INSIGHTEC

Focused Ultrasound & Alzheimer's Disease

An Emerging Research and Clinical Trial Program

Investigational Device — Research Use Only

October 2026

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Cautionary Note

This presentation concerns Insightec's research and clinical-trial activity in Alzheimer's disease. The use of Exablate to open the blood–brain barrier for oncology and neurodegenerative indication, including Alzheimer's disease, is investigational and has not been approved by the FDA or any other regulatory authority. Exablate is FDA-approved only for the treatment of medication-refractory essential tremor, tremor-dominant Parkinson's disease and advanced idiopathic Parkinson's disease with medication-refractory motor complications and additional Parkinson's disease motor-complication indications.

This presentation summarizes publicly available clinical trial registrations, peer-reviewed publications, and public statements by Insightec and its academic and clinical collaborators. It does not represent all material developments, and outcomes from early or ongoing research should not be read as predictive of eventual safety, efficacy, or regulatory approval. This presentation is not intended to promote any unapproved or off-label use of the Exablate device.

"Exablate," "Exablate Neuro," and the "Insightec" logo are protected trademarks of Insightec.

Pioneering focused ultrasound innovation since 1998

From technology to standard of care: each stage built the next.

1998
Pioneering FUS innovation for over 25 years

#1
FUS manufacturer in the market worldwide

>30,000
patients treated



GE HealthCare

First FDA clearance for ET

SIEMENS Healthineers

First BBBO Tx under FDA IDE for AD

2nd side ET FDA cleared

Exablate Prime launched



PHILIPS

PD bilateral FDA cleared

2016 2017 2018 2019 2020 2021 2022 2023 2024 2025

Partner MRI platforms

Movement disorders: commercial installed base

214 systems across three regions



214 systems worldwide

Our technology: a transformative platform

Exablate™ Neuro Type 1 | MR-guided focused ultrasound

Two FDA cleared indications
Treats both essential tremor and Parkinson's disease

Intelligent energy delivery
Advanced hardware and algorithms for skull shape and density correction to target and deliver energy deep in the brain

MRI compatible
Integrated with leading MRI manufacturers

Two proven technologies
MR-guided focused ultrasound combines magnetic resonance imaging and focused ultrasound



HOW DOES IT WORK?

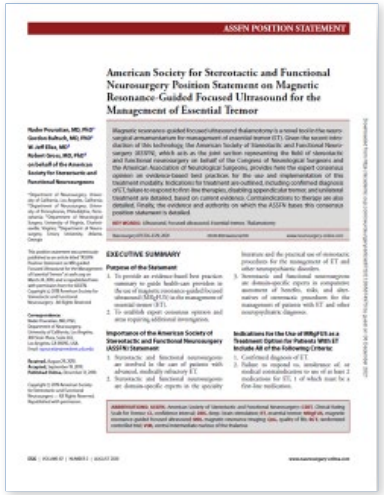
>1,000
beams of sound

Like a magnifying glass focusing sunlight on a single point, more than 1,000 ultrasound beams intersect precisely on a target deep in the body.

From investigational to guideline-recommended

A track record of taking a platform from first-in-human to guideline-endorsed therapy

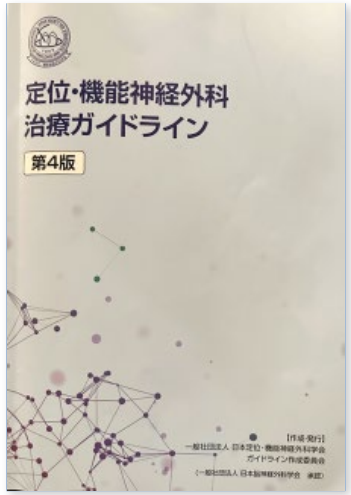












2019 — **MDS**

2020 — **ASSFN**

2021 — **Swiss Consensus**

2022 — **German Guidelines**

2024 — **Chinese Consensus**

2025 — **JSSFN / JSN**

6 guidelines and consensus statements across North America, Europe and Asia in 7 years

Sources: MDS 2019; ASSFN 2020; Swiss Consensus 2021; German S2k-Leitlinie 2022; Chinese Consensus 2024; JSSFN/JSN 2025.

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Why Alzheimer's Disease

High unmet need, a delivery barrier, and a new class of disease-modifying therapies

6.7M
Americans living with Alzheimer's
Expected to double in the next 25 years

1–2%
of drugs cross the blood–brain barrier
At effective concentrations

15–20 yrs
Earlier detection now possible
Blood tests flag biomarkers before symptoms appear

0
FDA-approved BBB devices for AD
Therapies described here are investigational



FDA-approved anti-amyloid antibodies

Target the underlying biology of early AD by clearing amyloid-beta

Leqembi®
lecanemab · Eisai/Biogen
- Approved Jul 2023
- IV q2w or SC autoinjector
- At-home SC start, Jul 2026

Kisunla™
donanemab · Eli Lilly
- Approved Jul 2024
- IV every 4 weeks
- Can stop once amyloid cleared

Both: early AD · modest slowing · ARIA MRI monitoring · Aduhelm discontinued 2024

Sources: FDA; Alzheimer's Association; Leqembi and Kisunla prescribing information.

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The Exablate 220: one platform, three applications in Alzheimer's

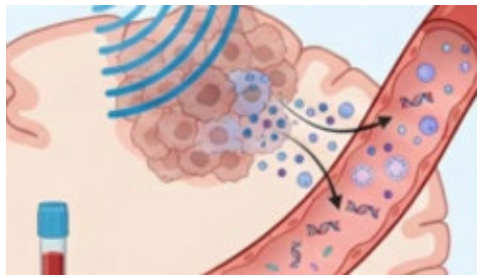
MR-guided focused ultrasound investigated for diagnoses, delivery and modulation

Exablate Neuro 4000 Type 2 (220 kHz): A Single, Versatile Platform

1 Diagnostics

LIQUID BIOPSY

Sonication transiently opens the BBB and releases brain-derived biomarkers into the bloodstream.

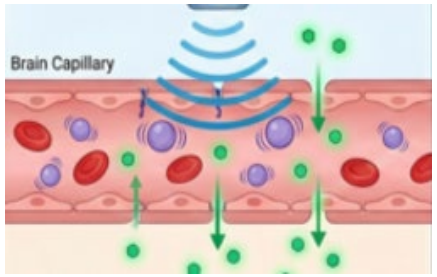


2 BBB opening

DRUG DELIVERY · IMMUNE MODULATION

Low-intensity sonication with circulating microbubbles opens the barrier transiently in a chosen volume, so antibodies, enzymes and gene vectors can reach the target. This also can promote amyloid clearance.

Enhanced immune modulation, with or without drugs.

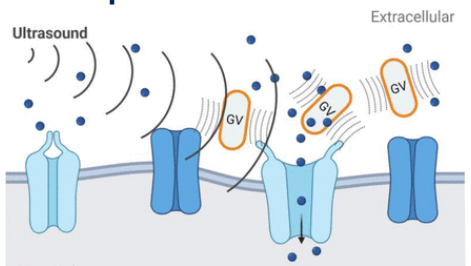


3 Neuromodulation

CIRCUIT MODULATION

The same array excites or suppresses a specific circuit, reversibly, as an alternative to lesioning. It may also enhance glymphatic clearance mechanizes.

Up to 50% of patients with Alzheimer's disease experience comorbid anxiety and depression.





Exablate Neuro 4000 Type 2

One versatile platform

- Deep targeting through an intact skull
- No incision, no ionizing radiation
- Continuous MR imaging for planning, targeting and verification in the same session
- Same array, same suite, three clinical modes

Investigational applications in Alzheimer's disease; not FDA-cleared for this indication.

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A decade of clinical evidence on BBB opening

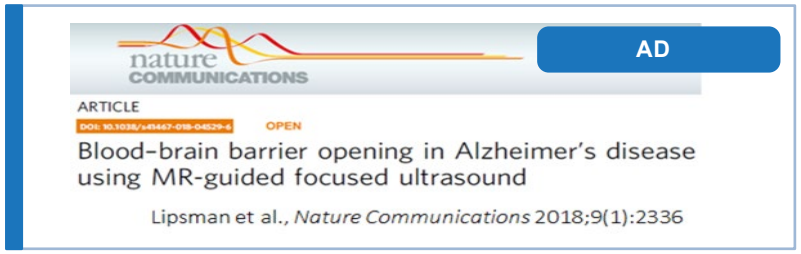
Reliable. Transient. Repeatable. Favorable safety profile

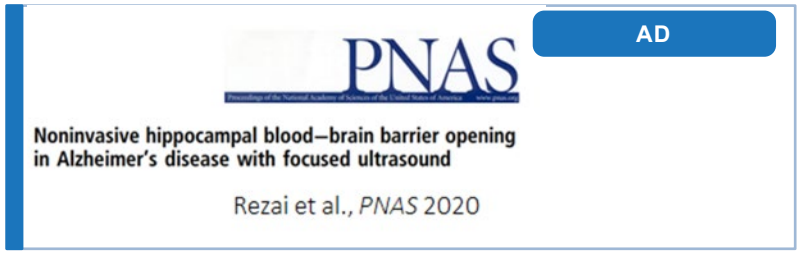
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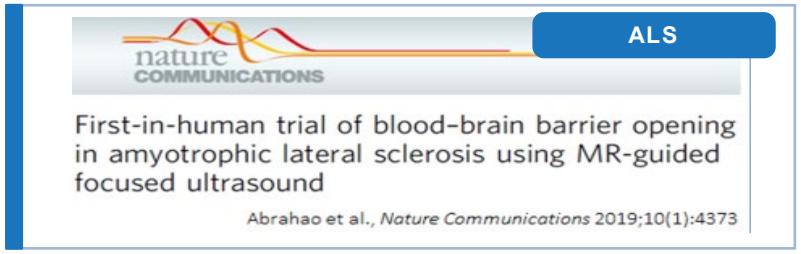
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Device-related serious safety events

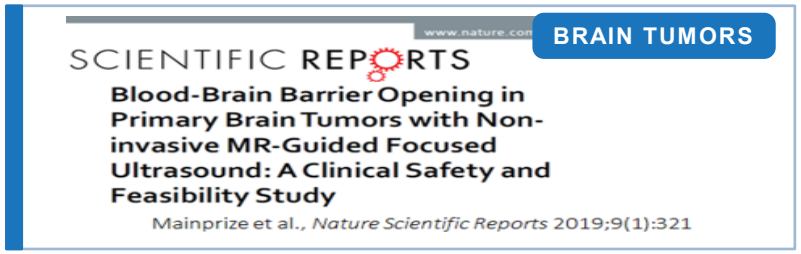
Consistent BBB opening across Alzheimer's, ALS, primary brain tumors and brain metastases

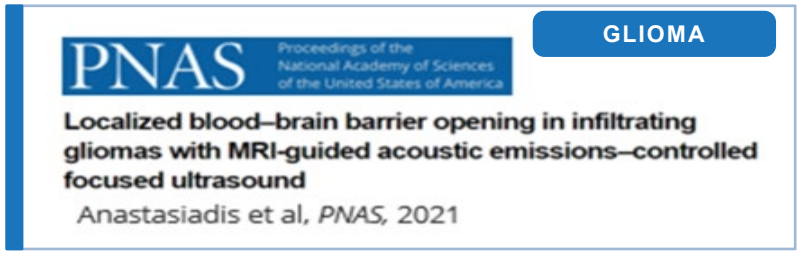


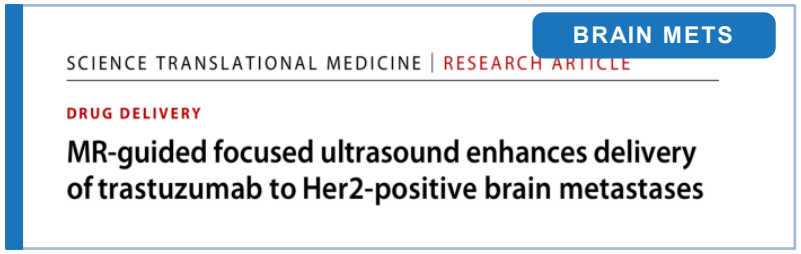












>20 clinical trials globally across 6 indications

Same platform, repeatable sessions, imaging-confirmed BBB opening and closure

Global Clinical Track and Current Experience

FUS BBB opening | Global expert presence

Canada | Dr. Lipsman

First-in-human BBB opening in Alzheimer's disease; Favorable results supporting continued investigation of FUS for Alzheimer's disease

Korea | Dr. Chang

Serial bilateral frontal opening across multiple sessions; feasibility, safety and cognitive follow-up.

Spain | Prof. Obeso

Parkinson's disease dementia: repeated parieto-occipital opening with imaging and neuropsychological endpoints.

USA | Dr. Rezai

Aducanumab + opening: ~32% additional SUVr reduction in sonicated regions vs. untreated homologue, at a below-label dose.

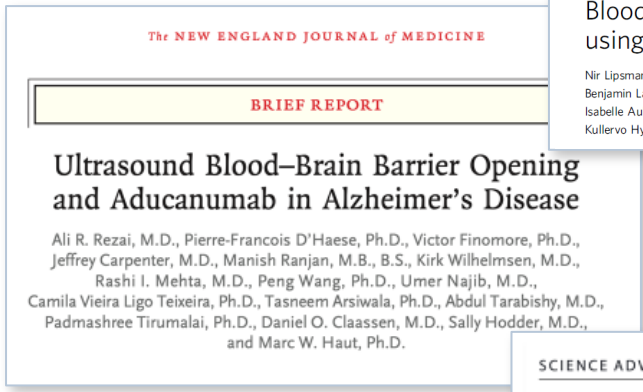

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-04529-6 OPEN

Blood–brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound

Nir Lipsman[1,2,3], Ying Meng[1,2], Allison J. Bethune[2,3], Yuexi Huang[4], Benjamin Lam[2,5], Mario Masellis[2,5], Nathan Herrmann[2,6], Chinthaka Heyn[4,7], Isabelle Aubert[2,4,8], Alexandre Boutet[7], Gwenn S. Smith[9], Kullervo Hynynen[4,10,11] & Sandra E. Black[2,5]


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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

Ali R. Rezai, M.D., Pierre-Francois D'Haese, Ph.D., Victor Finomore, Ph.D., Jeffrey Carpenter, M.D., Manish Ranjan, M.B., B.S., Kirk Wilhelmsen, M.D., Rashi I. Mehta, M.D., Peng Wang, Ph.D., Umer Najib, M.D., Camila Vieira Ligo Teixeira, Ph.D., Tasneem Arsiwala, Ph.D., Abdul Tarabishy, M.D., Padmashree Tirumalai, Ph.D., Daniel O. Claassen, M.D., Sally Hodder, M.D., and Marc W. Haut, Ph.D.


SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

BBB opening with focused ultrasound in nonhuman primates and Parkinson's disease patients: Targeted AAV vector delivery and PET imaging

Javier Blesa[1,2†], José A. Pineda-Pardo[1,2†], Ken-ichi Inoue[3], Carmen Gasca-Salas[1,2,4], Tiziano Balzano[1], Natalia López-González Del Rey[1,5], Alejandro Reinares-Sebastián[1], Esteban-García[1,5], Rafael Rodríguez-Rojas[1,2], Raquel Márquez[1], María Ciorraga[1], del Álamo[1], Lina García-Cañamaque[4,6], Santiago Ruiz de Aguiar[7], Itay Rachmilevitch[8], Lydia-Damas[1,2], Masahiko Takada[3,9], José A. Obeso[1,2,4*]


nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-21022-9 OPEN

Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia

Carmen Gasca-Salas[1,2], Beatriz Fernández-Rodríguez[1,8], José A. Pineda-Pardo[1,2,8], Rafael Rodríguez-Rojas[1,2], Ignacio Obeso[1,2], Frida Hernández-Fernández[1,3], Marta del Álamo[1,2], David Mata[1,2], Pasqualina Guida[1,2], Carlos Ordás-Bandera[4], J. Ignacio Montero-Roblas[5], Raúl Martínez-Fernández[1,2], Guglielmo Foffani[1,2,6], Itay Rachmilevitch[7] & José A. Obeso[1,2✉]

Trials completed to date: AD (FUS only), PD (FUS only), ALS (FUS only), ALS (IVIG), AD (aducanumab), PD (Cerezyme)

Sources: Lipsman, Nat Commun 2018; Rezai, PNAS 2020; Rezai, NEJM 2024; Park, J Neurosurg 2022 (long-term safety, imaging, cognition); Chang, Transl Neurodegener (extensive frontal opening); Gasca-Salas, Nat Commun 2021 (PD dementia); Blesa, Sci Adv 2023; Frontiers in Neuroscience (hippocampal plaque reduction).

Repeated frontal BBB opening alone in Alzheimer's disease

Dr. J.W. Chang and Ye et al., J Neurosurg 2025 | n = 6, open-label, no antibody

Study design

Exablate Neuro 4000 (220 kHz) · bilateral frontal · amyloid PET pre/post

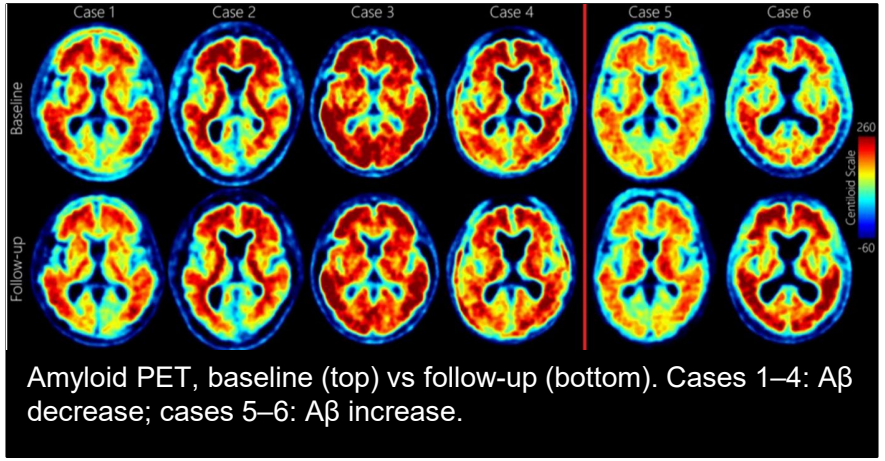
Screening	BBBO 1	BBBO 2	BBBO 3	Final eval
−4 wk	Day 0	Month 2	Month 4	Month 6

43.1 cm³
mean opening volume (>2× prior study)

−14.9 CL
global amyloid in 4 of 6 patients (67%)

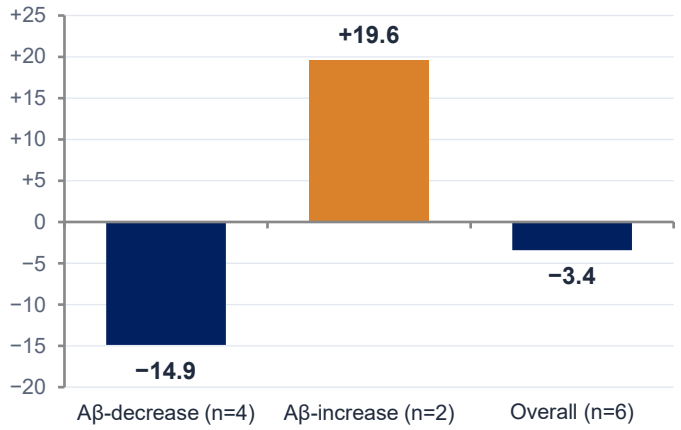
5 of 6
favorable neuropsychiatric (CGA-NPI) scores

0
serious adverse events or hemorrhage



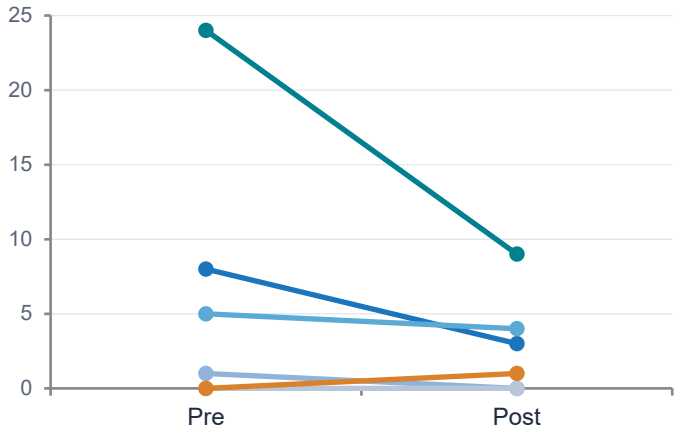
Amyloid PET, baseline (top) vs follow-up (bottom). Cases 1–4: Aβ decrease; cases 5–6: Aβ increase.

Change in global amyloid (Centiloid)



Decrease group: range −9.9 to −17.2 (p = 0.003). Increase group: +0.3 and +39.0 (p = 0.495).

Neuropsychiatric symptoms (CGA-NPI)



Mean 6.3 → 2.8 (lower = better); not significant

Takeaways

- Three openings at 2-month intervals were safe and feasible
- First trial to report neuropsychiatric improvement with BBB opening alone
- No change in K-MMSE or cognitive tests (frontal-only targeting)
- 2 of 6 had amyloid increase; possible Lewy co-pathology or MRI quality issues
- Authors call for combining FUS with anti-amyloid antibodies

Source: Ye BS, Chang KW, Kang S, Jeon S, Chang JW. J Neurosurg 2025;142:1263–1270. doi:10.3171/2024.8.JNS24989. PET image: Fig. 3, CC BY-NC-ND 4.0.

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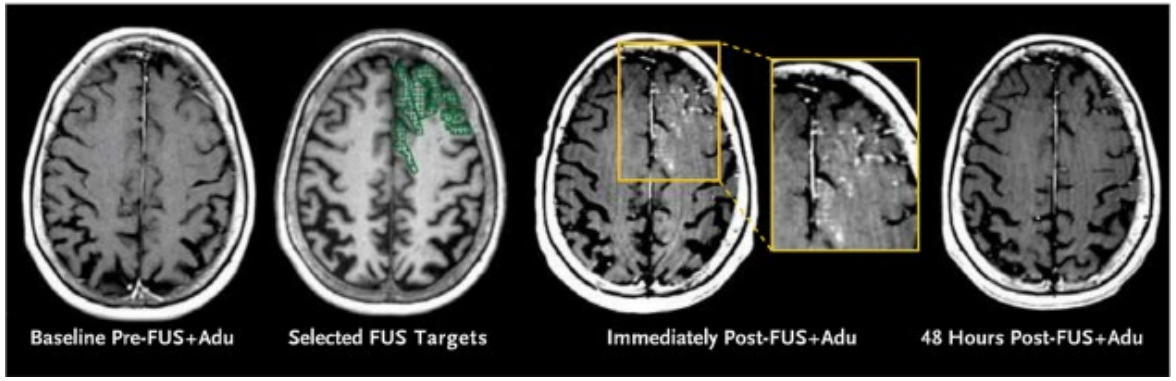
Opening the barrier holds potential to increase drug potency

Rezai et.al N Eng l J Med 2024 | FUS BBB opening + Aducanumab | n = 3

BRIEF REPORT

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

Ali R. Rezai, M.D., Pierre-Francois D'Haese, Ph.D., Victor Finomore, Ph.D., Jeffrey Carpenter, M.D., Manish Ranjan, M.B., B.S., Kirk Wilhelmsen, M.D., Rashi I. Mehta, M.D., Peng Wang, Ph.D., Umer Najib, M.D., Camila Vieira Ligo Teixeira, Ph.D., Tasneem Arsiwala, Ph.D., Abdul Tarabishy, M.D., Padmashree Tirumalai, Ph.D., Daniel O. Claassen, M.D., Sally Hodder, M.D., and Marc W. Haut, Ph.D.

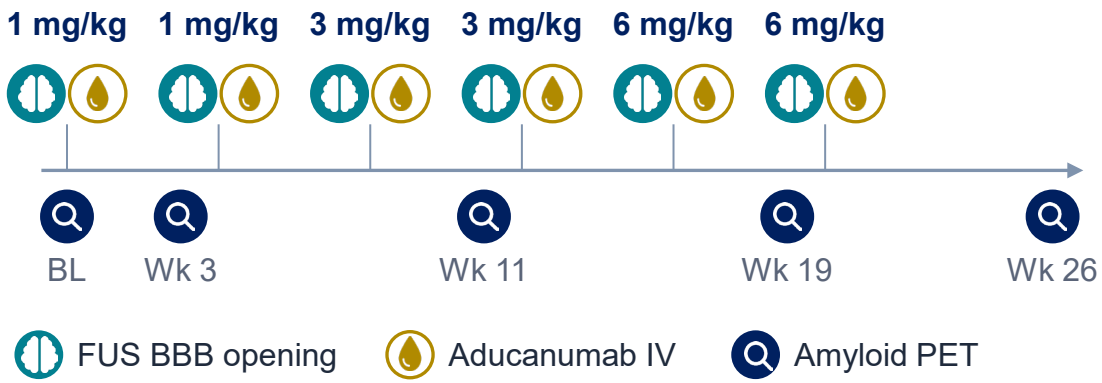


BBB opening confirmed on MRI: gadolinium enhancement in the targeted left frontal lobe immediately after FUS + aducanumab, resolved by 48 hours.

Source: Rezai AR et al. N Engl J Med 2024;390:55–62. doi:10.1056/NEJMoa2308719

Treatment protocol

6 monthly sessions over 26 weeks



Average SUVR reduction in the opened region

32%

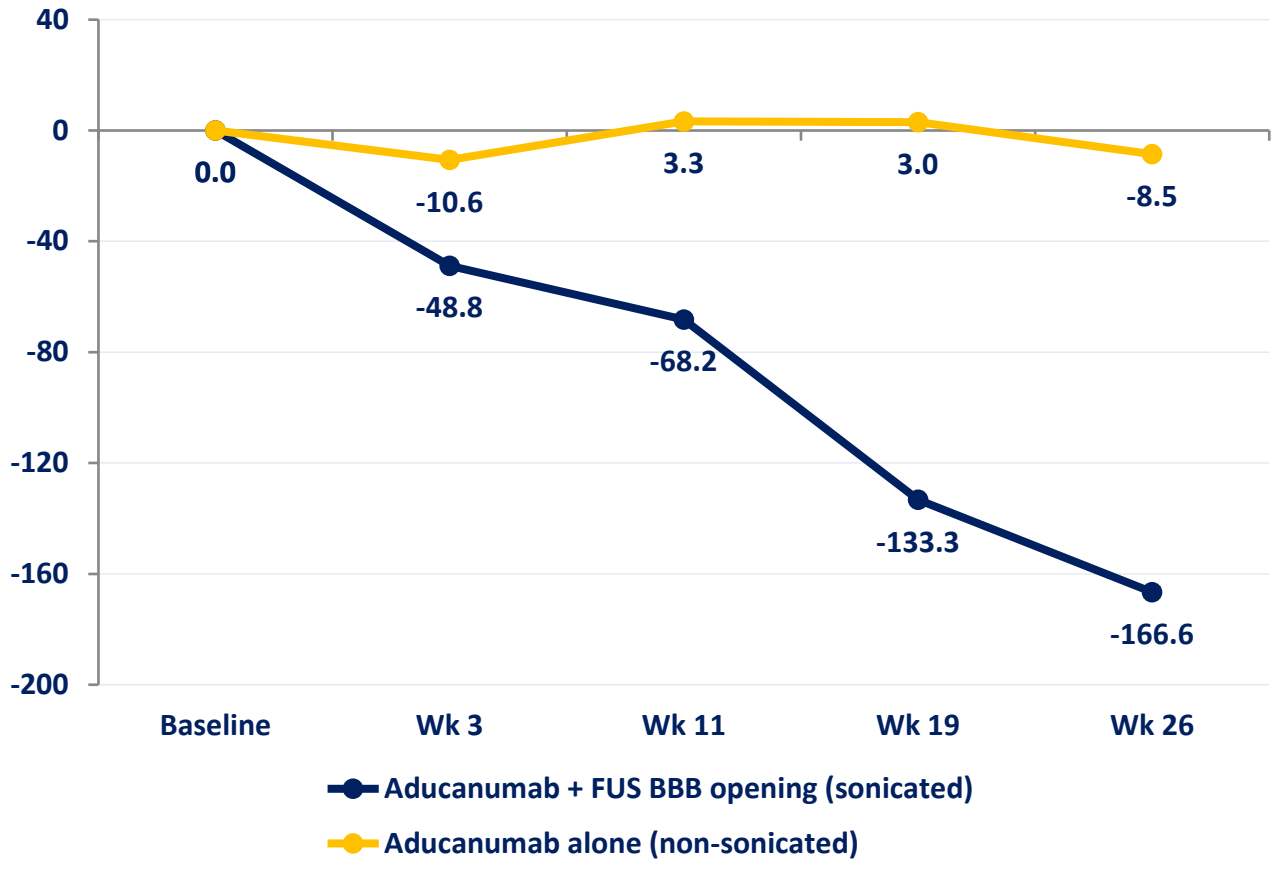
Interim reporting also described roughly half of baseline amyloid cleared in targeted regions at six months, clearance greater in targeted than untargeted areas, and no ARIA - in a small, APOE4-negative cohort. The trial has since moved to lecanemab.

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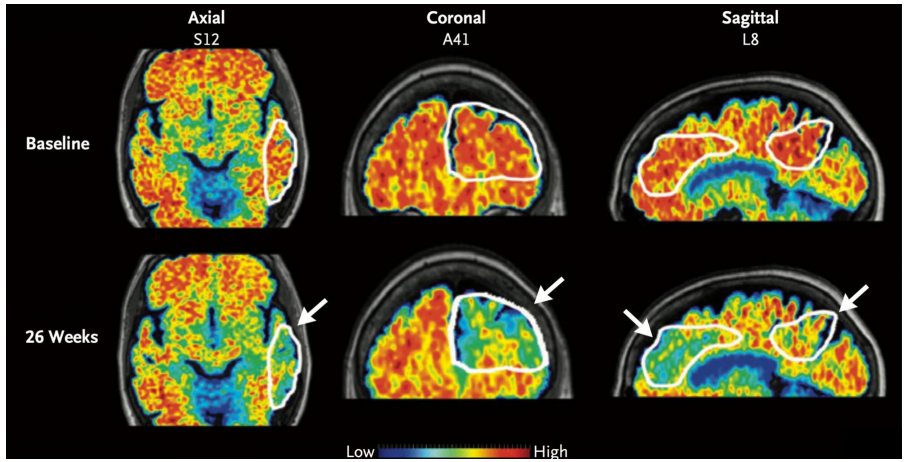
Efficacy of Combined Treatment: Beta-Amyloid Reduction

Example of Patient 3 Rezai et.al N Eng | FUS volume: 40 cm³ | Aducanumab + FUS BBB opening

Mean change in amyloid PET from baseline (Centiloid)



Amyloid PET: baseline vs. 26 weeks



Sonicated regions outlined; arrows mark amyloid reduction

−166.6

Centiloid, wk 26 with FUS

−8.5

Centiloid, wk 26 without FUS

~20×

greater reduction with FUS

Source: Rezai AR, D'Haese PF, Finomore V, et al. Ultrasound blood–brain barrier opening and aducanumab in Alzheimer's disease. N Engl J Med. 2024;390(1):55–62. doi:10.1056/NEJMoa2308719

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AL002: Exablate BBB opening in probable AD

Assessment of safety and efficacy in patients with probable Alzheimer's disease



Actively screening

1. Advent Health
2. Baptist Health
3. Broward Health
4. Tampa General Hospital
5. Tenet Delray
6. UF Shands
7. Weill Cornell

Follow-up

Ohio State University
long-term F/U
West Virginia University
long-term F/U
UTSW
closed

27 / 50

patients enrolled and treated; five in 2026 to date

54% of target enrollment

0

device-related serious adverse events

Opening alone

Current AL002 design

Isolates the antibody-independent contribution: microglial activation, perivascular clearance, endogenous autoantibody.

Opening + antibody

In development

The combination, with the untreated contralateral homologue as a within-patient control in every subject.

Study design Exablate Neuro 4000 (220 kHz) · Targeting up to 40 cc of peak beta-amyloid deposit · amyloid PET screening and post 3rd BBBO

Screening	BBBO 1	BBBO 2	BBBO 3	Flow up visits
	Day 0	Week 2	Week 4	

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What comes next

The opportunity is large; Strategic partnerships can advance the science and patient care

6.7M

Americans living with Alzheimer's today – projected to double within 25 years

0

FDA approved devices for Alzheimer's disease treatment to date

1 We're closest & continuously need more collaborators

Insightec has the most mature safety and delivery data in field to date.
We want to keep partnering with FDA and agencies to find the fastest and clearest evidentiary route to highest standard and positions the U.S. as the innovation leader in this space.

2 Other countries are moving faster

Evidence from China's pilot study of high-intensity FUS oscillation in AD with >100 patients presented at WSSFN 2026, shows how quickly this field can advance abroad.

3 Enhanced Healthcare provider partnerships for trial execution

Combination studies require expensive, multi-year efforts in a population with unique identification, consent, and retention challenges. NAPA partnership brings disease expertise, patient networks, and caregiver infrastructure to address each.

The need is clear. The pathway exists. Partnership strengthens execution.

Aligned FDA guidance on investigational device-drug combinations, combined with NAPA and provider partnerships, holds potential to enable rapid, rigorous advancement of this science for our patients.

Investigational applications in Alzheimer's disease; not FDA-cleared for this indication.

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Transforming Tomorrows, Today.

Advancing focused ultrasound research toward a new investigational option for Alzheimer's disease.

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September 2026