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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	• Medidata RAVE Electronic Data Capture system, used as electronic case report forms for collection and management of clinical data • Medavante Virgil, the eSource platform, provides digital clinical outcome assessments and data management for clinical scales outcomes • Cogstate Datapoint Software System, a secure online portal, enabling efficient data collection and storage for ongoing review of data quality • Cogstate Box system served for uploading documents and recordings produced by investigational sites • PPD Preclarus central laboratory database for recording and management of central laboratory data • InfoMED LabIS, a laboratory information system enabling lab data collection and storage • IXICO's online image data management system TrialTracker, a web-based platform designed to facilitate the live tracking, upload, and reporting of imaging data for MRI and FDG PET outcomes • eRT EXPERT Clinical Data Management System for acquisition, measurement and cardiology review and all associated processes • Cenduit's Interactive Response Technology providing Interactive Web Response System for allocation and tracking of treatment of study subjects • Simoa HD-1 instrument software v1.5 was used to evaluate neurofilament light chain protein and pT217 tau levels in the respective assays. • SIENA 2.6 (part of FSL, FMRIB Oxford) and Freesurfer v6.0 were used for volumetric analyses. FSL 6.0 (FMRIB Software Library, Oxford) was used to evaluate diffusion-weighted scans.
Data analysis	We performed the statistical analyses using the R programming environment version 4.0.5 (R Development Core Team 2020; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and GraphPad Prism version 8.4.3 (GraphPad software, CA, USA). For ANCOVA we used SAS software (SAS(R) Proprietary Software 9.4 (TS1M5)).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding author PN upon reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	An overall dropout rate of 25% was assumed. Sample sizes were increased to correct for dropout. Dropouts were not to be replaced. For the primary objective (safety assessment): The study was powered to detect an AE with an incidence of 7% and higher. At least 83 subjects on AADvac1 treatment were required to complete the study to show an AE incidence of 7% and higher as statistically significant with a power of 0.80 at the significance level of 0.05, using a one-sided one-sample Wald Z-test. Correcting for 25% dropout, at least 111 subjects would need to be enrolled and randomised in the AADvac1 arm. Given a 3:2 AADvac1 to placebo allocation, at least 55 subjects on placebo treatment were required to complete the study. Correcting for 25% dropout and given a 3:2 AADvac1 to placebo allocation, at least 74 subjects needed to be enrolled and randomised in the placebo arm. With 111 patients enrolled in the AADvac1 group and 83 patients on AADvac1 treatment expected to complete the 2-year trial, 194 patient-years of on-treatment safety data were to be generated (assuming linear dropout). Given this data set, the study had a > 95% chance to observe at least one occurrence of hypothetical AEs with a true annual incidence of 1:65 or higher. A non-inferiority post-hoc power calculation was also undertaken. With a 15% non-inferiority margin, a trial with 97 subjects on AADvac1 and 65 on placebo (162 patients in total) has 80% power in a one-sided non-inferiority test at the significance level of 0.1, to demonstrate non-inferiority of AADvac1 to placebo with respect to incidence of AEs if AADvac1 has a 7% higher incidence of AEs compared to placebo; using a two-sample Wald z-test with adjustment according to [Agresti, A. and B. Caffo, Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures. The American Statistician, 2000. 54(4): p. 280-288.] (H0: the incidence of AEs in AADvac1 minus Placebo >= 0.15; H1: the incidence of AEs in AADvac1 minus Placebo < 0.15). For the secondary clinical and cognitive endpoints: With 138 patients targeted to complete the study, the ADAMANT trial was powered to detect an effect size of 0.5 with a power of 0.80 at a two-tailed significance level of 0.05 (taking the 3:2 randomisation ratio into account). No sample size calculations were done for exploratory endpoints. (The study size was set primarily according to the safety analysis, and informed by the power calculations for secondary clinical endpoints. No sample size calculation was done for exploratory and research endpoints; the intent was simply to analyze whatever the resulting amount of data would be. For many novel endpoints, e.g., NfL, pT217 tau or DTI, a sample size calculation was not feasible because of the paucity of data on longitudinal change of these endpoints over time – especially considering the study was designed in 2015).
Data exclusions	One site (#31802) was excluded from analysis due to severe misconduct identified during a for-cause audit (data manipulation, deficiencies in data quality and integrity, issues with attributability of data, deficiencies in safety reporting). Data from this site are not included in any analyses.
Replication	For immunogenicity, antibody response measurements were performed in duplicate. For fluid biomarkers, all measurements were performed in duplicate. Cognitive and functional assessments are inherently non-replicable. Patients were assessed every 3 months over the course of the study to evaluate the consistency of assessment. MRIs were subjected to quality control, and scans that failed quality control either repeated, or excluded from analysis. Attempts are replication were successful. Where the duplicate analyses did not align, samples were re-assessed.
Randomization	Patients were randomised via an interactive web-based response system (IWRS). The AADvac1: placebo randomisation ratio was 3:2. The randomisation block size was 10.
Blinding	AADvac1 and placebo vials were identical in appearance. Each vial was labelled with a unique identifier code assigned by an independent vendor, and the specific vial to be administered to a given patient at a given visit was allocated prior to administration by the interactive web-

based response system. Patients, caregivers, investigators, outcome assessors, and all other personnel involved in trial conduct were blinded to treatment allocation.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Antibodies

Antibodies used

See Methods section "Antibodies used in this study"
* Humanized Mab AX004, targeting the tau assembly-regulating domains in MTBR region, generated by AXON Neuroscience, patent WO2016079597A1 [Weisova, P., et al., Therapeutic antibody targeting microtubule-binding domain prevents neuronal internalization of extracellular tau via masking neuron surface proteoglycans. Acta Neuropathol Commun, 2019., Zilkova, M., et al., Humanized Tau Antibodies Promote Tau Uptake By Human Microglia Without Any Increase Of Inflammation. Acta Neuropathologica Communications, 2020.];
* mouse DC2E7, targeting tau phospho-threonine pT217, generated by AXON Neuroscience, patent WO 2019/186276 A2. 2019-10-03 [Hanes, J., et al., Novel Immunoassay Detecting p-Tau Thr217 Distinguishes Alzheimer's Disease from Other Dementias. . Neurology, 2020.];
* mouse DC2E2, targeting tau 164-174, generated by AXON Neuroscience, patent WO 2019/186276 A2. 2019-10-03 [Hanes, J., et al., Novel Immunoassay Detecting p-Tau Thr217 Distinguishes Alzheimer's Disease from Other Dementias. . Neurology, 2020.]; .
* Goat anti-Human IgG (H+L); Secondary Antibody, HRP conjugate, Catalogue Number: 31410, Lot Number: QE2020434; (Thermo Fisher Scientific, Rockford, IL 61105, USA)
* Mouse anti-Human IgG1 heavy Chain Secondary Antibody, HRP conjugate, Catalogue Number: MH1715, Lot Number: 1870367; Clone: HP6070; (Thermo Fisher Scientific, Rockford, IL 61105, USA)
* Mouse anti-Human IgG2 heavy Chain Secondary Antibody, HRP conjugate, Catalogue Number: MH 1722, Lot Number: 1873763, Clone: HP6014; (Thermo Fisher Scientific, Rockford, IL 61105, USA)
* Mouse anti-Human IgG3 heavy Chain Secondary Antibody, HRP conjugate, Catalogue Number: 05-3620, Lot Number: QD215257, Clone: HP6047; (Thermo Fisher Scientific, Rockford, IL 61105, USA)
* Mouse anti-Human IgG4 heavy Chain Secondary Antibody, HRP conjugate Catalogue Number: MH1742, Lot Number: 1831840, Clone: HP6023 (Thermo Fisher Scientific, Rockford, IL 61105, USA)

Validation

See Methods section "Antibodies used in this study"
Primary antibodies: humanized Mab AX004, specific to the tau assembly-regulating domains in MTBR region, validated using tau protein in ELISA, published in [Weisova, P., et al., Therapeutic antibody targeting microtubule-binding domain prevents neuronal internalization of extracellular tau via masking neuron surface proteoglycans. Acta Neuropathol Commun, 2019., Zilkova, M., et al., Humanized Tau Antibodies Promote Tau Uptake By Human Microglia Without Any Increase Of Inflammation. Acta Neuropathologica Communications, 2020.] and patented in WO2016079597A1; mouse DC2E7, specific to tau phospho-threonine pT217; mouse DC2E2, specific to tau protein targeting tau epitope 164-174, both validated in [Hanes, J., et al., Novel Immunoassay Detecting p-Tau Thr217 Distinguishes Alzheimer's Disease from Other Dementias. . Neurology, 2020.] and patented in WO 2019/186276 A2. 2019-10-03;
Secondary antibodies: all secondary antibodies were validated by each respective manufacturer, as per the pertinent DataSheets.

Human research participants

Policy information about studies involving human research participants

Population characteristics

The study enrolled patients of both sexes aged 50-85 with a diagnosis of Alzheimer's disease dementia according to the 2011 NIA-AA criteria (McKhann et al., 2011), with evidence of medial temporal lobe atrophy (Scheltens score 2+) and/or an AD amyloid and tau biomarker profile in the CSF. Patients were required to be on standard acetylcholinesterase inhibitor therapy; concomitant therapy with memantine was allowed.
Baseline demographic characteristics of the population are listed in Table 1 in the article.

Recruitment

The investigational sites, hospitals and outpatient clinics, pre-selected the potential study participants from their own databases and in some instances based on references. After providing informed consent, patients underwent the screening procedures set

by the study protocol, such as assessments of clinical status including clinical scales, blood tests and MRI, and optionally CSF biomarkers. After all required data for a specific patients was collected, the Investigator and the Sponsor evaluated its consistency with the Inclusion and Exclusion criteria. Only after the eligibility was centrally confirmed the patient was enrolled and randomized to one of the treatment arms. No waivers to Inclusion and Exclusion criteria were granted. No selection biases were identified.

Ethics oversight

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Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Study registration: EudraCT 2015-000630-30; NCT02579252.
Study protocol	The study protocol will be uploaded with the submission.
Data collection	The data included in the analyses were collected in the period from the first visit of the first patient screened on the 10th of May 2016 until the end-of-study visit of the last patient which took place on the 25th of May 2019. The first subject was randomised 16th June 2016. The last safety follow-up was on 25 June 2019. The data were collected through electronic data capture systems at investigation sites and through centralized vendors databases such as MRI readings and volumetry, DTI data, FDG PET data, laboratory results and ECG results.
Outcomes	Full statistical methodology is provided in the supplement.

Magnetic resonance imaging

Experimental design

Design type	Resting state.
Design specifications	140 volumes, repetition time = 3 s, total duration = 7 min
Behavioral performance measures	No behavioral performance measures were used.

Acquisition

Imaging type(s)	structural and diffusion
Field strength	3T
Sequence & imaging parameters	T2 FLAIR (TR/TI/TE = 10,000/2,600/100-120 ms, slice thickness = 5mm, slice gap = 0 mm, field of view = 240mm, matrix=256x256); T2 TSE (TR/TE = 2,000-4,000/80-120 ms, slice thickness = 5mm, slice gap = 0 mm, field of view = 240mm, matrix=256x256); T2* gradient echo (TR/TE= 600-700/20 ms, flip angle = 20°, slice thickness = 5mm, slice gap = 0 mm, field of view = 240mm, matrix=256x256); T1W 3D (MPRAGE or T1-TFE, 1mm isotropic resolution with whole brain coverage)
Area of acquisition	whole brain

Diffusion MRI ☒ Used ☐ Not used

Parameters: TR = 7s, TE = 80–100 ms, 41 diffusion directions with b = 1000 s/mm2, 5 repeats of b=0 s/mm2, 2.7 mm isotropic resolution, single shot echo planar imaging readout with SENSE/GRAPPA factor of 2-3.

Preprocessing

Preprocessing software: Whole brain volume loss was calculated with SIENA 2.6 (part of FSL, FMRIB Oxford); Regional atrophy was assessed with the longitudinal Stream of FreeSurfer version 6 (Fischl B, Neuroimage 2012;62:774).

Normalization: 3D T1 scans were normalized by non-linear registration to a template. Diffusion weighted scan were registered through the corresponding 3D T1 scans and by using the b0 scan as reference. The obtained transformation matrix then was applied to the entire diffusion weighted (b=1000 s/mm2) series.

Normalization template: MNI305

Noise and artifact removal: All scans that were affected by noise and motion artefacts were repeated or excluded from analysis

Volume censoring: not done

Statistical modeling & inference

Model type and settings: Following preprocessing (motion correction, spatial smoothing, temporal high-pass filtering), a temporal-concatenation independent component analysis approach was used to calculate group-level components of the resting state networks. The following networks have been assessed: Default mode network, the right fronto-parietal network, the left fronto-parietal network, and the salience network. Based on a general linear model, a dual regression approach was applied to obtain time courses of these networks for each patient.

Effect(s) tested: Non-parametric testing for temporal differences and for between-group effects (placebo versus verum).

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both

Anatomical location(s): Anatomical locations were determined from automated labeling with FreeSurfer

Statistic type for inference (See Eklund et al. 2016): Not applicable for the employed paradigms.

Correction: Correction for multiple comparisons with FDR

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis