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**LATE BREAKING RESEARCH RESULTS FROM THE
ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2011**

PARIS, July 20, 2011 – Late breaking research results reported today at the Alzheimer's Association International Conference 2011 (AAIC 2011) in Paris include:

- Findings from a survey by Alzheimer Europe and the Harvard School of Public Health of experiences with and attitudes about Alzheimer's disease, especially regarding diagnosis, in France, Germany, Poland, Spain and the U.S. It reveals that while people fear Alzheimer's second only to cancer, the overwhelming majority says they would go to the doctor or take a loved one for further evaluation if they saw symptoms of memory loss and confusion.
- Two studies reported at AAIC 2011 describe (1) a re-evaluation of the Phase II safety results for bapineuzumab (Pfizer, Janssen Alzheimer Immunotherapy), a passive immunotherapy being tested for mild to moderate Alzheimer's disease, and (2) the first report of long-term safety data for bapineuzumab treatment beyond 78 weeks.
- Two other studies investigate new methods of early detection of Alzheimer's, tracking progression of the disease, identifying participants for research trials and measuring the impact of therapies. One study uses blood measurements for estimating the amount of a toxic substance known as beta amyloid deposited in the brain; the other study suggests that abnormal levels of certain proteins in cerebrospinal fluid (including beta amyloid) in people with mild cognitive impairment may indicate who will develop Alzheimer's within the next 10 years.

“Findings from these studies highlight the collective advancement of knowledge and understanding found at the Alzheimer's Association International Conference,” said William Thies, Ph.D., Chief Medical and Scientific Officer at the Alzheimer's Association. “The progress we have seen will improve current diagnosis, bring the field closer to earlier detection and treatment options, and ultimately lead to effective disease-modifying therapies.”

“That said, Alzheimer's is the sixth-leading cause of death in the U.S., and the fifth-leading cause of death for those aged 65 and older, yet it is the only cause of death among the top 10 without a way to prevent it, cure it or even slow its progress. More broadly, the total estimated worldwide costs of dementia are \$604 billion in 2010, according to the latest World Alzheimer Report, and are already affecting health systems around the world. For the families who are forced to face Alzheimer's the anguish is universal. We must escalate the commitment to ending Alzheimer's disease and dementia around the world,” Thies said.



International Survey Reveals Experiences with and Attitudes Towards Alzheimer's Disease

Concerns that people with early symptoms of Alzheimer's might not seek medical evaluation, and thus miss opportunities for early detection and medical intervention, led Alzheimer Europe to survey the public about their attitudes and beliefs concerning the disease.

“The reason for the survey is related to the importance of promoting early Alzheimer's diagnosis, and the fact that early diagnosis is included in national dementia plans in France, England, Norway and Scotland,” said Jean Georges, Executive Director of Alzheimer Europe. “In Europe, we are still encountering resistance from some in the medical profession due to their nihilistic views regarding the value of an early diagnosis and the benefits of current treatments. We were hoping that a public opinion survey would show a willingness to gain a diagnosis and the value of confronting the disease.”

Data reported at AAIC 2011 are derived from a five-country survey conducted by the Harvard School of Public Health. The study was supported by a grant to Alzheimer Europe from Bayer. A total of 2,678 adults aged 18 and over were interviewed by telephone in France (n=529), Germany (n=499), Poland (n=509), Spain (n=502), and the United States (n=639) in February 2011.

In four of the five countries, Alzheimer's was the disease that people were second most afraid of getting, behind cancer. In the fifth country, Poland, Alzheimer's was third behind cancer and heart disease. The percentage of respondents who most feared getting cancer/Alzheimer's were: France 41.0/26.9 percent, Germany 43.8/23.0 percent, Poland 43.1/12.1 percent, Spain 48.5/23.6 percent, U.S. 39.3/21.9 percent. A large proportion of respondents were worried that they or a family member will get Alzheimer's, with significant differences between the countries (43 percent to 95 percent).

This strong fear exists even though the survey shows that Alzheimer's is under recognized as a fatal disease, especially outside the U.S. The percentage of people who answered “yes” to the question, “Do you think that Alzheimer's disease is a fatal disease or not?” was: France 44.4 percent, Germany 32.7 percent, Poland 34.3 percent, Spain 41.7 percent, U.S. 61.0 percent

A very high percentage of respondents – more than eight in ten (85–95 percent) in each of the five countries – said that if they were exhibiting confusion or memory loss, they would go to a doctor to determine if the cause of the symptoms was Alzheimer's disease. The numbers were even higher (94–99 percent) for wanting a family member experiencing memory loss to see a doctor for evaluation.

Many of the respondents believe there is now an effective medical or pharmaceutical treatment to slow the progression of Alzheimer's disease and make the symptoms less severe (27–63 percent). Between 38 and 59 percent believed there was a reliable test currently available to determine if a person is in the early stages of Alzheimer's disease (though neither of these statements is true).

“Many of the public have high expectations about the possibilities of treatment alternatives and medical testing. It is important for doctors to talk to patients about what treatment and testing options are or are not available,” said Robert Blendon, ScD, Professor of Health Policy and Political Analysis from the Harvard School of Public Health.

Respondents expressed strong support for increasing government spending for research on new treatments for Alzheimer's disease: France 82.6 percent, Germany 68.2 percent, Poland 74.7 percent, Spain 83.0 percent, U.S. 67.4 percent. However, the majority of survey respondents said it "would not make much difference" in how they voted for a candidate for national office.

"The fear and concern uncovered by our survey is evidence of the urgency with which the public wants the Alzheimer's issue addressed, and eventually eliminated. Governments should follow the expressed desires of their constituents and increase funding for Alzheimer's research," Georges said.

"The willingness to get a diagnosis that was expressed by the survey respondents is encouraging, however better public education is needed. We need to address potentially unrealistic expectations about the availability of a definitive early test and effective treatment for the disease, while providing positive reasons for seeking a diagnosis in the absence of disease modifying treatments," Georges added.

Two Studies Report Updated Phase II and Long-Term Safety Data on Bapineuzumab, an Experimental Immunotherapy for Alzheimer's

Initial reports of Phase II study results of bapineuzumab, a humanized monoclonal antibody to beta amyloid being tested as therapy for mild to moderate Alzheimer's disease by Pfizer and Janssen Alzheimer Immunotherapy, raised concerns due to side effects of vasogenic edema (VE) – an abnormal accumulation of fluid in the brain. Symptoms can include headache, loss of coordination, weakness, disorientation, memory loss and hallucinations.

In the wake of concerns that all amyloid-modifying therapies may cause VE, a workgroup of the Alzheimer's Association Research Roundtable, a consortium of scientists from the pharmaceutical, biotechnology, diagnostics, imaging and cognitive testing industries, and senior staff and advisors from the Association, reviewed the relevant publicly available information. This included natural history studies and spontaneous occurrence of these adverse events in aging and Alzheimer's populations, occurrence in the setting of trials of amyloid-lowering agents for Alzheimer's and similar clinical conditions from which parallels might be drawn, and existing animal models that may elucidate the underlying mechanisms.

The workgroup developed specific recommendations regarding the conduct of Alzheimer's clinical trials in the setting of what are now referred to as amyloid-related imaging abnormalities (ARIA), which were published last week in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. ARIA include MRI signal abnormalities thought to represent "vasogenic edema" and sulcal effusions (ARIA-E) and GRE/MRI signal abnormalities thought to represent hemosiderin deposits (ARIA-H).

Two studies reported at AAIC 2011 describe a re-evaluation of the Phase II study safety results in the light of these new perspectives on ARIA and the first report of long-term safety data for bapineuzumab treatment beyond 78 weeks.

Long-term Safety Data

Stephen Salloway, MD, MS; Butler Hospital and Brown University, Providence, Rhode Island, and colleagues monitored the long-term safety of bapineuzumab in an ongoing open-label Phase II extension study in 194 participants; 158 were from a 78-week study in mild to moderate Alzheimer's and 36 were from a study evaluating bapineuzumab delivered subcutaneously. Treatment was given every 13 weeks without a placebo group. Eighty-six (86) people received bapineuzumab treatment for at least three years and 43 for at least four years at the time of this interim analysis.

The researchers found that most participants (91 percent) in the study population reported adverse events (AEs). AEs in more than 10 percent of subjects were: fall (14.4 percent), agitation (13.4 percent), urinary tract infection (12.4 percent), upper respiratory tract infection (12.4 percent) and anxiety (10.8 percent).

Approximately 24 percent of patients reported AEs that were considered related or possibly related to bapineuzumab; most of these (approx. 85 percent) were considered mild or moderate. Reported treatment-related AEs in more than one percent of study participants included: Amyloid-Related Imaging Abnormalities or ARIA-E (9.3 percent), headache (2.1 percent), evidence of microscopic bleeding in the brain (1.5 percent), convulsion (1.5 percent) and flushing (1.5 percent).

Approximately 35 percent of participants reported serious AEs (SAEs); SAEs in more than two percent of subjects included: ARIA-E (6.2 percent), fall (2.6 percent), hip fracture (2.1 percent), convulsion (2.1 percent), worsening dementia of the Alzheimer's type (2.1 percent), and confusion (2.1 percent).

The risk of developing ARIA-E diminished with an increasing number of infusions of the drug; cumulative risk of developing ARIA-E dropped from 6.7 percent for infusions 1-3 compared to 2.7 percent for infusions 4-10.

“Overall, bapineuzumab was generally well-tolerated and side-effects tended to be mild,” Salloway said. “Open label extension studies such as this one can supplement randomized trial data to help us better understand safety and long term clinical effects. However, only adequately powered, randomized, prospective, placebo-controlled clinical trials can give us objective evaluations of safety and efficacy. Phase III trials with bapineuzumab are now underway.”

Re-evaluation of Phase II Safety Data

Reisa Sperling, MD, MMSc; Brigham and Women's Hospital, Harvard Medical School, Boston, and colleagues conducted a systematic review of more than 2,000 MRI scans from 262 Alzheimer's patients who participated in the Phase II bapineuzumab studies to investigate the occurrence of amyloid-related imaging abnormalities on MRI thought to represent vasogenic edema and sulcal effusions (ARIA-E).

“Because radiologists may not have detected all ARIA-E during the Phase II studies, we conducted a systematic, central review of all study MRIs to better estimate the incidence and risk factors for ARIA-E related to bapineuzumab,” Sperling said.

Subjects included in risk analyses had at least one dose of bapineuzumab, no evidence of ARIA-E abnormalities at baseline, and at least one post-treatment MRI.

The researchers identified 36 cases that were thought to be associated with bapineuzumab treatment, 21 (60 percent) of which were identified during the Phase II trials. Eight subjects with ARIA-E, all previously identified during the clinical studies, had symptoms reported as related to study drug. The additional 15 cases (40 percent) of ARIA-E identified only during this study showed more subtle MRI changes, according to the researchers. These patients did not appear to exhibit symptoms related to ARIA-E.

The scientists found that risk factors for ARIA-E included both the apolipoprotein E e4 allele (APOE-e4, a common genetic risk factor for Alzheimer's) and a higher dose of bapineuzumab, consistent with previous observations.

“The underlying cause of ARIA-E is under active investigation,” Sperling said, “but the risk factors identified in this study suggest that these imaging abnormalities may be related to accumulation and clearance of amyloid from blood vessels in the brain. The Phase 3 bapineuzumab trials have incorporated adjustments to dose and attention to APOE e4 status, and these data support those choices.”

“Clinical observations from the more subtle ARIA-E cases are encouraging and suggest that the milder end of the ARIA-E spectrum may be asymptomatic,” Sperling added.

“The most encouraging finding from these studies is that ARIA-E seems to occur less frequently as time goes on,” Thies observed. “In addition, the risk factor findings suggest that we may be able to test people ahead of time for increased risk of this side effect and possibly administer a lower dose to patients identified as being at higher risk to minimize the likelihood that the side effect will occur. The other side effect findings are generally consistent with clinical trials in almost any disease with a patient population in this older age group.”

Two Studies Illuminate Possible Alzheimer's Biomarkers in Blood and Spinal Fluid

Early detection of Alzheimer's – even before outward memory and thinking symptoms are evident – is very important as the next generation of disease-modifying therapies are most likely to be effective if initiated during the earliest stages of the disease. To that end, it is believed that build-up of a toxic molecule known as beta amyloid in the brain of people with Alzheimer's occurs prior to cognitive decline. Thus, an accurate measurement or indicator of increased amyloid deposits in the brain could possibly provide an earlier diagnosis compared to current methods of cognitive testing, and also possibly indicate the severity or progression of the disease.

Estimating Amyloid Build-up in the Brain Using Blood Measurements

One of the stated objectives of the Australian Imaging, Biomarker and Lifestyle (AIBL) study is to find a prognostic blood test for Alzheimer's, driven by the need for an early, cost effective and easily accessible screening test for the disease.

According to the AIBL scientists, an accurate indicator of increased levels of deposited amyloid in the brain holds the possibility for early detection of Alzheimer's. They state that PET scans for brain amyloid, although powerful and informative about deposits of amyloid in the brain, are not widely available and are considered too costly for widespread population screening. Thus, they are generally reserved for research purposes. Spinal fluid amyloid measurements have been shown to correlate with the amount of deposited amyloid in the brain; however, the procedure for obtaining spinal fluid is considered too invasive by some.

Samantha Burnham, PhD, CSIRO, Perth, Australia and colleagues in AIBL are working towards a more economic and accessible blood-based alternative. To this end, AIBL scientists have been monitoring, over time, the blood chemistry, cognitive ability and lifestyle factors of 768 healthy elderly people, 133 people with mild cognitive impairment (MCI) and 211 people with Alzheimer's. They have also performed genetic and neuroimaging testing on 288 of the study participants.

The researchers found that a small group of blood measurements, including amounts of certain proteins and hormones, correlated with the amount of deposited amyloid seen in the brain. More specifically, they generated a model using nine blood-based markers (including A β 1-42, ApoE, and cortisol) to estimate the amount of deposited amyloid in the brain. With 83 percent sensitivity and 85 percent specificity, this estimate then determines if an individual has an abnormally high amount of amyloid deposited in the brain, indicating risk of Alzheimer's. The model was validated using a second cohort of 74 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). For the ADNI validation study, measurements for two of the markers were unavailable; sensitivity and specificity of 76 percent were achieved.

"This model, if fully validated, may provide a means for assessing research outcomes for drug treatments and lifestyle intervention strategies," Burnham said. "It may also lead to an effective and economical screen that indicates if an individual is in the early stages of, or at risk of developing, Alzheimer's, and to justify further tests such as PET scans."

Measuring Amyloid in Cerebrospinal Fluid (CSF)

According to Henrik Zetterberg, MD, PhD, Department of Psychiatry and Neurochemistry, University of Gothenburg, Sweden and colleagues, previous studies have shown that the Alzheimer's-related abnormal proteins found in CSF – known as Abeta42, total-tau and phospho-tau – can accurately identify mild cognitive impairment (MCI) due to Alzheimer's up to 10 years before conversion to Alzheimer's dementia. However, they say, it remains unclear exactly when these biomarkers turn positive.

To investigate this question, the scientists performed lumbar puncture on 137 people with MCI and clinically followed them for more than nine years. During that time, 54 percent of the subjects developed Alzheimer's and 16 percent progressed to other forms of dementia.

The researchers found that:

- Baseline CSF A β 42 levels were reduced and T-tau and P-tau were elevated in patients who converted to Alzheimer's during follow-up period, as compared with non-converters (p<0.0001).

- CSF A β 42 levels were equally reduced at baseline in patients with MCI who converted to Alzheimer's within 0–5 years (early converters) compared with those who converted to Alzheimer's between 5–10 years (late converters). However, CSF T-tau and P-tau were significantly higher in the early converters compared with the late converters.
- A ratio of baseline A β 42/P-tau predicted the development of AD within 9.2 years with a sensitivity of 88 percent, specificity of 90 percent, positive predictive value of 91 percent and negative predictive value of 86 percent.

“In this study, we show that around 90 percent of MCI patients with pathological CSF biomarkers at baseline will develop Alzheimer's within nine to 10 years,” Zetterberg said. “Our results suggest that the CSF biomarker profile is highly predictive.”

“We also found that CSF Abeta42 seems to be an earlier biomarker than CSF tau proteins. High CSF tau protein levels indicate an intense neurodegenerative process and predict rapid progression to dementia. These biomarkers may be useful to select patients for early intervention in clinical trials, and to identify and monitor treatment effects,” Zetterberg said.

About AAIC

The Alzheimer's Association International Conference (AAIC) is the world's largest conference of its kind, bringing together researchers from around the world to report and discuss groundbreaking research and information on the cause, diagnosis, treatment and prevention of Alzheimer's disease and related disorders. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

About the Alzheimer's Association

The Alzheimer's Association is the leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit www.alz.org or call 800-272-3900.

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- Robert J. Blendon, ScD, Jean Georges et al. Five-country survey of public experiences, attitudes and beliefs concerning Alzheimer's disease and the value of a diagnosis (Funder: Bayer)
- Stephen Salloway, MD, MS, et al. Long term follow up of AD patients treated with bapineuzumab in phase 2. (Funders: Janssen Alzheimer Immunotherapy and Pfizer)
- Reisa Sperling, MD, MMSc, et al. Revised estimates of incidence and risk factors for Amyloid Related Imaging Abnormalities (ARIA) in the Phase 2 studies of bapineuzumab for mild to moderate Alzheimer's disease. (Funders: Janssen Alzheimer Immunotherapy and Pfizer)
- Samantha Burnham, PhD, et al. A Blood Based Predictor for Neocortical Amyloid Load in Alzheimer's Disease. (Funder: Science and Industry Endowment Fund)
- Henrik Zetterberg, MD, PhD, et al. The CSF levels of A β 42, but not tau, are fully changed already 5-10 years before onset of Alzheimer's dementia. (Funders: Swedish Research Council; Swedish Brain Power; ALF funding for medical training and research; Johan and Jacob Söderberg Foundation; Swedish Alzheimer Foundation; Wachtmeister Foundation)

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Five-country survey of public experiences, attitudes and beliefs concerning Alzheimer's disease and the value of a diagnosis

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Background: Researchers have expressed concern that people with early symptoms of Alzheimer's disease might not seek medical evaluation because of the perceived lack of effective treatment and potential financial or employment problems or social stigma that might result from a diagnosis.

Methods: Data are derived from a five-country survey, conducted by the Harvard School of Public Health and Alzheimer Europe, of public experiences, attitudes, and beliefs concerning Alzheimer's disease. A total of 2,678 adults aged 18 and over were interviewed by telephone (landline and cellphone) in France, Germany, Poland, Spain, and the United States in February 2011. The study was supported by a grant to Alzheimer Europe from Bayer.

Results: More than eight in ten adults (85 percent to 95 percent) in each of the five countries said that if they were exhibiting confusion or memory loss, they would go to a doctor to determine if the cause of the symptoms was Alzheimer's disease. A large proportion of adults were worried that they or a family member will get Alzheimer's disease with surprising differences between countries (43 percent to 95 percent). More than half of adults (54 percent to 77 percent) said they had known someone who has Alzheimer's disease. Between 13 percent and 27 percent reported that they had been one of the people most involved in decision-making, financial support, or day-to-day care for someone with Alzheimer's disease. More than half of adults (52 percent to 71 percent) believed there was now or will be in the next five years an effective treatment for Alzheimer's disease. Between 38 percent and 59 percent believed there was a reliable test currently available to determine if a person is in the early stages of Alzheimer's disease.

Conclusions: If educational campaigns were undertaken to persuade the public to seek medical evaluation when they exhibited early symptoms of an illness that could be Alzheimer's disease, a large proportion would likely do so. However, such educational campaigns would need to address potentially unrealistic expectations about the availability of a definitive early test and effective treatment for the disease whilst providing positive reasons for seeking a diagnosis in the absence of disease modifying treatments

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Long term follow up of AD patients treated with bapineuzumab in phase 2

Presenting author: Stephen Salloway, MD, MS; Butler Hospital and Brown University, Providence, Rhode Island

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Background: To describe the long term safety and clinical course of AD patients treated with bapineuzumab in an ongoing open label extension study (251).

Methods: 194 patients were treated in study 251. 158/194 participants completed study 201, a phase two, placebo controlled 78-week study with bapineuzumab in mild to moderate AD (Salloway et al. Neurology 2009). 36/194 participants completed a study evaluating bapineuzumab subcutaneously. Patients in 251 received IV bapineuzumab every 13 wks; ADAS-COG, NTB, MMSE, DAD and CDR-SB were assessed. Adverse events (AEs) were collected.

Results: Approximately 86 subjects received bapineuzumab treatment for at least 3 years and 43 for at least 4 years. As of April 1, 2011, 91 percent of participants in 251 reported AEs. AEs in >10 percent of subjects were: fall (14.4 percent), agitation (13.4 percent), upper respiratory tract infection (12.4 percent), urinary tract infection (12.4 percent), and anxiety (10.8 percent). Approximately 24 percent of patients reported AEs considered related or possibly related to bapineuzumab, of which ~85 percent were considered mild or moderate. Reported treatment-related AEs in >1 percent of subjects included: ARIA-E (9.3 percent), headache (2.1 percent), cerebral microhemorrhage (1.5 percent), convulsion (1.5 percent) and flushing (1.5 percent). ARIA-E, previously referred to as “vasogenic edema”, refers to brain Amyloid Related Imaging Abnormalities with parenchymal Edema or sulcal Effusions. The cumulative risk of developing ARIA-E dropped from 6.7 percent for infusions 1-3 compared to 2.7 percent for infusions 4-10. Approximately 35 percent of participants reported serious AEs (SAEs); SAEs in >2 percent of subjects included: ARIA-E (6.2 percent), fall (2.6 percent), hip fracture (2.1 percent), convulsion (2.1 percent), (worsening) DAT (2.1 percent), and confusion (2.1 percent). Compared to patients originally on placebo in 201, patients receiving bapineuzumab in 201 showed a pattern on clinical outcome measures in study 251 similar to that observed during study 201, however, the limited sample size precludes definitive conclusions.

Conclusions: This is the first report of long-term safety data with bapineuzumab treatment beyond 78 weeks. The risk-benefit profile of bapineuzumab continues to be assessed. Large randomized, double-blind, phase 3 trials are underway to evaluate safety and efficacy; however, open label extension studies can supplement randomized trial data to better understand safety and potential effects on clinical course.

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Revised estimates of incidence and risk factors for Amyloid Related Imaging Abnormalities (ARIA) in the Phase 2 studies of bapineuzumab for mild to moderate Alzheimer's disease

Presenting author: Reisa Sperling, MD, MMSc; Brigham and Women's Hospital, Harvard Medical School, Boston

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Background: Amyloid Related Imaging Abnormalities (ARIA) have been reported in AD patients treated with bapineuzumab, a humanized monoclonal antibody to ABeta. ARIA include FLAIR/MRI signal abnormalities thought to represent "vasogenic edema" and sulcal effusions (ARIA-E) and GRE/MRI signal abnormalities thought to represent hemosiderin deposits (ARIA-H). As local radiologists may not have detected all ARIA during the Phase 2 studies, a systematic, central review of all study MRIs was performed to better estimate the incidence and risk factors for ARIA-E related to bapineuzumab.

Methods: Two neuroradiologists independently reviewed over 2000 FLAIR/MRI sequences from 262 participants in three Phase 2 studies. Subjects included in risk analyses had at least 1 dose of bapineuzumab, no evidence of ARIA-E abnormalities at baseline, and at least 1 post-treatment MRI as of 1/31/09 (n=210). Trends were evaluated with univariate Cox PH models without adjusting the corresponding p-values from these post-hoc analyses for multiple comparisons.

Results: Thirty-six subjects developed incident ARIA-E during treatment, including 15 cases newly identified during the review. Incidence of ARIA-E increased with bapineuzumab dose (7.1 percent, 9.8 percent, 22.1 percent and 30.8 percent, for the 0.15, 0.5, 1.0 and 2.0mg/kg doses respectively; HR 2.25 (per 1.0 mg/kg); 95 percentCI (1.40,3.62); nominal p<0.001) and by number of ApoE4 alleles (6.8 percent, 17.6 percent and 36.4 percent for 0, 1 and 2 alleles; HR 2.55 (per allele); 95 percent CI (1.57,4.12); nominal p<0.001). Eight/36 subjects with ARIA-E, all previously identified during the clinical studies, had symptoms reported as related to study drug. Seven/8 symptomatic patients were ApoE4 carriers and 6 were dosed at 1mg/kg or greater. Thirteen/15 asymptomatic patients, detected only during the central review, received additional infusions during the period that ARIA-E was present without associated symptoms reported.

Conclusions: This MRI review found that ~60 percent of ARIA-E cases were detected during the clinical trials. The risk of ARIA-E increased with bapineuzumab dose and ApoE4 allele number. The additional cases identified only in central review were more subtle than those detected by local radiologists, and did not report clinical symptoms when treated through ARIA-E. Further analyses may help clarify the relationship between ARIA-E, ARIA-H and clinical course.

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A Blood Based Predictor for Neocortical Amyloid Load in Alzheimer's Disease

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Background: With the increasing prevalence of Alzheimer's disease (AD) comprehensive research is required for earlier disease detection. Neocortical Amyloid burden (NAB) represents one marker for early detection; currently NAB is quantitatively assessed by expensive positron emission tomography (PET) requiring radiotracers (e.g. PiB) that are not widely available. CSF markers have reported correlation with NAB and represent one alternative to PET, but testing is considered invasive. Here, an alternative blood-based predictor of NAB is explored as the basis for an accessible and cost effective early screening test.

Methods: 273 samples from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, with baseline blood and PiB-PET measurements were utilised. Cross-validated machine-learning models to predict NAB, as measured by PiB-PET (standardised-uptake-value-ratio; SUVR), resulted in a panel of markers and NAB predictions. Predictions were also made for 817 non-imaged AIBL participants and 74 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) for validation. Subjects with SUVR predictions greater than a 1.5 threshold were deemed to have high NAB.

Results: A model based on 9 markers (including A β 1-42, ApoE, VCAM1 and Cortisol) was generated which achieved sensitivity, specificity and an R² value of 83 percent, 85 percent and 77 percent, respectively, (Figure 1). Applied to the non-imaged participants, the percentages of high NAB predictions were consistent with literature when grouped by clinical diagnosis: 34 percent of Healthy Controls, 87 percent of Mild Cognitively Impaired and 100 percent of AD. Further, 88 percent of all AIBL participants transitioning towards AD at 18-month follow-up were predicted to have high NAB. For the ADNI validation study, measurements for 2 markers were unavailable but sensitivity and specificity of 76 percent were still achieved.

Conclusions: The described mode provides an accurate prediction of NAB based on blood measures. In the validation study accuracy is reduced; likely because 2 markers were unavailable (removal of these from the AIBL study drops accuracy to a comparable 74 percent). Given NAB is a predictor for progression to AD and that this model can accurately predict NAB, it follows that this work may lead to an effective and economical screen for early detection of individuals at risk of developing AD, in-turn providing justification for further confirmatory tests (e.g. PET).

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The CSF levels of A β 42, but not tau, are fully changed already 5-10 years before onset of Alzheimer's dementia

Presenting authors: Henrik Zetterberg, MD, PhD, Department of Psychiatry and Neurochemistry, University of Gothenburg, Sweden; Oskar Hansson, PhD, MD; Lund University, Sweden
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Background: Early detection of prodromal Alzheimer's disease (AD) is important as new disease-modifying therapies are most likely to be effective if initiated during early stages of the disease.

Methods: 137 patients with mild cognitive impairment (MCI) underwent lumbar puncture at baseline and were followed clinically for a median duration of 9.2 years (range 4.1–11.8). Baseline cerebrospinal fluid (CSF) was analysed for total-tau (T-tau), phosphorylated tau (P-tau) and amyloid- β 1-42 (A β 42).

Results: During follow-up 54 percent of the subjects developed AD and 16 percent progressed to other forms of dementia. Baseline CSF A β 42 levels were reduced and T-tau and P-tau were elevated in patients who converted to AD during follow-up as compared with non-converters ($p < 0.0001$). CSF A β 42 levels were equally reduced at baseline in patients with MCI who converted to AD within 0–5 years (early converters) compared with those who converted to AD between 5–10 years (late converters). However, CSF T-tau and P-tau were significantly higher in the early converters compared with the late converters. A ratio of baseline A β 42/P-tau predicted the development of AD within 9.2 years with a sensitivity of 88 percent, specificity of 90 percent, positive predictive value of 91 percent and negative predictive value of 86 percent.

Conclusions: Around 90 percent of MCI patients with pathological CSF biomarkers at baseline will develop AD within 9–10 years. A β 42 levels are already fully decreased at least 5-10 years before conversion to AD dementia, while T-tau and P-tau seem to be later markers. These results provide direct support in humans for the hypothesis that altered A β metabolism precedes tau-related pathology and neuronal degeneration.

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