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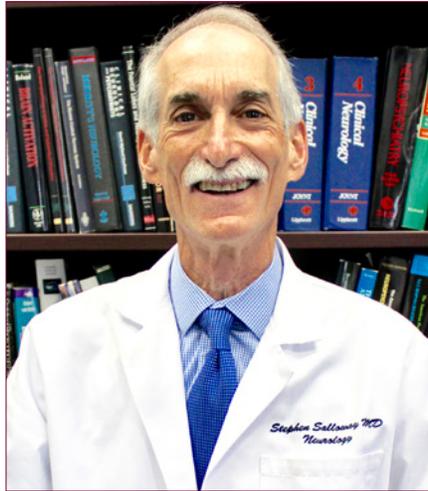
## Biogen seeking FDA review in early 2020 for Aducanumab to treat early AD

*Investigational drug studied at Butler Hospital's Memory and Aging Program may become first new treatment for Alzheimer's disease in 16 years*

Biogen, maker of the investigational drug Aducanumab, announced on Oct. 22nd that it will seek review of the drug by the US Food and Drug Administration (FDA) in early 2020. If approved, it will become the first drug to remove amyloid protein from the brain and slow the progression of Alzheimer's disease (AD). The drug was studied in multiple clinical trials at sites across the country including at Butler Hospital's Memory and Aging Program, a world leader in Alzheimer's research.

**STEPHEN SALLOWAY, MD, MS**, Director of Neurology and the Memory and Aging Program at Butler Hospital and the Martin M. Zucker Professor of Psychiatry and Human Behavior and professor of neurology at the Warren Alpert Medical School of Brown University, says he is hopeful that the drug will be approved and optimistic about its potential to slow the progression of Alzheimer's in those with the early stages of the disease.

"In March of this year, Biogen abruptly halted its ongoing studies of



aducanumab when an analysis of the initial data showed it was unlikely to be successful in meeting the benchmarks necessary to be considered a viable therapy. It was a crushing blow to researchers and study participants around the nation, including the 60 trial participants here at the Memory and Aging Program. Many of our patients had seemed to be benefitting from the drug," Dr. Salloway said.

"But as additional data came in, particularly from trial participants who had been administered a higher dose of the drug, it became apparent that aducanumab yielded clinically significant results for the successful treatment of early Alzheimer's disease," Dr. Salloway continued. "With this new information, Biogen is now moving forward with the process to make the drug available to the public, and I'm very happy that Biogen will start a new re-dosing study so that patients who participated in the initial trials will be able to restart treatment with the drug."

"This is very exciting news for our patients. Rhode Islanders who participated in the original study made a huge contribution to the success of this trial and their courage and dedication is very inspiring," said Dr. Salloway. "We are proud of our participants and the role our program at Butler Hospital has played in bringing this potential treatment for Alzheimer's disease to fruition." ❖

## Biogen plans regulatory filing based on new analysis of larger dataset from Phase 3 studies

CAMBRIDGE, MASS. AND TOKYO, OCT. 22, 2019 (GLOBE NEWSWIRE) – Biogen and Eisai, Co., Ltd. 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.

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.

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. ❖

## Women & Infants' Dr. Erika Werner and OB/GYN Dept. receive \$2.5M grant

*Dr. Werner also awarded a National Institute of Child Health and Human Development (NICHD) five-year, \$7 million grant*



**ERIKA WERNER, MD, MS**, division and fellowship director of the Division of Maternal Fetal Medicine, associate professor of obstetrics and gynecology at The Warren Alpert Medical School of Brown University, and associate professor of epidemiology at The Brown University School of Public Health, in connection with the Department of Obstetrics and

Gynecology at Women & Infants Hospital, was recently awarded a grant from the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) last week.

The organization, whose mission is to conduct and support research on many of the most common, costly, and chronic conditions to improve health, awarded a five-year \$2.5 million grant which will allow Dr. Werner and her team to work with four other centers focused on diabetes in pregnancy (MGH, Yale, Northwestern, and Kaiser) across the country, to identify better ways to diagnose glucose metabolism abnormalities in pregnancy, in an effort to optimize maternal and child health.

While the study began October 1, participant recruitment will likely begin next year at several Care New England prenatal clinics. Individuals involved in the study will be asked to wear small devices to monitor their glucose continuously for several days during their pregnancy.

In addition, Dr. Werner was also awarded a National Institute of Child Health and Human Development (NICHD)

five-year, \$7 million grant last month, to investigate health disparities.

This grant is in collaboration with RTI, Brown University's **DAVID SAVITZ**, associate dean for research, and professor of epidemiology, obstetrics and gynecology, and pediatrics, as well as the Hassenfeld Child Health Innovation Institute, in a research effort to better understand the developmental origins of health disparities, or differences in developmental outcomes between socially advantaged and disadvantaged groups.

The study entitled, "The Prenatal and Childhood Mechanisms of Health Disparities", is designed to recruit a diverse cohort of pregnant parents in the first trimester and follow them throughout pregnancy and during the first year of life.

"Specifically the study will recruit 2,000 pregnant women, 500 of whom are Black or African American, and 500 of whom are Hispanic or Latina, to better understand how socioeconomic and race/ethnic disparities during pregnancy and in the first year of life, affect health-related behaviors, maternal neuroendocrine-immune, and metabolic responses during pregnancy, and children's health and development."

Said Dr. Werner, "I would like to express my thanks to both agencies for their recognition and acknowledgment of this most important work and the clinical advancements that could result from these studies. I would also like to extend my sincere appreciation to all of my colleagues, research collaborators, Brown University, and especially the Hassenfeld Child Health Innovations Institute and Women & Infants Hospital for fostering an environment of academic and clinical excellence." ❖

### The Rhode Island Medical Society's Eleventh Hour CME Event

On a biennial basis, Rhode Island physicians are required to document to the Board of Medical Licensure and Discipline that they have earned a minimum of forty (40) hours of American Medical Association, Physician Recognition Award or American Osteopathic Association (AOA Category 1a) continuing medical education credits. At least four (4) hours of continuing medical education shall be earned on topics of current concern as determined by the director of the RI Department of Health.

#### 2020 topics will be announced soon. Prior years' topics have included:

- Risk Management
- Opioid Pain Management and Chronic Pain Management
- End of Life and Palliative Care
- Antimicrobial Stewardship

**Watch your email for more information regarding the date, topics, and registration deadlines for the 2020 event.**

#### Spring 2020 date to be announced

The Rhode Island Medical Society's **Eleventh Hour Educational Event** is usually held on a Saturday in April from 7:30am to 1pm, and is designed to assist physicians obtain the four hours of required CME before re-licensure applications are due on June 1, 2020.

RIMS members will receive a reduced registration fee.

## Dr. Linda J. Resnik awarded \$1.5M grant for prostheses research project



**Dr. Linda J. Resnik**, center right, career research scientist with the VA Rehabilitation Research and Development Service's Center for Neurorestoration and Neurotechnology at the Providence VA Medical Center, with team members, from left to right, **Matthew Borgia**, **Rachel Underwood**, **Josephine Airoidi**, **Eileen Small** and **Sarah Biester**, at the Providence VAMC Sept. 24, 2019. Dr. Resnik was awarded a three-year, \$1.5 million contract by the Department of Defense for a research study that will compare the effectiveness of different prostheses types.

[PROVIDENCE VA MEDICAL CENTER PHOTO BY WINFIELD DANIELSON]

PROVIDENCE – A career research scientist with the VA Rehabilitation Research and Development Service's Center for Neurorestoration and Neurotechnology at the Providence VA Medical Center was awarded a three-year contract by the Department of Defense Sept. 30th for a research study that will compare the effectiveness of different prostheses types.

"This study will be the largest, most comprehensive study comparing upper limb prostheses and components," said **DR. LINDA J. RESNIK**, the principal investigator for the study, who is also a professor in the Department of Health Services, Policy and Practice at Brown University. "Providing prostheses that are optimally matched to the patient will improve satisfaction, reduce abandonment rates and improve overall quality of life for people with upper-limb amputations."

The nearly \$1.5 million contract, awarded by DOD's Orthotics and Prosthetics Outcomes Research Program to Ocean State Research Institute Inc., the nonprofit associated with the Providence VAMC, will provide evidence to guide prosthesis prescription by comparing effectiveness of upper limb prostheses and whether specific groups of patients are more likely to benefit from different device types. It builds on an existing study and will allow comparisons of outcomes for approximately 300 upper limb prosthesis users. ❖

## Bystander CPR: 'Off-Duty' Kent Hospital staff save local child's life

Earlier this summer, **BRYDIE THOMASIAN, MSW, LICSW**, director of behavioral health and clinical social work at Kent Hospital, was relaxing in her yard in Coventry, RI, with friends and their young children. She had recently completed recertification in basic life support and cardiopulmonary resuscitation (CPR), but had no idea her skills would be needed that afternoon.

Suddenly, her friend Paulina Oliveira's 14-month-old daughter began choking on a piece of fruit and stopped breathing, quickly becoming unresponsive and presenting discoloration of the skin. Taking action quickly, Brydie initiated back blows followed by chest compressions to try and dislodge the food while others called 9-1-1. **EMILY COLYER, DO**, emergency medicine physician at Kent Hospital, who lives nearby, ran over after hearing the calls for help.

Together, the two were able to open the child's airway while waiting for the ambulance to arrive. The child was briefly hospitalized but made a quick and complete recovery greatly due to the training and teamwork demonstrated by these two Kent employees.

Paulina Oliveira, mother of the toddler, said, "I would never wish this experience upon any parent. We are so lucky to have had a positive outcome, due to Brydie's quick reaction, knowledge, and composure. She saved my child's life."

Paulina continued, "This event drove home the importance of being certified in CPR. After this experience, both my husband and I went to take classes."

According to the National Safety Council, choking is the fourth leading cause of unintentional injury or death. Choking is also a leading cause of death in children and infants, who require a different rescue procedure than adults.

Thomasian said, "I think that CPR training is easy to overlook because we all hope we will never find ourselves in a situation that calls for it. I certainly never thought I would have to use the training, but I'm extremely grateful for it now. I encourage everyone to consider taking a course. No one ever wants to witness a life-threatening crisis but we absolutely don't want to be wishing we took a course if that crisis comes."

Dr. Colyer added, "In this event, as well as many pediatric airway obstruction and respiratory arrest cases, time is of the essence. It was a blessing that Brydie was there, trained in CPR and basic life support, and was able to take action immediately. Had that not been the case, the outcome for Paulina's daughter may not have been as bright." ❖



Pictured from left to right: **Emily Colyer, DO**, Kent Hospital emergency medicine physician, and **Brydie Thomasian, MSW, LICSW**, director of behavioral health and clinical social work.