Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Supplementary materials for:

Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease

Michael F. Egan, MD[1], James Kost, PhD[1], Tiffini Voss, MD[1], Yuki Mukai, MD[1], Paul S. Aisen, MD[2], Jeffrey L. Cummings, MD, ScD[3], Pierre N. Tariot, MD[4], Bruno Vellas, MD, PhD[5], Christopher H. van Dyck, MD[6], Merce Boada, MD[7,8], Ying Zhang, PhD[1], Wen Li, PhD[1], Christine Furtek, BS[1], Erin Mahoney, BA[1], Lyn Harper Mozley, PhD[1], Yi Mo, PhD[1], Cyrille Sur, PhD[1], David Michelson, MD[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA;[2]University of Southern California, San Diego, CA, USA; [3]Cleveland Clinic, Las Vegas, NV, USA; [4]Banner Alzheimer's Institute, Phoenix, AZ, USA; [5]Gerontopole, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France;[6]Yale University School of Medicine, New Haven, CT, USA; [7]Research Center and Memory Clínic, Fundació ACE, Institut Català de Neurociènces Aplicades – Universitat International de Catalunya, Barcelona, Spain;[8]Network Center for Biomedical Research in Neurodegenerative Diseases, (CIBERNED), Institute Carlos III, Ministry of Health, Spain.

Corresponding author: Michael Egan, Merck & Co., Inc., UG 4C-06, P.O. Box 1000, North Wales, PA 19454-1099, USA. Tel: 001 267 305 7678, Fax: 001 267 305 6440 email: michael.egan@merck.com

Contents

APECS Principal Investigators

Argentina: Ricardo Allegri, FLENI, Buenos Aires; Eduardo Amado Cattaneo, Clinica Privada Banfield, Banfield, Buenos Aires; Raul Dominguez, Hospital Sirio Libanes, Caba; Ramon Carlos Leiguarda, Sanatorio de los Arcos, Caba; , Daniel Politis, Instituto de Investigaciones Metabólicas, Buenos Aires; Daniel Bernardo Seinhart, Hospital Italiano (Buenos Aires), Caba; Fernando Taragano, Instituto Geriatrico Nuestra Señora de las Nieves, Caba.

Australia: Roger Clarnette, McCusker Alzheimer's Research Foundation Inc., Nedlands, WA; Robert Prowse, Queen Elizabeth Hospital, Woodville South, SA; Henry Zeimer, Heidelberg Repatriation Hospital, Heidelberg West, VIC.

Austria: Michael Rainer, Ordination Dr. Michael Rainer, Wien; Reinhold Schmidt, Univ Klink Graz, Graz; Margot Schmitz, Institut fuer Psychosomatik, Wein.

Belgium: Olivier Deryck, AZ Sint-Jan, Brugge, Brugge; Nina De Klippel, Jessa Ziekenhuis - dienst Neurologie, Hasselt; Sylvie Van Snick, CHC Clinique de L'Esperance, Montegnee.

Brazil: Paulo Henrique Ferreira Bertolucci, Nucleo de Ensino e Pesquisa de Envelhecimento Cerebral UNIFESP, Sao Paulo; Norton Marcos Sayeg Castro, CCBR Synarc International Research - Clinica Dr Norton Sayeg, Sao Paulo; Wilson Jacob Filho, Hospital Sirio Libanes, Sao Paulo; Ivan Hideyo Okamoto, Centro Pesq Clinica Inst Israelita de Ensino Pesquisa Albert Einstein, Sao Paulo; Ronaldo Delmonte Piovezan, AFIP - CDEC Brasil, Sao Paulo.

Canada: Richard Bergeron, Recherches Neuro Hippocampe Inc., Gatineau, QC; Michael Borrie, Parkwood Inst.-Div. Geriatric Med.-Main Bldg Loading Dock A, London, ON; Sharon Cohen, Toronto Memory Program, Toronto, ON; Andrew Frank, Bruyere Continuing Care, Ottawam, ON; Jennifer Ingram, Kawartha Centre – Redefining Healthy Aging, Peterborough, ON; Mark Johnston, True North Clinical Research Kentville INC., Kentville, NS; Mark Johnston, True North Clinical Research Halifax, Halifax, NS; Guy Lacombe, CSSS - Institut Universitaire de Gériatrie de Sherbrooke, Sherbrooke, QC; Giovanni Marotta, The Centre for Memory and Aging, Toronto, QN; Vasavan Nair, Douglas Mental University Health Institute, Montreal, QC; Ziad Nasreddine, Center for Diagnosis & Research on Alzheimer disease, Greenfield Park, QC; Paule Royer, Q & T Research Sherbrooke Inc., Sherbrooke, QC.

Finland: Merja Hallikainen, Ita-Suomen yliopisto, Kuopio; Juha Rinne, CRST oy, Turku.

France: Karim Bennys, Hopital Gui de Chauliac, Montpellier; Claire Boutoleau-Bretonierre, CHU Nantes - Hopital Laennec, Nantes; Mathieu Ceccaldi, CHU Hopital de la Timone Adultes, Marseille; Thierry Dantoine, CHU Dupuytren, Limoges; Bruno Dubois, Hopital de la Pitie Salpetriere, Paris; Therese Jonveaux, C.H.U. de Nancy, Hopital de Brabois, Vandoeuvre-les-Nancy; Pierre Krolak-Salmon, Centre Hospitalier de Vienne - Lucien Hussel, Vienne; Pierre Krolak-Salmon, Hopital des Charpennes, Villeurbanne; Pierre Krolak-Salmon, L'hopital Nord-Ouest - Centre Hospitalier de Villefranche sur Saone, Villefranche sur Saone; Pierre Ousset, Hopital La Grave, Toulouse.

Germany: Ralf Bodenschatz, Pharmakologisches Studienzentrum Chemnitz GmbH, Mittweida; Reinhard Ehret, Dr. med. Reinhard Ehret Private Praxis, Berlin; Lutz Froelich, Zentralinstitut für Seelische Gesundheit, Mannheim; Andreas Hufnagel, Prof. Andreas Hufnagel Privatpraxis, Duesseldorf; Joerg Peltz, Neuropsychiatrisches Facharztzentrum Stiepel, Bochum; Kathryn

Reetz, Aachen Universitatsklinikum, Aachen; Erik Strauss, AFL Arzneimittelforschung Leipzig GmbH, Leipzig; Ralf Uebelhack, ASR Advanced Sleep Research, Berlin.

Hungary: Janos Kalman, Szegedi Tudomanyegyetem - Szent-Gyorgyi Albert Klinikai Kozpont, Szeged; Ferenc Nagy, Javorszky Odon Korhaz, Vac; Gyula Panczel, Pest Megyei Flor Ferenc Korhaz, Kistarcsa; Maria Satori, Vaszary Kolos Korhaz, Esztergom.

Ireland: Sean Kennelly, The Adelaide and Meath Hospital, Tallaght, Dublin 24 County Dublin; Ronan O Caoimh, University College Hospital Galway, Galway, Galway.

Italy: Carlo Ferrarese, Azienda Ospedaliera San Gerardo, Monza; Giovanni Frisoni, IRCCS - San Giovanni di Dio – Fatebenefratelli, Brescia; Carlo De Lena, Azienda Policlinico Umberto I, Roma; Simona Luzzi, AOU Ospedali Riuniti di Ancona, Ancona; Patrizia Mecocci, Ospedale Santa Maria della Misericordia, Perugia; Flavio Nobili, IRCCS A.O.U. San Martino – IST, Genova; Lucilla Parnetti, Ospedale S. Maria della Misericordia, Perugia; Paolo Rossini, Policlinico Universitario Gemelli, Roma; Stefano Ruggieri, I.R.C.C.S. Neuromed - Istituto Neurologico Mediterraneo, Pozzilli, Isernia; Elio Scarpini, IRCCS Osp. Maggiore Policlinico, Milano.

Japan: Yoshiaki Aihara, Medical Corporation Ikuseikai, Shinozuka Hospital, Fujioka, Gunma; Hiroyuki Arai, Tohoku University Hospital, Sendai, Miyagi; Tetsuaki Arai, University of Tsukuba Hospital, Tsukuba, Ibaraki; Nobuo Araki, Saitama Medical University Hospital, Iruma-gun, Saitama; Takashi Asada, Memory Clinic Ochanomizu, Tokyo, Tokyo; Shizuo Hatashita, Shonan Atsugi Hospital, Atsugi, Kanagawa; Yasuto Higashi, Himeji Central Hospital's Clinic, Himeji, Hyogo; Kazuhiro Honda, National Hospital Organization Chiba East Hospital, Chiba, Chiba; Yosuke Ichimiya, Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Tokyo; Tadashi Ino, Rakuwakai Otowa Hospital, Kyoto, Kyoto; Mitsunori Ishikawa, Ishikawa, Clinic(Kyoto-shi), Kyoto, Kyoto; Nobutaka Ishizu, National Hospital Organization Tokyo National Hospital, Kiyose, Tokyo; Yoshiaki Itoh, Osaka City University Hospital, Osaka, Osaka; Tetsumasa Kamei, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Kanagawa; Kiyoshi Kanaya, Tokyo Medical University Hachioji Medical Center, Hachioji, Tokyo; Takashi Kanda, Yamaguchi University Hospital, Ube, Yamaguchi; Chikako Kaneko, Southern Tohoku Medical Clinic, Koriyama, Fukushima; Junya Kawada, Shonan Kamakura General Hospital, Kamakura, Kanagawa; Masahisa Katsuno, Nagoya University Hospital, Nagoya, Aichi; Noriyuki Kimura, Oita University Hospital, Yufu, Oita; Shin Kitamura, Nippon Medical School Musashikosugi Hospital, Kawasaki, Kanagawa; Noriyuki Matsukawa, Nagoya City University Hospital, Nagoya, Aichi; Shigeo Murayama, Tokyo Metropolitan Geriatric Hospital And Institute Of Gerontology, Tokyo, Tokyo; Yusaku Nakamura, Kindai University Sakai Hospital, Sakai, Osaka; Satoshi Orimo, Kanto Central Hosp. of the Mutual Aid Assoc. of Public School Teachers, Tokyo, Tokyo; Tsuneyoshi Ota, Juntendo University Hospital, Tokyo, Tokyo; Yoshinori Ozawa, Chiba Rousai Hospital, Ichihara, Chiba; Shunichiro Shinagawa, The Jikei University Hospital, Tokyo, Tokyo; Yoshihisa Shoji, Kurume University Hospital, Kurume, Fukuoka; Shinji Sudoh, National Hospital Organization Utano Hospital, Kyoto, Kyoto; Masakazu Sugino, Aino Hospital, Ibaraki, Osaka; Hideki Takubo, Tokyo Metropolitan Health and Medical Treatment Corporation Ebara HP, Tokyo, Tokyo; Norifumi Tsuno, Kagawa University Hospital, Kita-gun, Kagawa; Hiroyuki Umegaki, Nagoya University Hospital, Nagoya, Aichi; Yukihiko Washimi, National Center for Geriatrics and Gerontology, Obu, Aichi; Chigusa Watanabe, National Hospital Organization Hiroshima-Nishi Medical Center, Ohtake, Hiroshima; Mineo Yamazaki, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Chiba; Hisashi Yonezawa, Iwate Medical University Hospital, Morioka, Iwate; Yasuhiro Yoshii, Association of Healthcare Corporation Koukankai Koukan Clinic, Kawasaki, Kanagawa.

Netherlands: P.L.J. Dautzenberg, Jeroen Bosch Ziekenhuis, s Hertogenbosch; N.D. Prins, Brain Research Center., Amsterdam.

New Zealand: Nigel Gilchrist, Canterbury Geriatric Medical Research Trust, Burwood, Christchurch; Christian Schwabe, Auckland Clinical Studies Limited, Auckland.

Norway: Dag Aarsland, Stavanger Universitetssjukehus, Stavanger; Tormod Fladby, Akershus Universitetssykehus HF, Loerenskog.

Poland: Maciej Czarnecki, Centrum Mediczne Neuroprotect, Warszawa; Jacek Dobryniewski, Podlaskie Centrum Psychogeriatrii, Bialystok; Gabriela Klodowska-Duda, Neuro Care Gabriela Klodowska, Katowice, slaskie; Robert Kucharski, NZOZ Dom Sue Ryder, Bydgoszcz.

South Korea: Seong Hye Choi, Inha University Hospital, Incheon; Hyun Jeong Han, Myongji Hospital, Goyang-si; Seol-Heui Han, Konkuk University-Medical Center, Seoul; Jee Hyang Jeong, Ewha Womans University Mokdong Hospital, Seoul; Hee-Jin Kim, Hanyang University Hospital, Seoul; SangYun Kim, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do; Jae-Hong Lee, Asan Medical Center, Seoul; So Young Moon, Ajou University Hospital, Suwon, Gyeonggi-do; Duk L. Na, Samsung Medical Center, Seoul; YongSoo Shim, The Catholic University of Korea, Bucheon St. Mary's Hospital, Bucheon, Gyeonggido; Dong Won Yang, Seoul St. Mary's Hospital, Seoul.

Spain: Miguel Aguilar Barbera, H. Mutua de Terrassa, Terrassa, Barcelona; Rafael Blesa, Hospital Santa Creu i Sant Pau, Barcelona; Merce Boada Rovira, Instituto Catalan de Neurociencias Aplicadas (Fundacion ACE), Barcelona; Manuel Fernandez Martinez, CAE Oroitu, Algorta; Guillermo Garcia Ribas, Hospital Ramon y Cajal, Madrid; Jose Molinuevo Guix, Hospital Clinic de Barcelona, Barcelona; Antonio del Olmo Rodriguez, Hospital Universitario Doctor Peset, Valencia, Valencia; Albert Puig Pijoan, Hospital del Mar (Barcelona), Barcelona.

Switzerland: Anton Gietl, Psychiatrische Universitaetsklinik Zuerich, Zuerich.

UK: Clive Ballard, Wolfson Centre for Age Related Diseases, London; Roger Bullock, Kingshill Research Centre, Swindon; Peter Garrard, St. Georges University Hospital NHS Foundation Trust, London; Alasdair Lawrie, Royal Cornhill Hospital, Aberdeen; Iracema Leroi, Manchester Royal Infirmary, Manchester; Jennifer Lynch, Glasgow Memory Clinic, Glasgow; Emer MacSweeney, Re-Cognition Health, London; Brady McFarlane, Memory Assessment and Research Centre, Southampton; Richard Perry, Charing Cross Hospital, London; Craig Ritchie, West London Mental Health NHS Trust, Isleworth; John Starr, University of Edinburgh, Edinburgh; Rohan Vanderputt, Warneford Hospital Oxford.

USA: Jeffrey Apter, Princeton Medical Institute, Princeton, NJ; Muhammad Aslam, University of Cincinnati College of Medicine, Cincinnati, OH; Sanjay Asthana, University of Wisconsin - The Office of Clinical Trials, Madison, WI; Matthew Barrett, University of Virginia, Charlottesville, VA; Mohammad Bolouri, Alzheimer's Memory Center, Charlotte, NC; Mark Brody, Brain Matters Research, Delray Beach, FL; James Burke, Duke University, Durham, NC; Richard Caselli, Mayo Clinic – Scottsdale, Scottsdale, AZ; Stanley Cohan, Providence Neurological Specialties, Portland, OR; Mario Cornacchione, Northeastern Pennsylvania Memory & Alzheimers Center, Plains, PA; Mark DiBuono, Richmond Behavioral Associates, Staten Island, NY; Michael Downing, FutureSearch Trials of Dallas, Dallas, TX; Ryan Drake, Ohio Clinical Research Partners, Canton, OH; Ranjan Duara, Wien Center/Mount Sinai Medical Center, Miami Beach,

FL; Eli Engel, Bayview Research Group, Valley Village, CA; Concetta Forchetti, Alexian Brothers Medical Center, Elk Grove, Village, IL; Noah Gilson, Neurology Specialists of Monmouth County, PA, West Long Branch, NJ; Ira Goodman, Compass Research, LLC, Orlando, FL; Marc Gordon, The Feinstein Institute for Medical Research, Manhasset, NY; Deborah Gould, Insight Clinical Trials LLC, Shaker Heights, OH; Carl Griffin, Lynn Health Science Institute, Oklahoma City, OK; Paul Gross, Lehigh Center for Clinical Research, Allentown, PA; Daniel Grosz, Pharmacology Research Institute, Encino, CA; Judith Heidebrink, University of Michigan, Ann Arbor, MI; M. Ismail, Psychiatry and Alzheimer's Care of Rochester, PLLC, Rochester, NY; Alan Jonas, Pharmasite Research, Inc., Baltimore, MD; William Justiz, Collier Neurologic Specialists, LLC, Naples, FL; Jeffrey Keller, Pennington Biomedical Research Center, Baton Rouge, LA; Shawn Kile, Sutter Medical Group, Neurology, Sacramento, CA; William Kreisl, Columbia University Medical Center [New York, NY], New York, NY; Sarah Kremen, Center for Neuro-Therapeutics, UCLA Medical Center, Los Angeles, CA; James Kyser, Clinical Research Associates, Nashville, TN; Allan Levey, Emory University School of Med- Wesley Woods Health Center, Atlanta, GA; Michael Lin, Weill Cornell Medical College, New York, NY; Gary Linker, Health Initiatives Research, PLLC, Fayetteville, AR; Scott Losk, Summit Research Network, Inc. (Oregon), Portland, OR; Scott McGinnis, Brigham and Women's Hospital Center for Alzheimer Research and Treatment, Boston, MA; Michael Mega, Center for Cognitive Health, Portland, OR; Jacobo Mintzer, Roper Saint Francis Healthcare, Charleston, SC; Johnson Moon, Neurology Center of North Orange County, Fullerton, CA; David Morin, Holston Medical Group, Kingsport, TN; Anette Nieves, Renstar Medical Research, Ocala, FL; Omid Omidvar, Collaborative NeuroScience Network, Long Beach, CA; Brian Ott, Rhode Island Hospital, Providence, RI; Ashok Patel, Bio Behavioral Health, Toms River, NJ; Nunzio Pomara, Nathan S. Kline Institute For Psychiatric Research, Orangeburg, NY; Anton Porsteinsson, Monroe Community Hospital [Rochester, NY], Rochester, NY; Ralph Richter, Tulsa Clinical Research, Tulsa, OK; Michael Rosenbloom, Heath Partners Center for Memory and Aging, Saint Paul, MN; Martin Sadowski, NYU Langone Medical Center, New York, NY; Stephen Salloway, Butler Hospital, Providence, RI; Douglas Scharre, The Ohio State University Medical Center, Columbus, OH; Jose Schuster, Schuster Medical Research Institute, Sherman Oaks, CA; Harvey Schwartz, Infinity Clinical Research LLC, Hollywood, FL; James Scott, Neurology Associates of Ormond Beach, Ormond Beach, FL; Sharon Sha, Stanford University School of Medicine, Stanford, CA; Raj Shah, Rush University Medical Center Alzheimer's Disease Center, Chicago, IL; Jiong Shi, St. Joseph's Hospital and Medical Center, Phoenix, AZ; Jeffrey Shy, Neurological Physicians of Arizona Inc., Gilbert, AZ; Amanda Smith, USF Health Byrd Alzheimer's Institute, Tampa, FL; Mary Stedman, Stedman Clinical Trials, Tampa, FL; Brock Summers, Southern California Research LLC, Simi Valley, CA; Pierre Tariot, Banner Alzheimer's Institute, Phoenix, AZ; Scott Teeter, Cotton-O'Neil Clinical Research Center, Topeka, KS; Gerald Tramontano, The NeuroCognitive Institute, Mt. Arlington, NJ; Duc Tran, Neurology Consultants of Dallas, PA, Dallas, TX; Michael Tuchman, Advanced Research Consultants, Inc./Palm Beach Neurological Center, Palm Beach Gardens, FL; Raymond Turner, Georgetown University Medical Center, Washington, DC; Christopher Van Dyck, Yale University School of Medicine, New Haven, CT; Cherian Verghese, Keystone Clinical Studies, LLC, Norristown, PA; David Weisman, Abington Neurological Associates, Willow Grove, PA; David Wolk, Hospital of the University of Pennsylvania, Philadelphia, PA; Shauna Yuan, University of California San Diego, La Jolla, CA; Edward Zamrini, Banner Sun Health Research Institute, Sun City, AZ.

Eligibility for Biomarker Substudies

All patients with valid baseline and post-dose MRI scans were included in the MRI volumetric substudy. All patients enrolled in the trial were eligible for participation in the CSF substudy provided that the investigative site was willing to participate. The PET substudy was restricted to sites that had appropriate capability for 18F-flutemetamol imaging.

Conduct of CDR

All raters were required to have clinical experience with AD patients and the CDR or a similar scale. All clinical interviews were recorded. A subset (~6,000) were reviewed by a group of central raters with high inter-rater reliability. Ratings were selected for review based on an algorithm which included the first two ratings for all raters and factored in time since last review and number of prior errors. Raters were provided feedback on administration, scoring errors, and interview quality.

Interim Analysis

The external Data Monitoring Committee (eDMC) met every six months to review a comprehensive package of data, including safety data, as specified in their Charter. Details of the interim analysis (IA) are provided in the final amendment of the protocol in section 8.2.13. Briefly, the protocol had an optional futility IA when 50% of the planned number of PET positive subjects had the opportunity to treat for 24 months.The eDMC conducted a futility IA in February 2018 using all longitudinal data on the primary endpoint. In addition, data from the ADAS-Cog13 and ADSC-ADL_{MCI} were also analyzed.

The decision of whether or not to terminate the trial for futility was to be based on the conditional powers (CP), (i.e., the likelihood of correctly detecting a treatment difference at the end of the trial given the results at the interim) from the comparisons of the high dose to placebo and the low dose to placebo. The CPs were to be computed assuming that the observed trend at the interim would continue to the end of the trial. Consideration could be given to terminate the trial for futility if the CP for the primary endpoint for both doses was less than 5%, The probability of incorrectly stopping the trial, β, at the IA would be <1% under the primary set of assumptions. The primary analysis model was used at the IA. The futility criteria were met.

Pharmacokinetics

Population pharmacokinetic analysis of the plasma and dried blood spot concentrations obtained during select clinic visits estimated the verubecestat mean steady-state area-under-the-curve as 1.56 (SD 0.32) and 5.15 (SD 1.07) μM·hr for the 12mg (n=483) and 40mg (n=480) doses, respectively.

Figure S1. Patient disposition for the extension

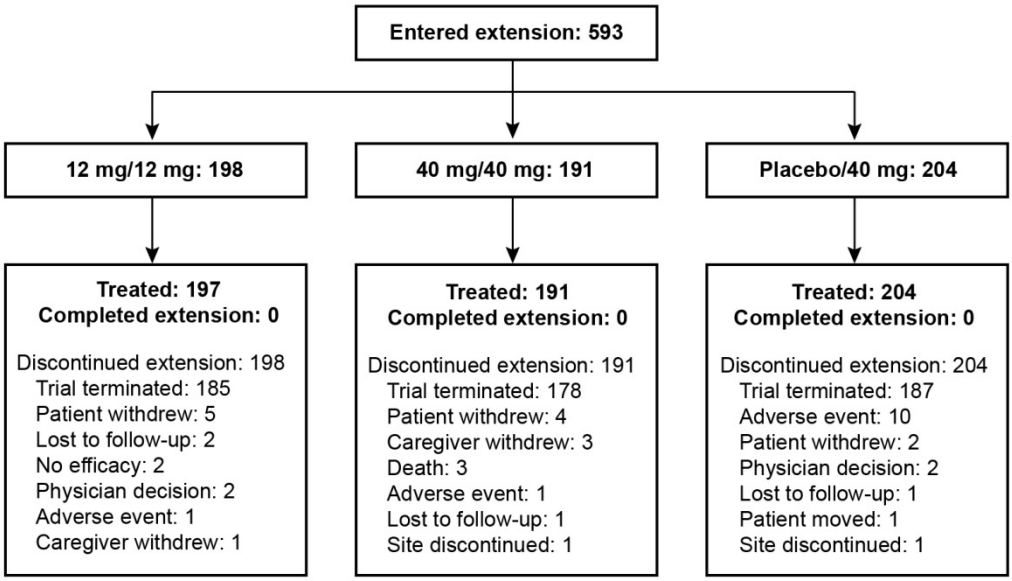
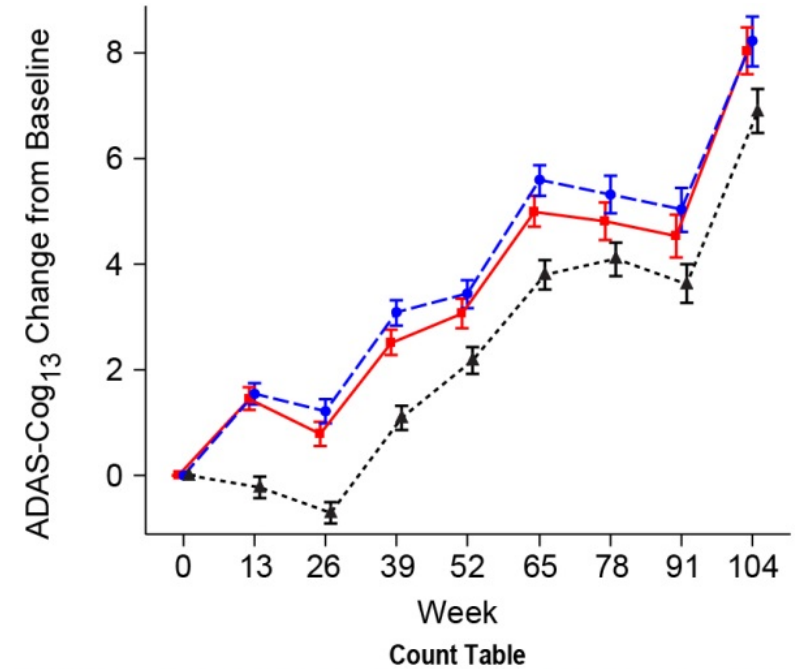


Figure S2. Model-based mean (SE) change from baseline ADAS-Cog$_{13}$ scores



Count Table

12 mg	467	458	452	438	424	402	338	281	233
40 mg	463	453	437	427	422	393	330	276	225
Placebo	474	470	458	453	443	417	349	286	233

Figure S3. Model-based mean (SE) change from baseline ADAS-Cog$_{11}$ scores

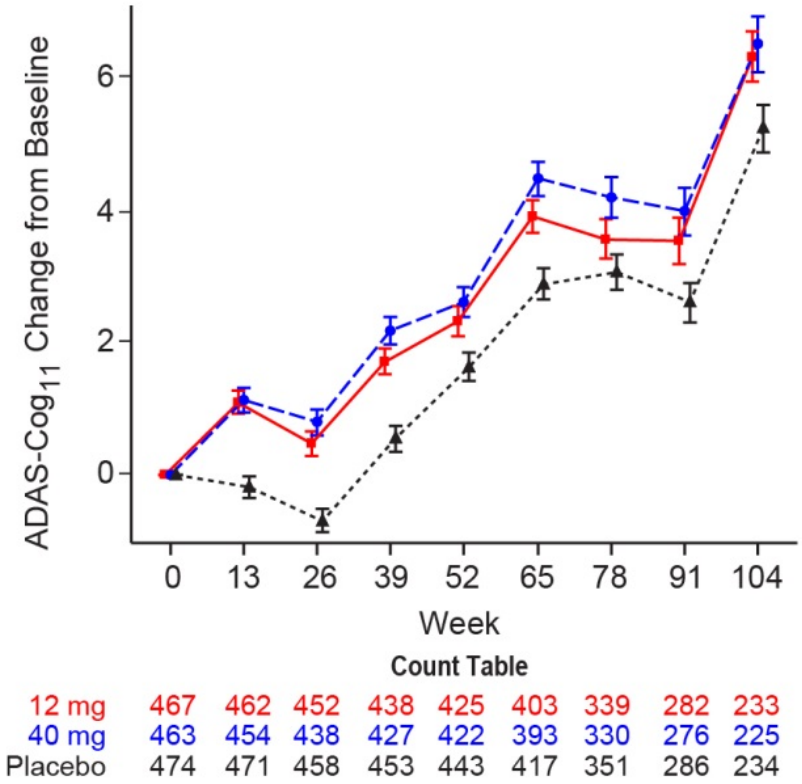
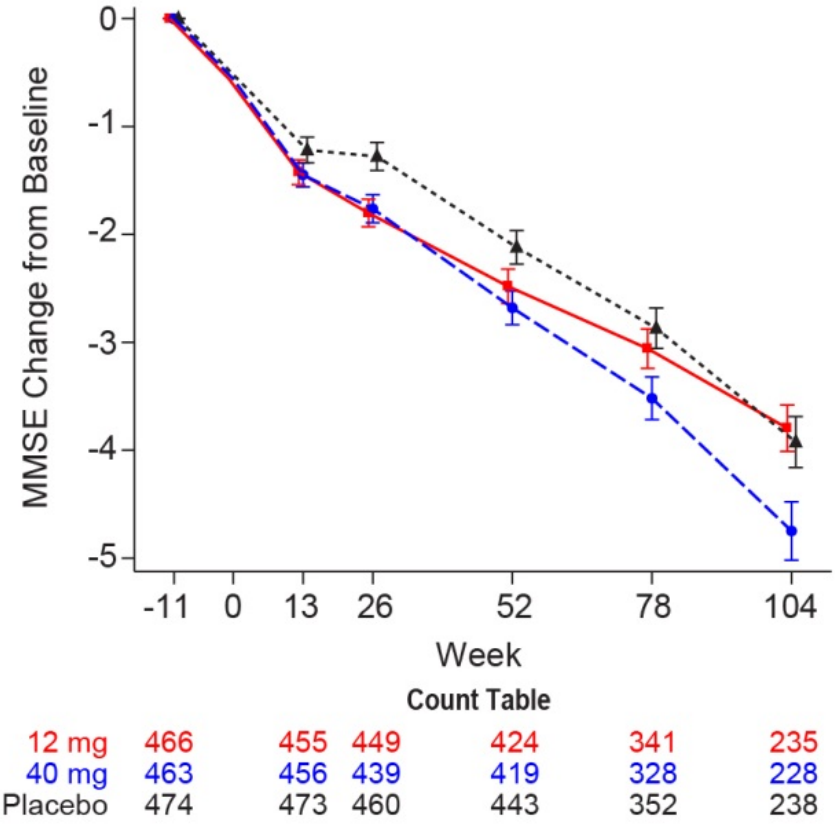
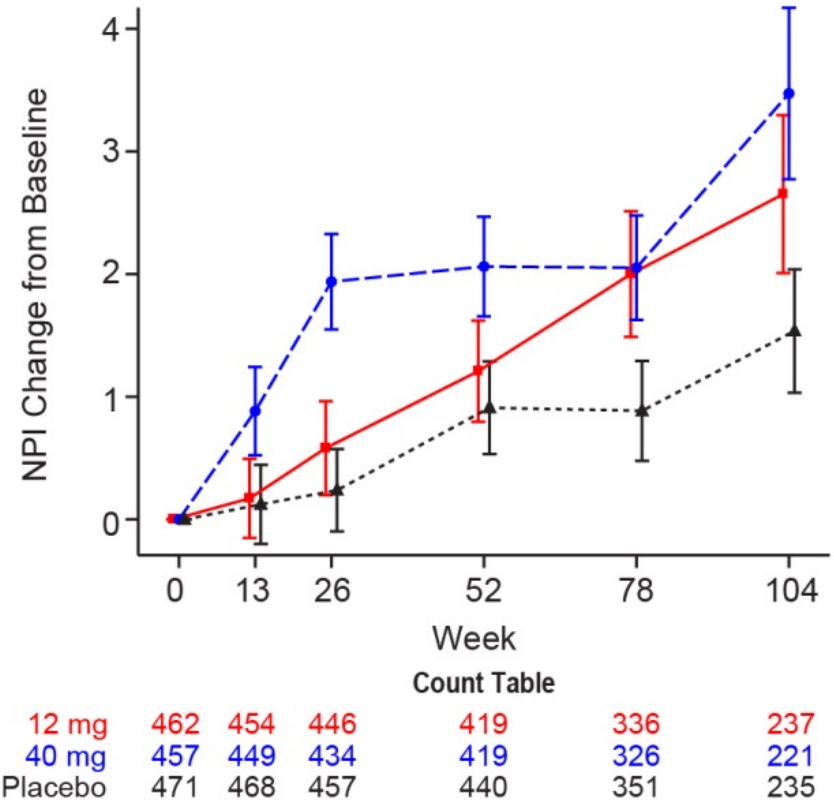


Figure S4. Model-based mean (SE) change from baseline MMSE scores



Baseline is plotted at Week -11, which is the mean assessment time of the baseline measurement as offset from the first dose of trial medication at Week 0. As a result, there is no data plotted at Week 0. The time course of the verubecestat arms between Week -11 and Week 0 was assumed to follow the same course as the placebo arm. From this Week 0 placebo coordinate, the time course for each respective verubecestat arm was extended to the estimate at the first scheduled postdose timepoint.

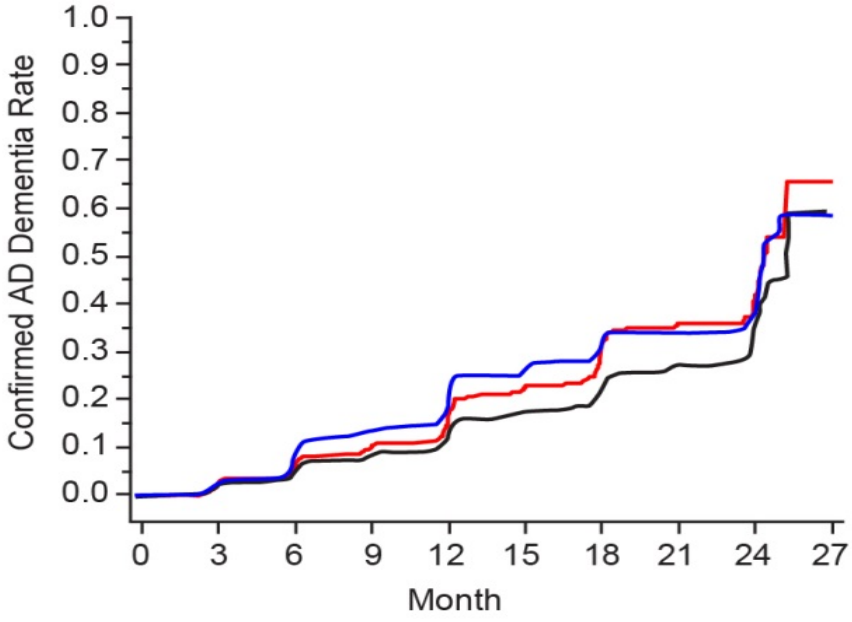
Figure S5. Model-based mean (SE) change from baseline NPI scores



Count Table

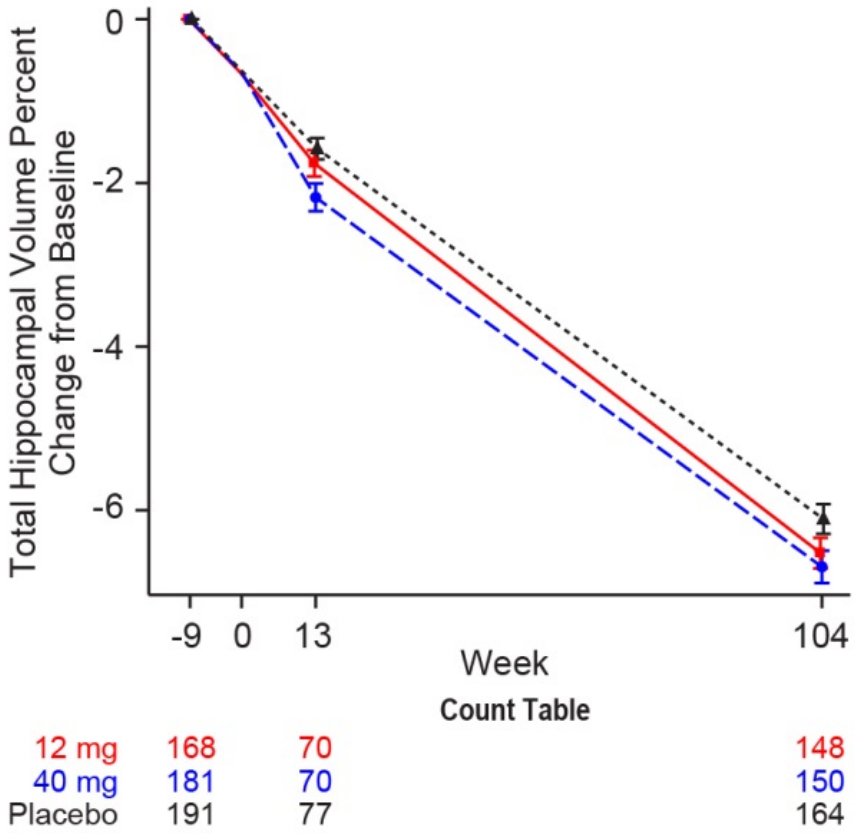
12 mg	462	454	446	419	336	237
40 mg	457	449	434	419	326	221
Placebo	471	468	457	440	351	235

Figure S6. Time to progression to AD dementia



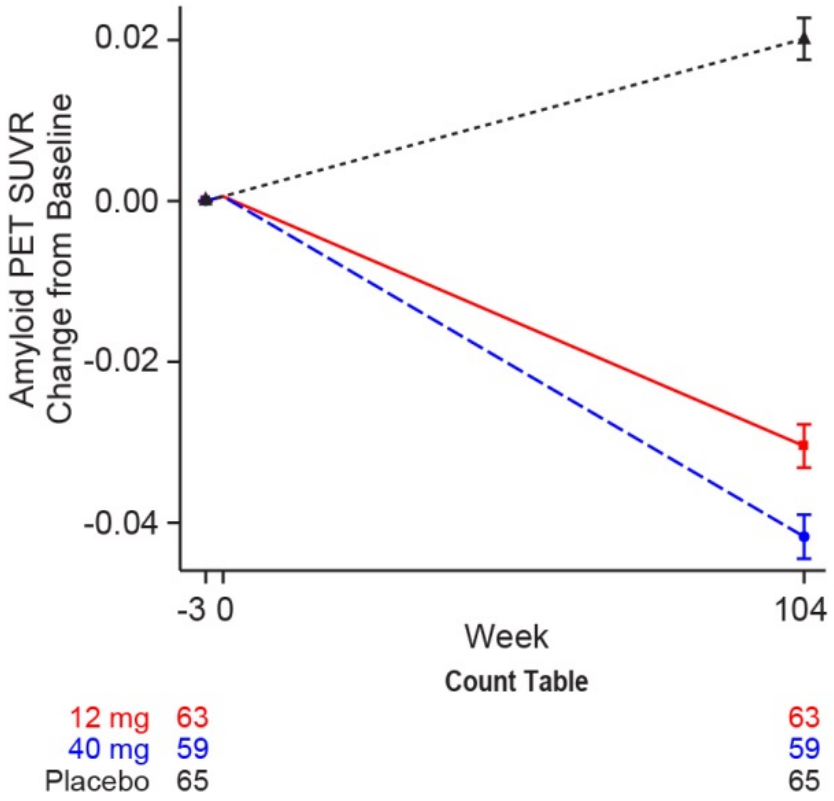
Patients at Risk										
12 mg	480	459	427	402	364	310	227	186	71	0
40 mg	481	450	414	386	350	295	225	184	80	0
Placebo	480	465	442	425	398	354	260	211	80	0
Cases										
12 mg	11	19	16	32	23	30	15	11	10	0
40 mg	10	28	24	27	27	23	4	13	13	0
Placebo	10	15	13	23	19	21	12	20	7	0

Figure S7. Model-based mean (SE) change from baseline in MRI hippocampal volume



Baseline is plotted at Week -9, which is the mean assessment time of the baseline measurement as offset from the first dose of trial medication at Week 0. As a result, there is no data plotted at Week 0. The time course of the verubecestat arms between Week -9 and Week 0 was assumed to follow the same course as the placebo arm. From this Week 0 placebo coordinate, the time course for each respective verubecestat arm was extended to the estimate at the first scheduled postdose timepoint.

Figure S8. Model-based mean (SE) change from baseline in PET amyloid



Baseline is plotted at Week -3, which is the mean assessment time of the baseline measurement as offset from the first dose of trial medication at Week 0. As a result, there is no data plotted at Week 0. The time course of the verubecestat arms between Week -3 and Week 0 was assumed to follow the same course as the placebo arm. From this Week 0 placebo coordinate, the time course for each respective verubecestat arm was extended to the estimate at the first scheduled postdose timepoint.

Figure S9. Plots of change from baseline in PET amyloid in individual patients (the dashed and solid lines are to differentiate patients for display purposes and have no other significance)

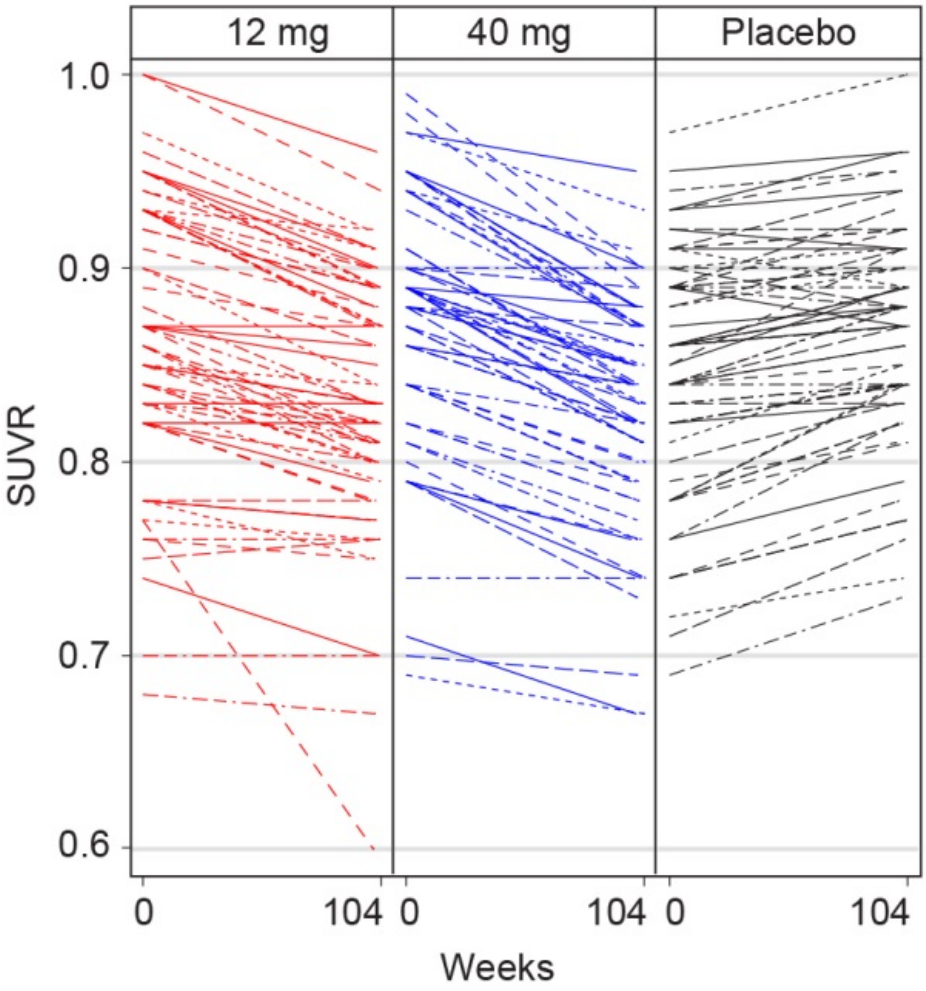


Table S1. Model-based least squares mean change from baseline to each time point for select outcomes, and difference (95% CI) versus placebo

	Mean Change			Difference	
Endpoint	**12mg**	**40mg**	**Placebo**	**12mg vs. placebo (95% CI)**	**40mg vs. placebo (95% CI)**
CDR-SB[a]					
Week 13	0.14	0.24	0.09	0.05 (-0.05, 0.16)	0.14 (0.03, 0.26)
Week 26	0.35	0.41	0.24	0.11 (-0.02, 0.24)	0.17 (0.03, 0.30)
Week 52	0.79	0.82	0.59	0.19 (0.02, 0.37)	0.23 (0.04, 0.41)
Week 78	1.29	1.22	1.05	0.24 (0.00, 0.48)	0.17 (-0.07, 0.41)
Week 104	1.65	2.02	1.58	0.07 (-0.25, 0.39	0.44 (0.09, 0.79)
CCS-3D[a]					
Week 13	0.06	0.09	-0.02	0.08 (0.02, 0.15)	0.12 (0.05, 0.18)
Week 26	0.10	0.10	0.00	0.11 (0.04, 0.18)	0.11 (0.04, 0.18)
Week 39	0.18	0.26	0.10	0.08 (0.00, 0.16)	0.16 (0.08, 0.24)
Week 52	0.26	0.30	0.19	0.07 (-0.02, 0.16)	0.11 (0.01, 0.20)
Week 65	0.42	0.47	0.35	0.06 (-0.03, 0.16)	0.12 (0.02, 0.22)
Week 78	0.46	0.51	0.45	0.02 (-0.10, 0.13)	0.07 (-0.05, 0.18)
Week 91	0.49	0.59	0.48	0.02 (-0.11, 0.15)	0.11 (-0.03, 0.25)
Week 104	0.77	0.78	0.77	0.00 (-0.16, 0.15)	0.01 (-0.16, 0.17)
ADCS-ADL$_{MCI}$[b]					
Week 13	-0.3	-0.5	-0.3	0.0 (-0.5, 0.5)	-0.2 (-0.7, 0.3)
Week 26	-1.2	-1.1	-0.8	-0.4 (-1.0, 0.2)	-0.3 (-0.9, 0.3)
Week 39	-2.0	-1.8	-0.9	-1.0 (-1.7, -0.3)	-0.8 (-1.5, -0.2)
Week 52	-2.3	-2.1	-1.5	-0.8 (-1.5, -0.1)	-0.6 (-1.3, 0.2)
Week 65	-3.1	-3.1	-2.3	-0.8 (-1.7, 0.1)	-0.8 (-1.7, 0.0)
Week 78	-4.1	-3.7	-3.0	-1.1 (-2.1, -0.1)	-0.7 (-1.7, 0.2)
Week 91	-4.7	-4.8	-3.3	-1.4 (-2.5, -0.3)	-1.5 (-2.6, -0.4)
Week 104	-5.2	-5.8	-4.1	-1.0 (-2.2, 0.2)	-1.7 (-3.0, -0.4)
ADAS-Cog$_{13}$[a]					
Week 13	1.5	1.5	-0.2	1.7 (1.1, 2.3)	1.8 (1.2, 2.3)
Week 26	0.8	1.2	-0.7	1.5 (0.9, 2.1)	1.9 (1.3, 2.5)
Week 39	2.5	3.1	1.1	1.4 (0.8, 2.1)	2.0 (1.3, 2.6)
Week 52	3.1	3.4	2.2	0.9 (0.1, 1.6)	1.3 (0.5, 2.0)
Week 65	5.0	5.6	3.8	1.2 (0.4, 2.0)	1.8 (1.0, 2.6)
Week 78	4.8	5.3	4.1	0.7 (-0.2, 1.7)	1.2 (0.3, 2.2)
Week 91	4.5	5.0	3.6	0.9 (-0.2, 2.0)	1.4 (0.3, 2.5)
Week 104	8.0	8.2	6.9	1.1 (-0.1, 2.3)	1.3 (0.1, 2.6)

[a]A higher positive mean change score corresponds to greater decline relative to baseline and a negative treatment difference indicates less decline for verubecestat versus placebo.
[b]A higher negative mean change score corresponds to greater decline relative to baseline and a positive treatment difference indicates less decline for verubecestat versus placebo.

Table S2. Subgroup analyses of model-based least squares mean change from baseline at week 104 for CDR-SB score, and difference (95% CI) versus placebo

	Mean Change			Difference (95% CI)[a]	
Subgroup status at baseline	**12mg**	**40mg**	**Placebo**	**12mg vs. placebo**	**40mg vs. placebo**
APOE4 genotype					
Non-carrier	1.5	2.4	1.5	0.0	0.9
Carrier	1.7	1.9	1.6	0.1 (-0.3, 0.5)	0.3 (-0.1, 0.7)
MMSE score					
≤26	1.7	2.4	1.9	-0.2 (-0.6, 0.3)	0.5 (0.0, 1.0)
≥27	1.6	1.6	1.3	0.3 (-0.2, 0.7)	0.3 (-0.2, 0.8)
Sex					
Male	1.8	1.8	1.6	0.2 (-0.3, 0.6)	0.2 (-0.3, 0.7)
Female	1.5	2.2	1.5	0.0 (-0.5, 0.4)	0.7 (0.2, 1.2)
Age					
<72 y	1.3	2.0	1.3	0.1 (-0.4, 0.5)	0.8 (0.3, 1.3)
≥72 y	2.0	2.0	1.8	0.1 (-0.4, 0.6)	0.1 (-0.4, 0.6)
PET SUVR					
≤0.86	1.6	1.7	1.4	0.2 (-0.3, 0.7)	0.3 (-0.2, 0.8)
>0.86	1.8	2.2	1.8	0.0 (-0.5, 0.6)	0.5 (-0.2, 1.1)

A higher positive mean change score corresponds to greater decline relative to baseline and a negative treatment difference indicates less decline for verubecestat versus placebo.

[a]Confidence intervals only produced for those treatment comparisons for which at least 75 subjects were present in both treatment groups.

Table S3. Sensitivity analysis of model-based least squares mean change from baseline at each timepoint for CDR-SB, and difference (95% CI) versus placebo: excludes assessments taken after announcement of trial termination

	Mean Change [N]			Difference	
Endpoint	**12mg**	**40mg**	**Placebo**	**12mg vs. placebo (95% CI)**	**40mg vs. placebo (95% CI)**
Week 13	0.14 [457]	0.24 [449]	0.09 [464]	0.05 (-0.05, 0.16)	0.14 (0.03, 0.26)
Week 26	0.35 [445]	0.41 [434]	0.24 [456]	0.11 (-0.02, 0.24)	0.17 (0.03, 0.30)
Week 52	0.79 [420]	0.82 [418]	0.59 [438]	0.20 (0.02, 0.37)	0.23 (0.04, 0.41)
Week 78	1.26 [300]	1.19 [290]	1.06 [302]	0.20 (-0.04, 0.45)	0.14 (-0.12, 0.39)
Week 104	1.60 [210]	1.98 [199]	1.59 [205]	0.01 (-0.33, 0.35)	0.39 (0.02, 0.76)

A higher positive mean change score corresponds to greater decline relative to baseline and a negative treatment difference indicates less decline for verubecestat versus placebo.

Table S4. Observed mean (SD) baseline, week 104, and % change-from-baseline scores for CSF biomarkers

Biomarker	Baseline	Week 104	% change-from- baseline
Aß40 (pg/mL)			
Placebo (n=6)	21600 (6563)	18783 (4871)	-9.0 (23.7)
12 mg (n=5)	16220 (6621)	5460 (2727)	-66.6 (9.1)
40 mg (n=6)	13448 (3478)	1640 (714.2)	-88.1 (2.8)
Aß42 (pg/mL)			
Placebo (n=6)	544.5 (134.1)	529.2 (137.2)	-2.4 (11.5)
12 mg (n=5)	407.0 (101.7)	160.6 (36.9)	-60.2 (4.7)
40 mg (n=6)	413.5 (130.2)	78.0 (25.0)	-81.0 (2.2)
sAPPß (ng/mL)			
Placebo (n=6)	316.2 (83.7)	290.7 (100.6)	-5.5 (29.5)
12 mg (n=5)	200.8 (44.0)	59.9 (5.4)	-69.1 (6.6)
40 mg (n=6)	238.3 (62.4)	20.7 (11.2)	-91.7 (2.9)
Total tau (pg/mL)			
Placebo (n=6)	243.5 (97.0)	254.2 (85.0)	10.2 (27.9)
12 mg (n=5)	203.8 (129.1)	243.0 (113.2)	33.2 (44.3)
40 mg (n=6)	159.3 (79.0)	205.0 (57.6)	42.8 (39.7)
Phosphorylated tau (pg/mL)			
Placebo (n=6)	124.2 (69.1)	102.1 (25.0)	-6.0 (28.0)
12 mg (n=5)	125.1 (133.8)	113.6 (114.9)	-6.4 (9.4)
40 mg (n=6)	69.0 (17.0)	68.4 (15.9)	-0.2 (12.0)

Table S5. Causes of deaths occurring over 104 weeks (up to 14 days after last dose) in part-1: number (%) of patients

	12mg N=483	40mg N=484	Placebo N=484
Total	3 (0.6)	1 (0.2)	3 (0.6)
Cardiac disorders			
Acute myocardial infarction	1 (0.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Intestinal obstruction	1 (0.2)	0 (0.0)	0 (0.0)
Infections and infestations			
Pneumonia	0 (0.0)	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications			
Road traffic accident	0 (0.0)	0 (0.0)	1 (0.2)
Neoplasms			
Lung adenocarcinoma	0 (0.0)	1 (0.2)	0 (0.0)
Pancreatic carcinoma	1 (0.2)	0 (0.0)	0 (0.0)
Psychiatric disorders			
Delirium	0 (0.0)	0 (0.0)	1 (0.2)

Table S6. Most severe treatment-emergent suicidal ideation and behavior event summary (within 14 days of last dose) in part-1 using the timeframe between the screening and randomization visits as the reference period

	12 mg	40 mg	Placebo
Category	**n/m (%)**	**n/m (%)**	**n/m (%)**
With one or more ideation or behavior events	31/483 (6.4)	44/482 (9.1)	26/482 (5.4)
Suicidal ideation	**31/483 (6.4)**	**44/482 (9.1)**	**26/482 (5.4)**
Passive - wish to be dead	18/ 479 (3.8)	27/477 (5.7)	20/475 (4.2)
Active - nonspecific (without regard to method, intent, or plan)	5/ 482 (1.0)	6/482 (1.2)	1/477 (0.2)
Active - method, (without regard to intent or plan)	5/483 (1.0)	8/482 (1.7)	3/478 (0.6)
Active - method and intent, (without regard to plan)	3/483 (0.6)	1/482 (0.2)	1/482 (0.2)
Active - method, intent and plan	0/483 (0.0)	2/482 (0.4)	1/482 (0.2)
Suicidal behavior	**2/483 (0.4)**	**1/482 (0.2)**	**1/482 (0.2)**
Preparatory actions or behaviors	1/483 (0.2)	0/482 (0.0)	0/482 (0.0)
Aborted attempt	0/483 (0.0)	0/482 (0.0)	0/482 (0.0)
Interrupted attempt	0/483 (0.0)	0/482 (0.0)	1/482 (0.2)
Suicide attempt	1/483 (0.2)	1/482 (0.2)	0/482 (0.0)
Completed suicide	0/483 (0.0)	0/482 (0.0)	0/482 (0.0)
Non-Suicidal Self-Injurious Behavior	**0/483 (0.0)**	**0/482 (0.0)**	**0/482 (0.0)**

For each category, the population (=m) only includes treated participants for whom worsening from baseline was possible. For Suicidal Ideation Categories, worsening is defined as an increasing progression from one category to another along the spectrum (from Passive down to Active – method, intent, and plan). For Suicidal Behavior Categories, worsening is defined as an increasing progression from one category to another along the spectrum (from Preparatory actions or behaviors down to Completed suicide).

Table S7. Adverse events within 14 days of last dose in the extension: number (%) of patients and treatment difference (95% CI) in percentages versus placebo/40mg

	12mg/12mg N=197	40mg/40mg N=191	Placebo/40mg N=204	Difference in %s 12mg/12mg vs. placebo/40mg (95 % CI)	Difference in %s 40mg/40mg vs. placebo/40mg (95% CI)
Adverse event summary					
Any adverse event	117 (59.4)	106 (55.5)	135 (66.2)	-6.79 (-16.16, 2.68)	-10.68 (-20.16, -1.04)
Any serious adverse event	10 (5.1)	22 (11.5)	24 (11.8)	-6.69 (-12.42, -1.29)	-0.25 (-6.68, 6.27)
Discontinued treatment due to adverse event	0 (0.0)	1 (0.5)	1 (0.5)	-2.42 (-6.03, 0.61)	-2.38 (-6.01, 0.71
Death	0 (0.0)	3 (1.6)	0 (0.0)	0.00 (-1.85, 1.92)	1.57 (-0.30, 4.52)
Prespecified adverse events					
ARIA-H[a]	1 (0.5)	0 (0.0)	0 (0.0)	0.51 (-1.35, 2.82)	0.00 (-1.85, 1.98)
ARIA-E[a]	0 (0.0)	0 (0.0)	0 (0.0)	0.00 (-1.85, 1.92)	0.00 (-1.85, 1.98)
Delirium	1 (0.5)	1 (0.5)	0 (0.0)	0.51 (-1.35, 2.82)	0.52 (-1.33, 2.91)
Rash[b]	1 (0.5)	3 (1.6)	5 (2.5)	-1.94 (-5.17, 0.61)	-0.88 (-4.25, 2.36)
Specific adverse events[c]					
Rash/dermatitis/urticaria[d]	8 (4.1)	9 (4.7)	17 (8.3)	-4.27 (-9.37, 0.50)	-3.62 (-8.81, 1.37)
Depression	6 (3.0)	2 (1.0)	6 (2.9)	0.10 (-3.62, 3.91)	-1.89 (-5.36, 1.13)
Anxiety	8 (4.1)	3 (1.6)	3 (1.5)	2.59 (-0.71, 6.52)	0.10 (-2.86, 3.22)
Sleep disturbance[d]	2 (1.0)	3 (1.6)	4 (2.0)	-0.95 (-4.05, 1.89)	-0.39 (-3.57, 2.79)
Weight decreased	6 (3.0)	0 (0.0)	8 (3.9)	-0.88 (-4.90, 3.06)	-3.92 (-7.55, -1.91)
Cough	2 (1.0)	1 (0.5)	4 (2.0)	-0.95 (-4.05, 1.89)	-1.44 (-4.48, 1.13)
Psychotic symptoms[d]	2 (1.0)	2 (1.0)	5 (2.5)	-1.44 (-4.73, 1.46)	-1.40 (-4.70, 1.56)
Pruritus	0 (0.0)	3 (1.6)	2 (1.0)	-0.98 (not calculated)[f]	0.59 (-2.12, 3.65)
Other adverse events of interest[e]					
Falls and injuries[d]	21 (10.7)	19 (9.9)	25 (12.3)	-1.60 (-7.97, 4.78)	-2.31 (-8.64, 4.04)
Suicidal ideation	7 (3.6)	6 (3.1)	7 (3.4)	0.12 (-3.83, 4.15)	-0.29 (-4.19, 3.67)
Hair color change	0 (0.0)	1 (0.5)	6 (2.9)	-2.94 (-6.27, -1.00)	-2.42 (-5.82, 0.26)
Syncope-like events[d]	0 (0.0)	1 (0.5)	4 (2.0)	-1.96 (-4.94, -0.02)	-1.44 (-4.48, 1.13)

12/12mg = patients on 12mg in part-1 who remained on 12mg in the extension; 40mg/40mg = patients on 40 mg in part-1 who remained on 40mg in the extension; placebo/40mg = patients on 40mg in part-1 who were switched to 40mg in the extension.
[a]ARIA-H includes incident microhemorrhage, superficial siderosis or macrohemorrhage, ARIA-E = incident vasogenic edema.
[b]Rash adverse events that were clinically significant in the investigator's judgment.
[c]Adverse events that met the ">5.0 % in a verubecestat group and >placebo" criteria in part-1 (see Table 3).
[d]Several specific adverse event terms that appeared to be related were combined in a post hoc and unblinded fashion into the composite items shown; psychotic symptoms included adverse event terms with paranoia, delusion and hallucination.
[e]Based on data from previous clinical trials.

[f]Confidence intervals only produced for those comparisons for which at least one of the treatment groups had an incidence >1%.

Table S8. Causes of deaths in the extension (up to 14 days after last dose): number (%) of patients

	12mg/12mg N=197	40mg/40mg N=191	Placebo/40mg N=204
Total	0 (0.0)	3 (1.6)	0 (0.0)
Cardiac disorders			
Cardio-respiratory arrest	0 (0.0)	1 (0.5)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.5)	0 (0.0)
Infections and infestations			
Pneumonia bacterial	0 (0.0)	1 (0.5)	0 (0.0)