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Results of the DIAN-TU prevention trial of solanezumab and gantenerumab in dominantly inherited AD

Solanezumab in-depth outcomes

Martin R. Farlow[1] | Randall J. Bateman[2] | Andrew J. Aschenbrenner[2] | Tammie L.S. Benzinger[2] | David Clifford[2] | Kelley Coalier[3] | Carlos Cruchaga[4] | Anne M. Fagan[5] | Alison M. Goate[6] | Brian A. Gordon[7] | Jason Hassenstab[2] | Clifford R. Jack Jr.[8] | Robert A. Koeppe[9] | Eric McDade[7] | Susan Mills[2] | John C. Morris[5] | Stephen P. Salloway[10] | Anna Santacruz[2] | Peter J. Snyder[11] | Guoqiao Wang[2] | Chengjie Xiong[2] | B. Joy Snider[3] | Catherine J. Mummery[12] | Ghulam M. Surti[13] | Didier Hannequin[14] | David Wallon[14] | Sarah Berman[15] | James J. Lah[16] | Ivonne Z. Jiménez-Velazquez[17] | Erik D. Roberson[18] | Christopher H. van Dyck[19] | Lawrence S. Honig[20] | Raquel Sanchez-Valle[21] | William S. Brooks[22] | Serge Gauthier[23] | Colin L. Masters[24] | Doug R. Galasko[25] | Jared R. Brosch[26] | Ging-Yuek Robin Hsiung[27] | Suman Jayadev[28] | Maïté Formaglio[29] | Mario Masellis[30] | Roger Clarnette[31] | Jeremie Pariente[32] | Bruno Dubois[33] | Florence Pasquier[34] | Scott W. Andersen[35] | Karen C. Holdridge[35] | Mark A. Mintun[35] | John R. Sims[35] | Roy Yaari[35] | DIAN-TU Study Team

[1] Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA

[2] Washington University in St. Louis School of Medicine, St. Louis, MO, USA

[3] Washington University, Saint Louis, MO, USA

[4] Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO, USA

[5] Washington University School of Medicine, St. Louis, MO, USA

[6] Ronald M. Loeb Center for Alzheimer's Disease, New York, NY, USA

[7] Knight Alzheimer Disease Research Center, St. Louis, MO, USA

[8] Mayo Clinic, Rochester, MN, USA

[9] University of Michigan, Ann Arbor, MI, USA

[10] Alpert Medical School of Brown University, Providence, RI, USA

[11] University of Rhode Island, Kingston, RI, USA

[12] University College London, London, United Kingdom

[13] Butler Hospital, Providence, RI, USA

[14] Normandie Univ, UNIROUEN, INSERM U1245 and Rouen University Hospital, Department of Neurology and CNR-MAJ, F 76000, Normandy Center for Genomic and Personalized Medicine, Rouen, France

[15] University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[16] Emory University School of Medicine, Atlanta, GA, USA

[17] University of Puerto Rico, School of Medicine, San Juan, Puerto Rico

[18] University of Alabama at Birmingham, Birmingham, AL, USA

[19] Yale School of Medicine, New Haven, CT, USA

[20] Columbia University Medical Center, New York, NY, USA

[21] Universitat de Barcelona, Barcelona, Spain

[22] University of New South Wales, Kensington, NSW, Australia

[23] McGill University Research Centre for Studies in Aging, Montreal, QC, Canada

[24] The Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia

[25] University of California, San Diego, San Diego, CA, USA

[26] Indiana Alzheimer Disease Center, Indianapolis, IN, USA

[27] Vancouver Coastal Health Research Institute, Vancouver, BC, Canada

[28] University of Washington, Seattle, WA, USA

[29] Hopital Neurologique Pierre Wertheimer, Lyon, France

[30] University of Toronto, Toronto, ON, Canada

[31] University of Western Australia, Perth, Australia

[32] Department of Neurology, CMRR and INSERM U825, Toulouse, France

[33] Institute of Memory and Alzheimer's Disease (IM2A), Department of Neurology, Pitié-Salpêtrière Hospital, AP-HP, Paris, France

[34] CHRU Lille, Lille, France

[35] Eli Lilly and Company, Indianapolis, IN, USA

Correspondence
Martin R. Farlow, Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA.
Email: mfarlow@iupui.edu

Abstract

Background: Solanezumab is a monoclonal antibody targeting soluble forms of β-amyloid protein important in the pathogenesis of Alzheimer's disease (AD). Three previous 18-month double-blind placebo-controlled trials of low-dose solanezumab in late-onset sporadic AD found inconsistent benefits on cognitive and functional assessments. Dominantly-inherited mutation-associated AD subjects both before and after onset of symptoms form an ideal population to study potential benefits of solanezumab therapy.

Method: Mutation-carrying asymptomatic (CDR 0, N=41) or mildly symptomatic (CDR 0.5 – 1, N=28) patients were treated for a minimum of 4 years and up to 7 years in a double-blind 3 to 1 active versus placebo randomized clinical trial that measured disease progression by clinical, neuropsychological and biomarker evaluations. The trial was initiated with a dose of 400 mg every 4 weeks and escalated to 1600 mg when low dose trials in sporadic AD did not meet their primary endpoints. The primary cognitive outcome measure was DIAN-MCE, composed of Delayed Recall Score of the International Shopping List Test, the Delayed Recall score of the Logical Memory IIa subtest from the Wechsler Memory Scale-Revised, the Digit Symbol Substitution Test total score from the WAIS-R and the MMSE total score. Secondary outcomes included a battery of other cognitive and functional measures. The study was powered to detect delay of cognitive disease progression in the DIAN-MCE. Biomarkers include imaging modalities (volumetric MRI, FDG, amyloid and Tau PET). CSF markers included β-amyloid, Tau and PhosphoTau species. NfL was measured in both CSF and plasma. The study used a pre-specified Bayesian multivariate disease progression model, which included dynamic borrowing of control subjects from the DIAN Observational study.

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Result: The topline efficacy, safety and biomarker results will be reported.

Conclusion: This study provides the first test of targeting soluble abeta forms in DIAD. It addresses the efficacy of early initiation of higher doses of solanezumab targeting soluble forms of amyloid as a disease modifying therapy. While these results are specific to DIAD, they have the potential to inform the application of anti-amyloid therapy in sporadic AD.