BRIEF REPORT

Ultrasound Blood–Brain Barrier Opening and Aducanumab in Alzheimer's Disease

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SUMMARY

Antiamyloid antibodies have been used to reduce cerebral amyloid-beta (Aβ) load in patients with Alzheimer's disease. We applied focused ultrasound with each of six monthly aducanumab infusions to temporarily open the blood–brain barrier with the goal of enhancing amyloid removal in selected brain regions in three participants over a period of 6 months. The reduction in the level of Aβ was numerically greater in regions treated with focused ultrasound than in the homologous regions in the contralateral hemisphere that were not treated with focused ultrasound, as measured by fluorine-18 florbetaben positron-emission tomography. Cognitive tests and safety evaluations were conducted over a period of 30 to 180 days after treatment. (Funded by the Harry T. Mangurian, Jr. Foundation and the West Virginia University Rockefeller Neuroscience Institute.)

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A challenge of therapeutics in Alzheimer's disease has been restriction by the blood–brain barrier of the delivery of therapeutic agents to brain tissue.[1] Low-intensity focused ultrasound guided by magnetic resonance imaging (MRI) has been shown to reversibly open the blood–brain barrier in patients with Alzheimer's disease[2-6] or other neurologic disorders, including Parkinson's disease,[7] brain tumors,[8-10] and amyotrophic lateral sclerosis.[11] Previous studies that applied focused ultrasound to regions of the brain without the use of a therapeutic agent in patients with Alzheimer's disease have resulted in modest reductions in the levels of amyloid-beta (Aβ) in those regions.[5,6,12,13] Anti-Aβ antibodies have shown promise in reducing levels of Aβ and slowing disease progression.[14,15] In experimental models, the use of focused ultrasound to open the blood–brain barrier resulted in a level of aducanumab delivery to targeted brain regions that was five to eight times as high as that in the untreated regions of the brain.[16,17] In this investigator-initiated, prospective, open-label, single-group, single-institution, proof-of-concept trial involving three participants, we aimed to evaluate the safety and feasibility of combining aducanumab infusion with focused ultrasound to open the blood–brain barrier to influence amyloid removal in Alzheimer's disease.

METHODS

TRIAL DESIGN AND OVERSIGHT

We measured the levels of Aβ with the use of fluorine-18 (^{18}F) florbetaben positron-emission tomography (PET) and performed serial assessments of neurologic,

cognitive, and behavioral outcomes in the participants. The trial was conducted with an investigational device exemption approved by the Food and Drug Administration and approval from the institutional review board at West Virginia University. Participants provided written informed consent in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Neither the manufacturer of the ultrasound device (Insightec) nor the manufacturer of aducanumab (Biogen) sponsored the research or participated in the trial design; collection, analysis, or interpretation of the data; or the writing of the manuscript. The trial was led by the first author and was designed by the first author and the second and last authors, who also analyzed the data.

PARTICIPANTS AND ENROLLMENT CRITERIA

Among patients between 50 and 85 years of age who had received diagnoses of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, we recruited a convenience sample of three participants from the Memory Health Clinic at the West Virginia University Rockefeller Neuroscience Institute. The diagnoses were made according to the National Institute of Aging–Alzheimer's Association research framework,[18] which includes evidence of pathologic changes in Alzheimer's disease as indicated by abnormal levels of Aβ accumulation, a standardized uptake value ratio (SUVR) greater than 1.4 in signature regions of the brain that are associated with Alzheimer's disease (i.e., the middle temporal gyrus, inferior temporal gyrus, temporal pole, superior frontal gyrus, middle frontal gyrus, precuneus, supramarginal gyrus, angular gyrus, and superior parietal lobule)[19] on ^{18}F-florbetaben PET scan, and elevated levels (>21.7 pg per milliliter) of phosphorylated tau in cerebrospinal fluid (individual levels along with inclusion and exclusion criteria are shown in Table S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Eligible participants had to have progressive cognitive loss and abnormal performance score that was at least 1 standard deviation below the expected performance on a standard neuropsychological examination (i.e., the California Verbal Learning Test, the Trail Making Test, Boston Naming Test, the Animal Naming Test, and the Repeatable Battery for the Assessment of Neuropsychological Status Line Orientation Test [RBANS]), and MRI of the brain showing atrophy in the temporal or parietal lobes (or both) without evidence of another pathologic process. The participants met indications for aducanumab treatment as specified by the prescribing information for the drug and appropriate-use recommendations.[20]

As part of a risk-mitigation strategy, carriers of the apolipoprotein E (APOE) ε4 genotype (heterozygotes or homozygotes) were excluded owing to the known heightened risk for amyloid-related imaging abnormalities among these carriers.[15] Approval from the data and safety monitoring board was required for escalation from the initial dose and successive participant enrollment (members of the data and safety monitoring board are listed in the Supplementary Appendix).

TREATMENT PROTOCOL

The protocol, available at NEJM.org, provided for two phases after participants had undergone screening: an intervention phase, which combined focused ultrasound to open the blood–brain barrier at the time of aducanumab treatment, and a follow-up phase in which the participant received an aducanumab infusion alone (Fig. S2 and Table S4). The intervention phase consisted of opening of the blood–brain barrier with focused ultrasound combined with aducanumab treatment for 6 months; during that time, participants received monthly treatments of intravenous aducanumab with dose escalation (1 mg per kilogram of body weight for 2 months, followed by 3 mg per kilogram for 2 months and 6 mg per kilogram for 2 months),[20] with opening of the blood–brain barrier with focused ultrasound initiated 2 hours after each infusion. Escalation of the aducanumab dose to a maximum of 6 mg per kilogram rather than the on-label dose of 10 mg per kilogram was planned as a risk-mitigation strategy to facilitate the safety of the combination treatment. The use of focused ultrasound to open the blood–brain barrier was restricted to one hemisphere in the frontal or temporal lobe or the hippocampus with high levels of Aβ. Homologous brain regions in the contralateral hemisphere that were not exposed to focused ultrasound served as controls. During

the follow-up phase, participants received a monthly infusion of aducanumab at a dose of 10 mg per kilogram, which is the standard of care, without focused ultrasound.

The MRI-guided focused ultrasound device that was used was the ExAblate-Neuro-Type2 (Insightec), a hemispherical phased-array transducer with more than 1000 ultrasound sources that converge on a focal point in the brain with real-time guidance by MRI.[3-13] Our technique for applying focused ultrasound to the blood–brain barrier has been published previously.[4,6,12] The final version of the protocol limited the targeted size of the opening of the blood–brain barrier to a maximal volume of 10 ml in the nondominant frontal lobe in the first participant and to 20 ml and 40 ml within any hemisphere in the second and third participant, respectively.

IMAGING AND ASSESSMENT OF THE BLOOD–BRAIN BARRIER OPENING

MRI of the brain was performed at baseline and before, during, immediately after, and 24 and 48 hours after the focused ultrasound treatment. MRI was performed with the use of a 3 Tesla Siemens Prisma scanner. MRI sequences included T2*-weighted gradient-echo sequence imaging, T2-weighted fluid attenuated inversion recovery imaging, T1-weighted rapid three-dimensional gradient-echo imaging, and turbo spin–echo imaging with gadolinium-based contrast (gadobutrol, administered intravenously at a dose of 0.1 mmol per kilogram). The blood–brain barrier opening was evaluated with the use of serial MRIs with gadolinium contrast enhancement immediately after the focused ultrasound procedure and again 24 and 48 hours later to assess the closure of the blood–brain barrier opening. All MRIs were reviewed by two board-certified neuroradiologists who were not masked to the side of the brain that was treated by means of focused ultrasound to assess changes related to the opening and closing of the blood–brain barrier and to evaluate for hemorrhage, edema, gliosis, amyloid-related imaging abnormalities, and other abnormalities. Follow-up MRIs were performed at 30 days and 1 year after the end of the combined-treatment phase.

PET IMAGING ANALYSES

^{18}F-florbetaben PET scans were performed with the use of a Siemens Biograph mCT system to quantify levels of Aβ at baseline and at 3, 11, and 19 weeks during the combined-treatment phase and at 26 weeks and 1 year in the follow-up phase. To assess the effects of using focused ultrasound to open the blood–brain barrier on Aβ in the targeted regions, PET scans were registered to their baseline T1-weighted MRI.[21] Segmentation of the whole brain by means of structural MRI was performed with the use of multiple three-dimensional convolutional networks.[22,23] Quantification of the SUVR was determined with the use of cerebellar gray matter as a reference and converted to centiloids for standardized quantification of Aβ load.[24] In each participant, we calculated the centiloid value for the entire focused ultrasound–targeted region and compared this value to that of the contralateral homologous brain region with no exposure to focused ultrasound at each prespecified time after baseline.

NEUROLOGIC, COGNITIVE, AND BEHAVIORAL ASSESSMENTS

So that neurologic safety could be monitored, participants completed the remote National Institutes of Health Stroke Scale daily during the first week after each combination treatment of aducanumab infusion and focused ultrasound opening of the blood–brain barrier and then weekly until the next combination treatment. A comprehensive neurologic examination was conducted by a board-certified neurologist at baseline, immediately before and immediately after each of the six monthly combination treatments, and 24 hours after each combination treatment. During the follow-up phase, neurologic examinations were conducted on days 30, 90, and 180, as well as at 12 and 18 months, and are planned to be conducted annually for up to 5 years (Table S4).

Cognitive and behavioral assessments were conducted at baseline with the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog 11), RBANS, Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI) questionnaire, Alzheimer's Disease Cooperative Study–Activity of Daily Living Inventory (ADCS–ADLI), and the Columbia Suicide Severity Rating Scale (CSSRS). In the intervention phase, the ADAS-Cog 11 assessment (and RBANS, if necessary) were conducted 7 days after each combination treatment

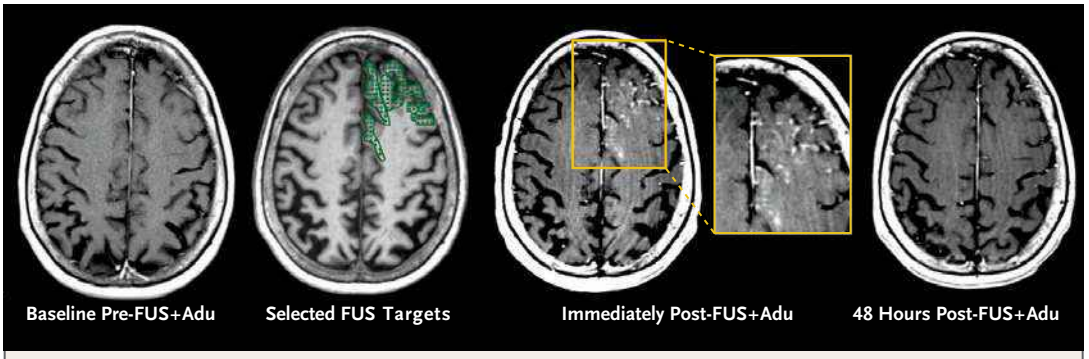


Figure 1. Blood–Brain Barrier Opening with Focused Ultrasound (FUS).

Axial gadolinium postcontrast T1-weighted magnetic resonance images at baseline, immediately after combination treatment of FUS plus aducanumab (Adu) infusion, and 48 hours after FUS plus aducanumab combination treatment show gadolinium enhancement as a reflection of the blood–brain barrier opening and closure in the left frontal lobe. The green outline denotes the targeted region of FUS used to open the blood–brain barrier. The yellow inset is an enlarged view of the left frontal lobe.

and 1 day before the next combination treatment. During the follow-up phase, participants completed the RBANS at 30, 90, and 180 days, as well as the ADAS-Cog 11, MMSE, GDS, NPI, CSSRS, and ADCS–ADLI assessments at 12 and 18 months and were asked to complete them annually for up to 5 years.

RESULTS

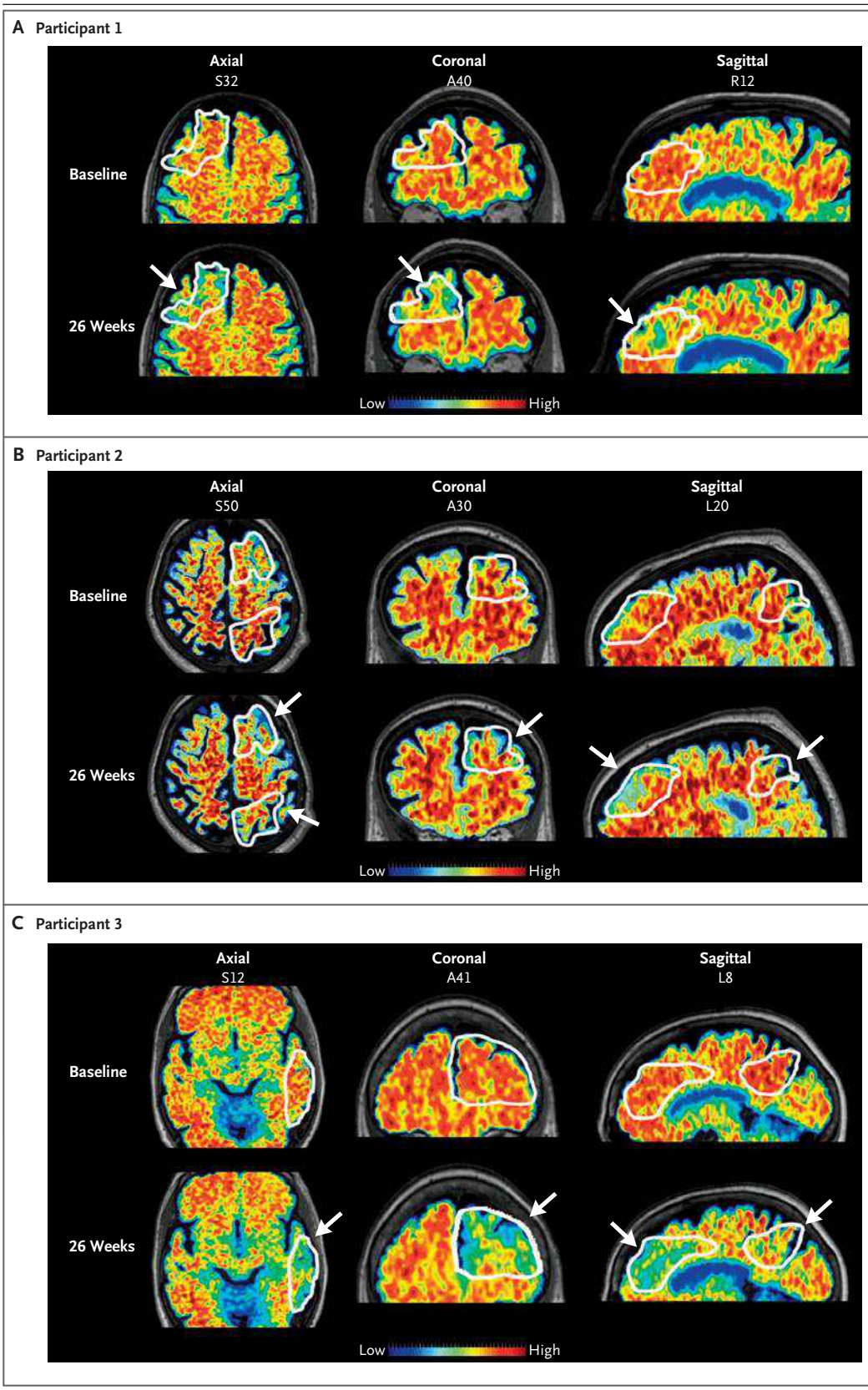
PARTICIPANTS

We enrolled three participants — Participant 1, a 77-year-old man; Participant 2, a 59-year-old man; and Participant 3, a 64-year-old woman. Their demographic and medical characteristics at baseline are shown in Table S2. These three participants are the only persons we have treated with the combined method to date. An additional patient was screened but did not meet the eligibility criteria because the results of the Aβ PET were negative. Given the staggered enrollment, participant follow-up visits to assess cognitive outcomes and safety after the 6-month active treatment period were as follows: Participant 1, follow-up at 180 days after the combination treatment phase; Participant 2, at 90 days; and Participant 3, at 30 days. All had received a diagnosis of Alzheimer's disease within the year before enrollment. None of the participants had previously received aducanumab therapy. Baseline levels of Aβ shown on PET in signature regions of the brain that are associated with Alzheimer's disease in Participants 1, 2, and 3 were measured as 203, 139, and 285 centiloids, respectively (Table S2). All participants completed six monthly combination treatments of aducanumab infusions and opening of the blood–brain barrier with focused ultrasound. The total brain volumes and locations for each treatment were as follows: Participant 1, up to 10 ml in the right frontal lobe; Participant 2, up to 20 ml in the left frontal and parietal lobes; and Participant 3, up to 40 ml in the left frontal, parietal, and temporal lobes and the hippocampus.

During the 6-month combined-treatment phase, there was opening of the blood–brain barrier in all focused ultrasound–targeted regions followed by closure of the blood–brain barrier within 24 to 48 hours after the procedure (Fig. 1) as assessed by gadolinium contrast enhancement in the treated region. No cognitive decline was observed in any of the participants during the combined-treatment phase.

Figure 2 (facing page). Reduction in Amyloid-beta (Aβ) Levels with Focused Ultrasound to Open the Blood–Brain Barrier.

Representative paired axial, coronal, and sagittal slices of positron-emission tomography (PET) brain images are shown for the three participants at baseline and 26 weeks. Slices are aligned with the Montreal Neurological Institute atlas as a reference. The white arrows and outlines indicate the regions with focused ultrasound opening of the blood–brain barrier in the frontal, parietal, and temporal lobes and indicate reduction in the Aβ level. Color intensity represents Aβ levels; red is associated with higher levels of Aβ.



CHANGES IN AMYLOID AND COGNITIVE MEASUREMENTS

Aβ PET analyses of regions of the blood–brain barrier opened with focused ultrasound (Fig. 2 and Fig. 3) showed reductions from baseline in the levels of Aβ to the 26-week assessment: in Participant 1, the centiloid value decreased from 224.2 to 115.2; in Participant 2, from 185.6 to 104.6; and Participant 3, from 251.5 to 84.9. Analyses of the homologous contralateral regions that were not exposed to opening of the blood–brain barrier with focused ultrasound showed similar levels of Aβ at baseline and at the 26-week follow-up: in Participant 1, 219.7 and 218.1 centiloids, respectively; in Participant 2, 129.3 and 135.8 centiloids; and in Participant 3, 246.9 and 238.4 centiloids. In each participant, the reduction in the level of Aβ was greater in the regions that were targeted with focused ultrasound than in the contralateral homologous brain regions that were not exposed to focused ultrasound (Fig. 3): in Participant 1, the reduction from baseline to 26 weeks was 107.5 centiloids greater with focused ultrasound than without (difference, 48 percentage points); in Participant 2, the reduction from baseline to 26 weeks was 87.6 centiloids greater with focused ultrasound than without (difference, 49 percentage points); and in Participant 3, the reduction from baseline to 26 weeks was 158.1 centiloids greater with focused ultrasound than without (difference, 63 percentage points). Figure 3 shows the adjusted mean change in centiloid values for the three participants at baseline and at approximately 3, 11, 19, and 26 weeks.

Cognitive and behavioral outcomes during the follow-up phase are described in Table S3. Participants 1 and 2 had no neurologic, cognitive, or behavioral changes at their last follow-up visit. At day 30 days of the follow-up phase, Participant 3 had cognitive decline indicated by the RBANS score (worsening from 76 to 61; RBANS scores range from 40 to 160 with lower scores indicating poorer neuropsychological performance), but no neurologic change or changes in scores on the ADLI were observed.

ADVERSE EVENTS

During the follow-up phase (180 days after the last combination treatment), there was one grade 1 adverse event (passive thoughts of death) that was defined as a serious adverse event. The event was adjudicated by members of the trial data and safety monitoring board, who concluded that it was not related to the trial intervention. No other serious adverse events were reported. All adverse events are shown in Table S5. Headaches were the most common adverse events and were mild except for one moderate headache; all headaches resolved. There were two severe adverse events during the focused ultrasound treatment in the same participant owing to head and neck positioning discomfort, which resolved immediately after the procedure. There were no amyloid-related imaging abnormalities and no neurologic changes observed by means of MRI, neurologic examinations, and the NIH stroke scale, with the exception of two instances of mild pronator drift of the left arm in Participant 2, a condition that was intermittently present before trial enrollment. A mild increase in behavioral symptoms, characterized by elevations in agitation, sleep disturbances, and appetite fluctuations measured with the use of the NPI questionnaire, was observed in Participant 3.

DISCUSSION

Several studies have shown that focused ultrasound can safely and transiently open the blood–brain barrier in patients with Alzheimer's disease and other neurologic disorders.[3-13] The effect of using focused ultrasound to open the blood–brain barrier alone, without application of antiamyloid treatment, on levels of Aβ in patients with Alzheimer's disease has been reported.[5,6,12,13,25] The results of these studies have varied with regard to the number of focused ultrasound treatments, treatment volumes, timelines, and brain regions treated. Reported reductions in the levels of Aβ with the use of focused ultrasound to open the blood–brain barrier alone have been nearly imperceptible in some studies; in studies with 5 to 10 patients, reductions in the levels of Aβ (measured as SUVRs) have been 1.6 to 6.6% over periods of 9 to 16 weeks.[3,5,6,12,13,25] Comparisons of our trial results with those from previous studies are limited, given the differences in designs. However, we found that the combination of focused ultrasound to open the blood–brain barrier and administration of aducanumab resulted in numerically greater reductions in Aβ

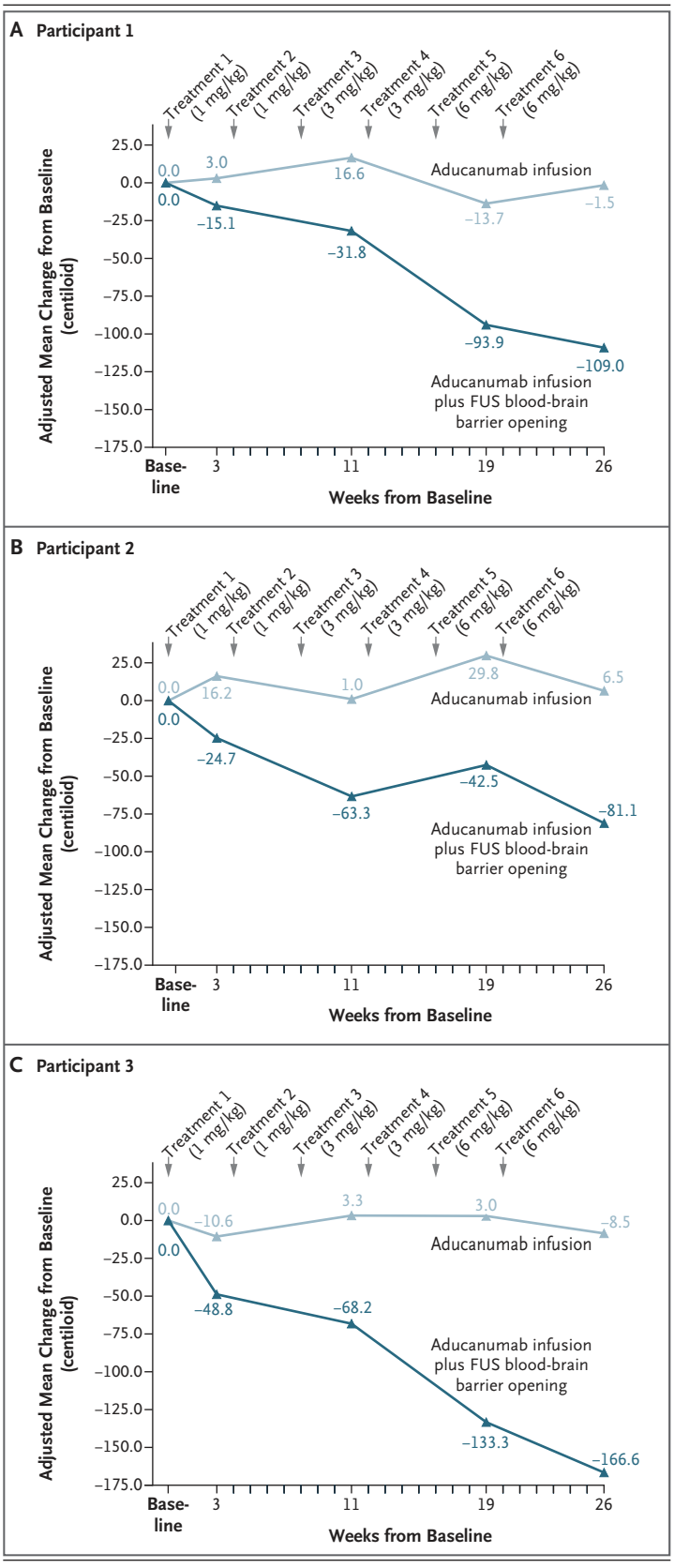


Figure 3. Longitudinal Changes in Aβ Centiloid Values.
Adjusted mean values in centiloids are shown for the three participants at baseline and at PET assessments at 3, 11, 19, and 26 weeks. Dark-blue lines depict the trajectory of centiloid values in the regions where focused ultrasound was used to open the blood–brain barrier, and light-blue lines show the trajectory of centiloid values in the contralateral corresponding homologous brain regions that did not receive focused ultrasound to open the blood–brain barrier.

levels, as measured as both SUVR and centiloid values, than previously observed in studies that assessed the use of focused ultrasound alone. We observed an average 32% reduction in SUVR (for the three participants combined) after 26 weeks in the regions that had received treatment to open the blood–brain barrier and six combination treatments. There was also a greater reduction in Aβ levels in the regions of the brain that had received treatment to open the blood–brain barrier than in the homologous regions in the contralateral hemisphere that were not treated with focused ultrasound. These results are consistent with those of experimental studies that have shown increased penetration of aducanumab when combined with focused ultrasound to open the blood–brain barrier.[16,17] However, our trial did not quantify monoclonal antibody penetration, and therefore enhanced delivery of the monoclonal antibody was not directly shown.

In our trial design, focused ultrasound was applied to one hemisphere only, allowing comparison between homologous brain regions in each participant. This design controls for several variables, such as antibody infusion, disease progression, and brain targets, and provides an appropriate comparator between homologous brain regions. In the three participants, brain regions with high levels of Aβ were treated with the use of focused ultrasound, and the Aβ results were averaged for comparison with those in homologous regions on the contralateral hemisphere of the brain.

Participants' clinical and cognitive aspects were assessed mainly for safety, because the trial was not powered to detect clinical changes. No serious adverse neurologic, cognitive, behavioral, or imaging–related adverse events were observed during the 6-month combination-treatment phase. We did not observe any amyloid-related imaging abnormalities; however, persons at highest

risk for amyloid-related imaging abnormalities (APOE-ε4 heterozygotes or homozygotes) were excluded as a risk-mitigation strategy. Although the cognitive worsening observed in Participant 3 at 30 days in the follow-up phase is of concern, there was no change in that participant's neurologic status or activities of daily life. Given the small number of participants, it is difficult to determine whether the cognitive changes were related to disease or a procedure. The neurologic scores of Participants 1 and 2 have remained essentially stable (at 180 and 90 days, respectively) in the follow-up phase.

In this proof-of-concept trial involving three participants, combining aducanumab infusion therapy with regional focused ultrasound to open the blood–brain barrier in participants with mild Alzheimer's disease was associated with few adverse events (mainly headache), and, during the 6-month combination-treatment phase, resulted in a greater reduction in the level of Aβ than aducanumab therapy alone in homologous regions that were not treated with the use of focused ultrasound.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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