 demonstrating a significant slowing of clinical decline compared to placebo at 18 months (47% slower decline, $p=0.017$). Furthermore, dose-dependent slowing in cognitive decline from baseline on CDR-SB was observed, surpassing the pre-specified difference of 25% over the duration of the study. At 18 months, slowing of clinical decline for the highest treatment dose of BAN2401 compared to placebo on CDR-SB was 26%. The rate of clinical decline for the placebo group was consistent with the results of research by the Alzheimer's Disease Neuroimaging Initiative (ADNI) in the United States.

In a Bayesian analysis of ADCOMS at 12 months, the estimated probability that the highest dose of BAN2401 slows clinical decline more than placebo was 98%. While the criteria for early success at 12 months was pre-specified as an 80% or higher estimated probability of demonstrating a clinically significant difference (a 25% or greater slowing in clinical decline) from baseline compared to placebo, the actual probability for this criteria was 64% according to Bayesian analysis.

A dose-dependent increase in Aβ levels in cerebrospinal fluid (CSF) in patients on BAN2401 (highest dose at 18 months: $p<0.0001$) was observed. Combined analysis of patients receiving BAN2401 at 10 mg/kg (either monthly or biweekly) demonstrated a statistically significant reduction in total tau over time compared to placebo ($p<0.05$).

BAN2401 demonstrated an acceptable tolerability profile through 18 months of study drug administration. The incidence rate of treatment-related adverse events was 26.5% for the placebo arm, 53.4% for the 10 mg/kg monthly treatment arm and 47.2% for the 10 mg/kg biweekly treatment arm. The most common treatment emergent adverse events were Amyloid Related Imaging Abnormalities (ARIA) and infusion-related reactions. Incidence of ARIA-E (edema) was 9.9% at the highest treatment dose, and not more than 10% in any of the treatment arms. Incidence of ARIA-E in APOE4 carriers was 14.6% at the highest dose. Per protocol, all patients presenting with ARIA-E on MRI were discontinued in the study. The incidence rate of serious adverse events was 17.6% for the placebo arm, 12.3% for the 10 mg/kg monthly treatment arm and 15.5% for the 10 mg/kg biweekly arm.

This release discusses investigational uses of an agent in development and is not intended to convey conclusions about efficacy or safety. There is no guarantee that any investigational uses of such product will successfully complete clinical development or gain health authority approval.

Biogen Safe Harbor Statement

This press release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 about results from the Phase II study of BAN2401; the potential clinical effects of BAN2401; the potential benefits, safety, and efficacy of BAN2401 and therapies for other neurological diseases; the clinical development program for BAN2401; risks and uncertainties associated with drug development and commercialization; the timing and status of current and future regulatory filings; Biogen's strategy and plans; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai; and the potential of Biogen's commercial business and pipeline programs, including BAN2401, elenbecestat, and aducanumab. These forward-looking statements may be accompanied by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," 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 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, unexpected concerns that may arise from additional data, analysis, or results obtained during clinical trials; 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 BAN2401, elenbecestat, and/or aducanumab; the occurrence of adverse safety events; risks of unexpected costs or delays; the risks of other unexpected hurdles; uncertainty of success in the development and potential commercialization of BAN2401, elenbecestat, and/or aducanumab, which may be impacted by, among other things, unexpected concerns that may arise from additional data or analysis, the occurrence of adverse safety events, failure to obtain regulatory approvals in certain jurisdictions, failure to protect and enforce Biogen's data, intellectual property, and other proprietary rights and uncertainties relating to intellectual property claims and challenges; uncertainty as to whether the anticipated benefits and potential of Biogen's collaboration arrangement with Eisai can be achieved; 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 Biogen 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 press 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.

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<Notes to editors>

1. About BAN2401

BAN2401 is a humanized monoclonal antibody for Alzheimer's disease that is the result of a strategic research alliance between Eisai and BioArctic. BAN2401 selectively binds to neutralize and eliminate soluble, toxic Aβ aggregates that are thought to contribute to the neurodegenerative process in Alzheimer's disease. As such, BAN2401 may have the potential to have an effect on disease pathology and to slow down the progression of the disease. Eisai obtained the global rights to study, develop, manufacture and market BAN2401 for the treatment of Alzheimer's disease pursuant to an agreement concluded with BioArctic in December 2007. In March 2014, Eisai and Biogen entered into a joint development and commercialization agreement for BAN2401 and the parties amended that agreement in October 2017.

2. About Study 201

Study 201 is a placebo-controlled, double-blind, parallel-group, randomized Phase II clinical study in 856 patients with mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's dementia (collectively known as early Alzheimer's disease) with confirmed amyloid pathology in the brain. This study used Bayesian Adaptive Randomization Design to automatically allocate newly enrolled patients into the study to treatment arms showing higher probability of efficacy based on the results of interim analyses. The study design included five dose regimens and placebo, and considered the efficacy of BAN2401 as an exploratory endpoint as well as dose responsiveness through 16 interim analyses that assessed potential for early success, an analysis based on ADCOMS at 12 months, and a comprehensive final analysis at 18 months. Patients who received treatment with BAN2401 were randomized to five dose regimens, 2.5 mg/kg biweekly (52 patients), 5 mg/kg monthly (51 patients), 5 mg/kg biweekly (92 patients), 10 mg/kg monthly (253 patients), or and 10 mg/kg biweekly (161 patients). Biomarker endpoints included changes in Aβ accumulated in the brain as measured by amyloid PET (positron emission tomography) as well as in cerebrospinal fluid (CSF), while ADCOMS (Alzheimer's Disease Composite Score), Clinical Dementia Rating Sum of Boxes (CDR-SB) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) were measured as efficacy endpoints (clinical).

3. About ADCOMS

Developed by Eisai, ADCOMS (AD Composite Score) combines items from the ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale), CDR-SB (Clinical Dementia Rating Sum of Boxes) and the MMSE (Mini-Mental State Examination) scales to enable a sensitive detection of changes in clinical functions of early Alzheimer's disease symptoms and changes in memory. This Study 201 utilizes ADCOMS as its key endpoint for assessing clinical symptoms.

4. About Amyloid PET Imaging

Amyloid PET (Positron Emission Tomography) imaging is a diagnostic method that enables the visualization of amyloid plaque present in the brain as well as the quantitative evaluation of amyloid plaque distribution and accumulation in the brain via administration of a minute amount of PET tracer, which specifically binds to amyloid plaque and marks it with positron. Amyloid PET imaging enables the assessment of pathology change and assistance of diagnosis of patients with Alzheimer's-disease including MCI, and estimates the clinical effect of disease modifiers based on the amyloid hypothesis. SUVr (Standard Uptake Value Ratio) calculates the ratio of strength of accumulation of PET tracer in a region of interest in the brain to an area of the brain (reference region) which shows low and stable accumulation of PET tracer. These SUVr values can be used to quantitatively compare and evaluate the accumulation of amyloid. When integrating and assessing biomarkers of the change in Aβ accumulation measured by different tracers, it is necessary to compensate for the differences in measured values between the PET tracers. This has led to the development of a 100-point scale by the GAIIN Centiloid project, termed "Centiloid," which is an average value of zero in "high certainty" amyloid negative subjects and an average of 100 in "typical" Alzheimer's disease (AD) patients (Klunk et al., 2015). In this study, this Centiloid scale was used to standardize SUVr measurement values to evaluate the decrease in amyloid burden.

5. About the Joint Development Agreement between Eisai and Biogen for Alzheimer's Disease

Eisai and Biogen are widely collaborating on the joint development and commercialization of Alzheimer's disease treatments. Eisai serves as the lead in the co-development of elenbecestat, a BACE inhibitor, and BAN2401, an anti-amyloid beta (Aβ) protofibril antibody, while Biogen serves as the lead for co-development of aducanumab, Biogen's investigational anti-amyloid beta (Aβ) antibody for patients with Alzheimer's disease, and the companies plan to pursue marketing authorizations for the three compounds worldwide. If approved, the companies will also co-promote the products in major markets, such as the United States, the European Union and Japan.

As to BAN2401 and elenbecestat, both companies will equally split overall costs, including research and development expenses. Eisai will book all sales for elenbecestat and BAN2401 following marketing approval and launch, and profits will be equally shared between the companies.

6. About Eisai Co., Ltd.

Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our *human health care* (*hhc*) philosophy. 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.

7. 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. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissman, Heinz Schaller, Kenneth Murray and Nobel Prize winners Walter Gilbert and Phillip Sharp, and today has the leading portfolio of medicines to treat multiple sclerosis; has introduced the first and only approved treatment for spinal muscular atrophy; and is focused on advancing neuroscience research programs in Alzheimer's disease and dementia, neuroimmunology, movement disorders, neuromuscular disorders, pain, ophthalmology, neuropsychiatry, and acute neurology. Biogen also manufactures and commercializes biosimilars of advanced biologics.

Biogen routinely posts information that may be important to investors on its website at www.biogen.com. To learn more, please visit www.biogen.com and follow Biogen on social media – Twitter, LinkedIn, Facebook, Youtube.

8. About BioArctic AB

BioArctic AB (publ) is a Swedish research-based biopharma company focusing on disease modifying treatments and reliable biomarkers and diagnostics for neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. The company also develops a potential treatment for Complete Spinal Cord Injury. BioArctic focuses on innovative treatments in areas with high unmet medical needs. The company was founded in 2003 based on innovative research from Uppsala University, Sweden. Collaborations with universities are of great importance to the company together with our strategically important global partners in the Alzheimer (Eisai) and Parkinson (AbbVie) projects. The project portfolio is a combination of fully funded projects run in partnership with global pharmaceutical companies and innovative in-house projects with significant market- and out-licensing potential. BioArctic's B-share is listed on Nasdaq Stockholm Mid Cap (STO:BIOA B). www.bioarctic.com.