Treating Alzheimer’s: A New Era Begins with Lecanemab

Few diagnoses in medicine are more devastating than Alzheimer’s disease (AD). Barely known to the public four decades ago, the number of people living with dementia – estimated to stand at 55 million in 2019 – is expected to rise to 139 million in 2050, and 75% of these individuals have not been diagnosed. The toll on patients, families, and society of this ubiquitous and ultimately fatal disorder is staggering. The number affected more than doubles if one includes the millions of cognitively normal older people who do not yet know the disease is underway in their brains. But breaking news from the Clinical Trials in Alzheimer’s Disease (CTAD) Conference late November 2022 suggests this bleak outlook is changing. A disease-modifying treatment for Alzheimer’s has finished a highly successful trial (called Clarity AD), the results of which will soon be reviewed by the U.S Food and Drug Administration, with approval widely expected to follow.

At the CTAD Conference in San Francisco, around 2000 physicians, scientists, pharmaceutical investigators and others viewed and intensively discussed the Clarity AD findings. The data presentations were detailed, comprehensive, and transparent. Most AD experts in the audience responded with enthusiastic approval, viewing this study of lecanemab, a monoclonal antibody which preferentially targets Abeta “protofibrils” (smaller Abeta assemblies), as the most clearly positive and encouraging AD trial yet completed. In this randomized, double-blinded, placebo-controlled trial of 1,795 patients with mild cognitive impairment (MCI) or mild AD dementia, intravenous lecanemab given every two weeks over 18 months led to statistically significant (p<0.001) slowing of cognitive and functional decline on the CDR-SB primary outcome and on all three secondary outcomes related to cognition and daily function (ADAS-cog14; ADCOMS; ADCS-MCI score on Activities of Daily Living). Sensitivity analyses showed similar effects, indicating the robustness of the study results. On average, the slowing of decline on the key endpoints ranged from 23% to 37% vs. placebo. Importantly, these meaningful effects of lecanemab over placebo widened from 3 to 18 months of treatment on all 5 key outcomes, signifying clinical benefit and providing a rational basis for hoping that even more slowing will occur over time. There were also sizeable and significant positive effects on classical biological markers of AD: amyloid plaques and neurofibrillary tangles on PET scans and blood and spinal fluid levels of the proteins that comprise these hallmark lesions of AD. Thus, lecanemab appears to reduce amyloid pathology in AD and beneficially slows the cascade of biological events which result in cognitive decline.

Throughout the meeting, clinicians who have collectively cared for millions of Alzheimer’s patients and families referred to this outcome as a foundational gamechanger in a disease which inexorably robs its victims of their most human qualities -- memory, judgment, equanimity, and independence (the conduct of everyday life). The results presented at CTAD suggest that over the course of the 18-month trial, those on lecanemab progressed almost 6 months slower than those on placebo. Treatments like lecanemab hold the promise of improving the quality of life of our patients and their families experiencing AD. Indeed, evidence of such benefits were observed in the form of 25-50% less decline on four scales of patient- and caregiver-reported quality of life and disease burden.

Regarding safety, the key adverse event, as expected, was the development of amyloid-related imaging abnormalities (ARIA) seen on MRI scans. ARIA with localized, typically transient brain edema (ARIA-E) occurred in 12.6% of lecanemab recipients and 1.7% of those on placebo overall. Less than 3% of patients had any symptoms associated with ARIA, and serious symptoms were even more rare. The
ARIA-E rate was lower than in previous trials of antibodies that target amyloid plaques directly. ARIA was well managed in the trial, with careful safety monitoring by knowledgeable clinicians. Other adverse events included infusion-related reactions occurring during the first infusion and not interfering with continued treatment. For appropriately selected patients under the care of proficient clinicians with sufficient resources to provide proper patient detection and monitoring, ARIA risk should be manageable in real-world clinical settings. The longer-term safety and efficacy of lecanemab in actual practice can be monitored in longitudinal registries, such as the recently launched Alzheimer’s Network (ALZNET).

The Clarity AD trial represents an unprecedented and foundational leap in the search for a disease-modifying treatment for AD. It is the first to show an unequivocal effect in changing the rate of decline on diverse clinical, cognitive, and functional endpoints, converging with validated, AD-associated brain, cerebrospinal fluid and blood biomarker endpoints. Further success may be possible with this treatment as we leverage biomarker-informed precision medicine approaches that should increase treatment benefits and reduce risk and burdens in subsets of AD patients.

The success of lecanemab is not a reason to pause our efforts or interrupt the momentum towards better treatments for AD. Lecanemab is not a cure for AD. Over months and years, treated patients will continue to decline but, on average, would be expected to do so more slowly. Some are likely to benefit more than others, as in all chronic diseases. Our patients will need ever more effective therapies, and their families need the hope and relief that these treatments will provide. The Clarity AD results will spur more investment in Alzheimer diagnostics and therapeutics. Non-pharmacological approaches that seek to reduce lifestyle factors or therapeutics that address other AD-associated pathways can be combined with this new medicine.

Yet even as we continue to work to push our field forward, we must get scientifically validated and clinically relevant therapies like lecanemab to patients as soon as possible. Lecanemab was developed and tested in patients with early-stage AD, and every day of delay in patient access to this therapy may result in treatable patients progressing beyond the window of therapeutic opportunity. We cannot allow the uninterrupted decline of AD patients we have known for decades to continue when effective therapies are available.

The many undersigned AD clinicians and other experts know this terrible disease all too well from witnessing it up close. We herald the foundational advance represented by the advent of lecanemab therapy. Now, we must build on the success of science to translate these gains into even better outcomes for patients and families. Autonomy and justice dictate that our patients have equitable access and the opportunity to make informed choices regarding reasonable treatments that can impact their lives and well-being. No barrier can be allowed to stand between our patients and a treatment that has a reasonable risk-benefit ratio and significantly reduces the causative pathology.

1. World Health Organization, https://www.who.int/news-room/fact-sheets/detail/dementia, last accessed 12/7/2022
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CONFLICT OF INTEREST DISCLOSURES
(declared by signees – updated Dec 20, 2022)

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Dr. Aisen has research agreements with Eisai and Lilly, and has consulted with Merck, Biogen, Genentech, Roche and Abbvie

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Dr. Atri discloses that over the last 20+ years as a practicing cognitive neurologist, neuroscientist and AD clinical trialist he has served as an investigator or consultant for many organizations (public, private, foundation, governmental and non-profits) and bio-pharmaceutical companies, including multiple biopharmaceutical companies that have AD-related or anti-amyloid monoclonal antibodies experimental therapeutics, drugs or pipelines. Directly relevant to this statement on lecanemab, Dr. Atri specifically discloses that he has consulted or served as a site-investigator on sponsored trials to his institution for the collaborating partners and makers of lecanemab: Eisai and Biogen. The views expressed by signing this letter on lecanemab are his own.

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Consulting Relationships (12 months): AC Immune, Eisai, Roche


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I have received research funding (paid to my institution) and consulting fees (paid to me) related to this class of therapy from Biogen, Eisai, and Genentech, as well as consulting fees (paid to me) by Lilly.

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None

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I served on an Alzheimer's advisory board for Eisai.

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None

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None

Marcia N. Gordon, PhD
None

Jürgen Götz, PhD
None

Joshua Grill, PhD
Received research support but not direct financial compensation from Eisai.

Lea Tenenholz Grinberg MD, PhD
I receive research funding from the Alzheimer’s Association, Rainwater Charity Foundation and Weill Neuroscience Institute. I am a part of the Alzheimer’s Association Medical and Scientific Advisory Board.

Christian Haass
I collaborate with Denali Therapeutics on microglial modulating antibodies. I am chief advisor of ISAR

Bioscience and a member of the advisory board of AviadoBio.

Dustin B. Hammers, PhD, ABPP-CN
None

Oskar Hansson, MD, PhD
OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Fujirebio, Genentech, Novartis, Novo Nordisk, Roche, and Siemens.

Suzanne B Hendrix, PhD
On Eisai's global advisory committee, advisor to Biogen, Lilly and many other companies in the Alzheimer's disease field.

Doris Molina Henry, PhD
Doris Molina Henry has received funding from American Heart Association and Eisai for the AHEAD 3-45 studies (as a public-private partnership). She is an unpaid member of the Alz IRGP Council for the Alzheimer's Association. Dr. Molina Henry was not involved in the CLARITY-AD trial.

Vered Hermush, MD
None

Annie Hiniker, MD, PhD
None

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None
David M. Holtzman, MD
Co-founder, with equity, C2N Diagnostics LLC. Scientific advisory boards/consulting: Genentech, Denali, C2N Diagnostics, Cajal Neurosciences, Alector. DMH is an inventor on a 1) a patent licensed by Washington University to NextCure on anti-apoE antibodies, 2) a patent licensed by Washington University to Eli Lilly on a humanized anti-Aβ antibody, 3) a patent licensed by Washington University to C2N Diagnostics on a humanized anti-tau antibody.

Lawrence S. Honig, MD, PhD, FAAN
Consultant for Biogen, Cortexyme, Eisai, Genentech, Medscape, Prevail, Roche. Recent research funding from Abbvie, Acumen, Alector, Biogen, Eisai, Genentech, Janssen, Eli Lilly, Roche, UCB, Transposon, Vaccinex.

Khalid Iqbal, PhD
Chief Scientific Officer of Phanes Biotech, which is carrying out drug discovery studies on immunotherapy targeting tau and Abeta pathologies and on neural regeneration that can prevent both tau and Abeta pathologies.

Atsushi Iwata, MD, PhD
I am a member of Eisai Global Advisory board

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SCJ has served as a consultant to Roche, Eisai and Prothena in the past three years.

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None

William Jagust, MD
Has consulted for Lilly, Eisai, Biogen, and Bioclinica

Gregory A. Jicha
Received compensation from Eisai for contract research activities in the Phase 2 study. CLARITY Phase 3, and the A345 AHEAD study.

Charles Jennings, PhD
Spouse is an employee of Prime Medicine, a biotech company that develops clinical applications of genome editing technologies.

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Receives research support from Avid Radiopharmaceuticals, Eli Lilly and is a paid consultant for Biogen

Anumantha Kanthasamy
Have two startup companies: PK Biosciences, Inc. and Probiome Therapeutics. The work performed in the startup companies is unrelated to this publication.

Jason Karlawish, MD
None

Diana R. Kerwin, MD
I am a site principal investigator for the CLARITY study, blinded to study data.

Vikram Khurana, MD, PhD
None

Hee Jin Kim
None

William E. Klunk, MD, PhD
None

David S. Knopman, MD
I am a site investigator in the EMBARK study (Biogen) and in the A4 (Lilly) but receive no personal compensation. I attended a meeting on Dec 2, 2022 with Eisai regarding lecanemab but received no personal compensation.

Rada Koldamova, MD, PhD
None

Joel Kramer, PsyD
None

Sarah Kremen, MD
Was a site PI for Biogen PRIME and ENGAGE studies and consultant for ICER's review of aducanumab, and has served on an advisory board for Eli Lilly.

Walter A. Kukull, PhD
I have grant support from NIH/NIA.

Robert Laforce, MD, PhD
None

Debomoy K. Lahiri, PhD, FAAAS
Dr. Lahiri acknowledges the support from the NIH, NIA (R01AG051086,
R56AG072810, R21AG076202, R21AG AG074539, P30AG10133, and P01AG014449), and also from Bentham Science Publications (as Editor-in-Chief, Current Alzheimer Research, and Current Aging Science). He has stock options in Annovis Bio, Inc, and serves as Chief Scientific Advisor, Peptide Therapeutics Provaidya, Indianapolis.

Bruce Lamb, PhD
Consultant for NervGen Inc., leader of multiple NIH-funded research programs, volunteer advisor as Chair of the Medical and Scientific Advisory Group (MSAG) of the Alzheimer's Association.

Susan Landau, PhD
I serve on a DSMB for KeifeRX and have received speaking honoraria from Eisai

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None

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Cynthia Lemere serves as a paid consultant to AC Immune, Acumen Pharmaceuticals, ADvantage Therapeutics, Apellis Pharmaceuticals, Biogen, Cognition Therapeutics, Cyclo Therapeutics, Novo Nordisk, MEDAcorp, and Cambridge Healthcare Research Consulting Group. She serve as an unpaid advisor to the Alzheimer's Association, BrightFocus Foundation, Cure Alzheimer’s Fund, LuMIND (DSMB), MODEL-AD and the US POINTER Study.

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None

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None

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None

Lei Liu, MD, PhD
None

Peter A. Ljubenko, MD
None

Justin M. Long, MD, PhD
I have no relevant financial disclosures. I served as sub-investigator for the Clarity AD study at the Washington University site.

Marissa Natelson Love, MD
I have served as a site investigator on the phase 2 trial for lecanemab and currently serve as the site Principal Investigator on a prevention trial involving lecanemab.

Val J. Lowe, MD
Dr. Lowe consults for Bayer Schering Pharma, Piramal Life Sciences, Life Molecular Imaging, Eisai Inc., AVID Radiopharmaceuticals, and Merck Research and receives support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals and the NIH (NIA, NCI).

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None

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Investigator in the AHEAD Study

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Co-investigator on Clarity AD trial

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Institutional support (clinical trial): Eisai, Eli Lilly, Roche

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None

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None

Richard G. M. Morris
None

Beth Mormino, PhD
NIH funding for research. Paid consultant to Eli Lilly, Neurotrack, and Hoffmann-La Roche.

Cath Mummery, MD, PhD
Consultant for Biogen, Eisai, IONIS, Roche, Lilly, Alnylam, Alector, WAVE but not directly
involved with the lecanemab trials

Melissa E. Murray, PhD
Dr. Murray served as a paid consultant and receives grant funding from Avid Radiopharmaceuticals.

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None

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None

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None

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None

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None

Rik Ossenkoppele, PhD
None

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None

Mike Pappolla, MD, PhD
None

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Roche, Merck, Biogen, Eisai, Genentech, Lilly, Nestle, consultant; Genentech DSMB

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None

Gil D. Rabinovici, MD, FAAN, FANA
Dr. Rabinovici receives research support (paid to institution) from Avid

Radiopharmaceuticals, Life Molecular Imaging, GE Healthcare and Genentech. In the past 3 years he has served as a scientific advisor for Eli Lilly, GE Healthcare, Genentech, Roche and Merck. He serves on a DSMB for Johnson & Johnson.

Rema Raman, PhD
Rema Raman has received funding from the National Institutes of Health, Alzheimer's Association, Eli Lilly for the A4 study (as a public-private partnership) and Eisai for the AHEAD 3-45 studies (as a public-private partnership). Dr. Raman was not involved in the CLARITY-AD trial. She is the Board Chair (unpaid) for the Alzheimer's Association's San Diego/Imperial chapter and a member of the Alzheimer's Association's AAIC Scientific Program Committee.

Vijay K Ramanan, MD, PhD
None

Kamalini Ranasinge
None

Katherine P. Rankin, PhD
None

P. Hemachandra Reddy, PhD
None

R. Ross Reichard
None

Ashley Reiff LCSW
None

Dorene M. Rentz, PsyD
Dr. Rentz has served as a consultant of Biogen, Eisai and Novartis

Robert Rissman, PhD
None

Erik Roberson, MD, PhD
None

Julio C. Rojas, MD, PhD
Julio C. Rojas is a site PI for clinical trials sponsored by Eisai and Eli-Lilly.

Howard Rosen, MD
I have worked as a consultant for Genentech, Wave Neuroscience, Eisai, Otsuka, Takeda, Biogen, and Ionis pharmaceuticals

Owen A. Ross, PhD
None

Christopher C. Rowe, BMBS, MD, FRACP
Research grants to institution received from Biogen, Eisai, Actinogen, Cerveau technologies. Scientific Advisory Board payments received from Prothena, Roche, Eisai Australia, Lilly Australia

Marwan Noel Sabbagh MD, FAAN
None

Carl Sadowsky, MD
None

S Ahmad Sajjadi, MD, PhD
I have served on Eisai advisory committee for Lecanemab

Stephen Salloway, MD, MS
Dr. Salloway was the co-chair of the Investigator Steering Committee for the Aducanumab phase 3 program and he served as a site PI for the aducanumab and lecanemab phase 3 studies,
the donanemab phase 2 trial and he was the Project Arm Leader for gantenerumab in DIAN-TU. He has provided consultation to Biogen, Lilly, Roche, Genentech, Bolden, Amylyx, Prothena and Eisai. He has no stock or royalties related to any medication in development. Dr. Salloway serves on the planning committee for ALZ-NET and he is a member of the ADRD Therapeutics Work Group. He is the first author for the report of ARIA in aducanumab phase 3 (Salloway, JAMA Neurology, 2022), the report of gantenerumab and solanezumab in DIAN-TU (Salloway, Nature Medicine, 2021). He is a co-author on the report of the donanemab phase 2 trial (Mintun, NEJM, 2021) and the Aducanumab Appropriate Use Recommendations (Cummings, Journal of the Prevention of Alzheimer’s Disease, 2021, 2022).

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None

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None

Andrew J. Saykin, PsyD
Dr. Saykin has received support from Avid Radiopharmaceuticals, a subsidiary of Eli Lilly (in kind contribution of PET tracer precursor); and consulted for Bayer Oncology (Scientific Advisory Board); Eisai (Scientific Advisory Board); Siemens Medical Solutions USA, Inc. (Dementia Advisory Board); NIH NHLBI (MESA Observational Study Monitoring Board); and Springer-Nature Publishing (Editorial Office Support as Editor-in-Chief, Brain Imaging and Behavior).

Prof. Philip Scheltens, MD, PhD
None

Julie Schneider
Consultant, Lilly and AVID Radiopharmaceuticals, Cerveau Technologies, Inc., National Hockey League, Takeda Development Centers Americas, Inc.

Michael Schöll, PhD
MS has research agreements with Roche and has consulted with Servier, NovoNordisk and Roche.

Professor Jonathan M. Schott, MD FRCP FAAN
I have received research funding and PET tracer from AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) and Alliance Medical; have consulted for Roche, Eli Lilly, Biogen, Merck and GE; received royalties from Oxford University Press, and Henry Stewart Talks. I am Chief Medical Officer for Alzheimer’s Research UK, and Clinical Advisor to UK Dementia Research Institute.

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None

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Director and consultant to Prothena Biosciences. Ad hoc consultant to Eisai

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None

Leslie M. Shaw, PhD
None

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Chief Medical Officer, Acumen Pharmaceuticals; Consultant, Vaccinex Inc.

Bryan Luke Smesler
None

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Our site is a study site for CLARITY AD and we receive research grants from Eisai.

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Site Principal investigator for Eisai sponsored Clarity trial

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None

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None

Weihong Song
None

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None

Reisa Sperling, MD
Dr. Sperling co-leads the AHEAD Study which is testing lecanemab at an earlier stage of preclinical Alzheimer’s disease, and receives research support from Eisai and the NIH for this public-private partnership clinical trial.

Salvatore Spina, MD, PhD
Dr. Spina has received consultations honoraria from Techspert.io, Acsel Health, Precision Xtract, and Putnam.
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Paid consultant to Alector, Eli Lilly/Prevail, Passage Bio, and Takeda

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None

Andrew Stern, MD, PhD
None

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None

Carmela Tartaglia
I run clinical trials in AD medications: Biogen, Janssen, Avanex, Roche, Green Valley, Merck, UCB, Novo Nordisk, Passage Bio.

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MGT is a member of the Medical and Scientific Advisory Group (MSAG) of the Alzheimer’s Association

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None

Marilù Gorno Tempini, MD, PhD
None

David B. Teplow, PhD
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Mahendra Kumar Thakur
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Lars Olof Tjernberg, PhD
None

Taisuke Tomita, PhD
None

Elena Tsoy, PhD
None

Raymond Scott Turner
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Lawren VandeVrede, MD, PhD
None

Robert Vassar, PhD
I have been an ad hoc consultant for Eisai’s BACE inhibitor program.

Prashanthi Vemuri, PhD
Funded by the NIH.

Everard (Jort) Vijverberg, PhD, MD
PI of clinical trials from AC immune, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Green Valley, Vivoryon, ImmunoBrain, GemVax, Alzheon, DIAN-TU and Alector, and sub-I from trials from Eli Lilly, Cortexyme, Biogen en Fuj Film Toyama.

Consultant for New Amsterdam Pharma, Treeway, ReMynd, Vivoryon, Biogen, Vigil Neuroscience and ImmunoBrain Checkpoint.

Qing Wang, PhD
None

Ruizhi Wang
None

David Weisman
I was site PI on the phase 2b trial of lecanemab. Currently site PI on AHEAD study with lecanemab.

Meredith Wicklund, MD
None

Michael W. Weiner, MD
Dr. Weiner serves on Editorial Boards for Alzheimer’s & Dementia, and the Journal for Prevention of Alzheimer’s disease. He has served on Advisory Boards for Acumen Pharmaceutical, Alzheon, Inc., Cerecin, Dolby Family Ventures, Merck Sharp & Dohme Corp. and NervGen. He also serves on the USC ACTC grant which receives funding from Eisai for the AHEAD study.

He has provided consulting to Baird Equity Capital, BioClinica, Cerecin, Inc., Cytox, Dolby Family Ventures, Duke University, Eisai, FUJIFILM-Toyama Chemical (Japan), Garfield Weston, Genentech, Guidepoint Global, Indiana University, Japanese Organization for Medical Device Development, Inc. (JOMDD), Medscape, Nestle/Nestec, NIH, Peerview Internal Medicine, Roche, T3D Therapeutics, University of Southern California (USC), WebMD, and Vida Ventures.

He has acted as a speaker/lecturer to The Buck Institute for Research on Aging; China Association for Alzheimer’s Disease (CAAD); Japan Society for Dementia Research; and Korean Dementia Society, and the following entities have provided funding for academic travel; University...
of Southern California (USC), NervGen, ASFNR, and the AD/PD and CTAD Congresses.

He holds stock options with Alzheon, Inc., Alzeca, and Anven.

Dr. Weiner received support for his research from the following funding sources:

National Institutes of Health (NIH), Department of Defense (DOD), Patient-Centered Outcomes Research Institute (PCORI), California Department of Public Health (CDPH), University of Michigan, Siemens, Biogen, Hillblom Foundation, Alzheimer’s Association, The State of California, Johnson & Johnson, Kevin and Connie Shanahan, GE, VUmc, Australian Catholic University (HBI-BHR), The Stroke Foundation, and the Veterans Administration.

Alexander White, MD
I am conducting BAN2401 301.

Donna M Wilcock, PhD
None

Charles Windsor, MD
Funding from NIH, Alzheimer's Association, LCN consulting

David A. Wolk, MD
I have received consulting fees from Eli Lilly, Qynapse, and GE Healthcare. I am site-PI of a study with Biogen (EMBARK) and have served on the DSMB for Functional Modulation.

Benjamin Wolozin, MD, PhD
I declare a conflict of interest because I am CSO and Co-Founder of Aquinnah Pharmaceuticals Inc.

Bryan Woodruff, MD
I have participated in industry-sponsored trials of investigational treatments for Alzheimer’s disease, but not specifically studies of lecanemab.

Pauline Wu, DO
None

Heather Wynne-Phillips, MSN, APRN, FNP-C
Our institution is a study site for CLARITY AD and we receive research grants from Eisai.

Hyun-Sik Yang, MD
None

Keir Yong, PhD
None

Tracy Young-Pearse
None

Ehud Zeltzer, MD
None

Henrik Zetterberg, MD, PhD
HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alecitor, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

Samuel N. Lockhart, PhD
I serve on a DSMB for the WALLe study
(Added Dec. 19, 2022)

Oscar L. Lopez, MD, FAAN
I have been a consultant for Eisai
(Added Dec. 19, 2022)