10.1148/radiol.2020200643

Table E1: Inclusion and Exclusion Criteria

Inclusion criteria
1. Male or Female between 50–85 years of age.
2. Able and willing to give informed consent, or has delegated this to Legally Authorized Representative
3. Probable AD consistent with NIA/AA criteria[1]
4. Modified Hachinski Ischemia Scale (MHIS) score of < = 4
5. Mini Mental State Examination (MMSE) scores 18–26
6. Short form Geriatric Depression Scale (GDS) score of < = 6
7. If receiving concurrent treatment with an acetylcholinesterase inhibitors (AChEI) and/or memantine, has been on the medication for at least 2 months with a stable dose for at least 3 months
8. Amyloid PET scan consistent with the presence of β-amyloid
9. Able to communicate sensations during the ExAblate MRgFUS procedure
10. Able to attend all study visits (ie, life expectancy of 1 year)
Exclusion criteria
1. MRI findings:
• Active or chronic infection/inflammation
• Acute or chronic hemorrhages, specifically > 4 lobar microbleeds, and no siderosis or macrohemorrhages
• Tumor/space occupying lesion
• Meningeal enhancement
• Intracranial hypotension
2. More than 30% of the skull area traversed by the sonication pathway is covered by scars, scalp disorders (eg, eczema), or atrophy of the scalp
3. Clips, shunts, or other metallic implanted objects in the skull or the brain and the presence of unknown or MR unsafe devices anywhere in the body
4. Significant cardiac disease or unstable hemodynamic status, including:
• Unstable angina pectoris on medication
• Documented myocardial infarction within six months of enrollment
• Significant congestive heart failure defined with ejection fraction < 40
• Subjects with unstable ventricular arrhythmias
• Subjects with atrial arrhythmias that not rate-controlled
• Cardiac pacemaker
• Uncontrolled hypertension (diastolic BP > 100 on medication)
• Patient has right-to-left, bidirectional, or transient right-to-left cardiac shunts
• Patients with relative contraindications to either Definity ultrasound contrast agent or PET amyloid tracer including subjects with a family or personal history of QT prolongation or taking concomitant medications known to cause QTc prolongation
• QT prolongation observed on screening ECG (QTc > 450 for men and > 470 for women)
5. History of a bleeding disorder, coagulopathy or a history of spontaneous hemorrhage
6. Receiving anticoagulant (eg, warfarin) or antiplatelet (eg, aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (eg, Avastin) within one month of focused ultrasound procedure
7. History of a liver disease, bleeding disorder, coagulopathy or a history of spontaneous hemorrhage
8. Abnormal coagulation profile (PLT < 100,000), PT (> 14) or PTT (> 36), and INR > 1.3
9. No more than 1 nonstrategic lacune < 1.5 cm
10. Known cerebral or systemic vasculopathy
11. Significant depression and at potential risk of suicide
12. A frequency or severity score of 2 or more on any of the ‘Delusions’, ‘Hallucinations’ or ‘Agitation/Aggression’ subscales of the Neuropsychiatry Inventory (NPI)

13. Known sensitivity/allergy to gadolinium (Gadovist), Definity or its components, or florbetaben.
14. Known hypersensitivity to DEFINITY or its components.

15. Any contraindications to MRI scanning, including:

• Large subjects not fitting comfortably into the scanner

• Difficulty lying supine and still for up to 3 hours in the MRI unit or claustrophobia

15. Any contraindication to lumbar puncture for collection of cerebral spinal fluid, including:

• Intracranial hypotension

16. Untreated, uncontrolled sleep apnea

17. History of seizure disorder or epilepsy which could be worsened by disruption of the blood brain barrier.
18. Impaired renal function with estimated glomerular filtration rate < 30 mL/min/1.73 m^2

19. Does not have a reliable caregiver in frequent contact with the subject and can accompany the subject to the clinic and treatment or be available by telephone at designated times. Participants living in retirement homes may be included. Caregiver not willing to sign the Informed Consent Form.
20. Currently in a clinical trial involving an investigational product or nonapproved use of a drug or device or in any other type of medical research.
21. Respiratory: chronic pulmonary disorders eg, severe emphysema, pulmonary vasculitis, or other causes of reduced pulmonary vascular cross-sectional area, patients with a history of drug allergies, uncontrolled asthma or hay fever, and multiple allergies where the benefit/risk of administering Definity is considered unfavorable by the study physicians in relation to the product monograph for Definity.
22. Brain atrophy severe enough to limit targeting.

23. History of drug or alcohol use disorder who may be at higher risk for seizure, infection, and/or poor executive functioning.
24. Positive human immunodeficiency virus (HIV) which can lead to increased entry of HIV into the brain parenchyma leading to HIV encephalitis.
25. Potential blood-borne infections, which can lead to increased entry to brain parenchyma leading to meningitis or brain abscess.
26. Known apolipoprotein E allele (ApoE4) homozygosity, which has been found to be associated with thinning of the blood brain barrier
Additional Exclusion Criteria for Cycles 2 and/or 3

1. A significant cognitive decline or significant mood/behavioral change

2. A significant and unresolved neurologic impairment noted at the 14 day assessment prior to the next ExAblate BBBD cycle.
3. A significant MRI finding (ie, overt cerebral hemorrhage or infarction).

Table E2: MRI Sequence Parameters

Pertinent MRI Parameters-3T GE Signa Architect

Series Description	T2* GRE	3D Ax SWAN	3D COR T2 Cube	T1 COR BRAVO ISO	Ax DTI B-1000 32 dir	T2 FLAIR AX (± Gd)	T2 AXIAL	T2 FLAIR COR Temporal Lobe	3D AX T1 FSPGR ± GD	T1 FSE COR Temporal Lobe +GD
Scanning Sequence	GR	GR	SE	GR	[“EP,” “SE”]	SE	Radial	SE	GR	SE
MR Acquisition Type	2D	3D	3D	3D	2D	2D	2D	2D	3D	2D
Slice Thickness (mm)	[4]	[2]	[1]	[1]	[4]	[4]	[4]	[2]	[1]	[2]
Repetition Time (ms)	[720]	[52.7]	[3002]	[8.672]	[8000]	[12000]	[4644]	[10000]	[8.537]	[785]
Echo Time (ms)	[15]	[24.748]	[110.463]	[3.236]	[89.9]	[143.792]	[129.664]	[138.176]	[3.516]	[8.704]
Inversion Time (ms)	N/A	N/A	N/A	[450]	N/A	[2506.15]	N/A	[2567.29]	N/A	N/A
Number of Averages	[1]	[0.700504]	[1]	[1]	[1]	[1]	[2.06316]	[3]	[0.86855]	[2]
Echo Number(s)	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]
Spacing Between Slices (mm)	[4.4]	[1]	[1]	[1]	[4]	[4.4]	[4.4]	[2.6]	[1]	[2.6]
Echo Train Length	[1]	[7]	[130]	[1]	[1]	[1]	[32]	[21]	[1]	[3]
Percent Sampling	[100]	[70.0504]	[100]	[100]	[100]	[100]	[100]	[100]	[86.855]	[100]
Percent Phase Field of View	[100]	[80]	[80]	[80]	[100]	[100]	[100]	[100]	[100]	[100]

Reconstruction Diameter (mm)	[230]	[230]	[256]	[250]	[240]	[230]	[230]	[200]	[256]	[200]
Receiving Coil	Head 34	Head 34	Head 34	Head 34	Head 24	Head 34	Head 34	Head 34	Head 34	Head 34
Acquisition Matrix	[0, 380, 260, 0]	[0, 300, 300, 0]	[0, 320, 320, 0]	[0, 256, 256, 0]	[128, 0, 0, 128]	[0, 260, 200, 0]	[0, 380, 380, 0]	[0, 320, 200, 0]	[0, 320, 320, 0]	[0, 320, 320, 0]
Flip Angle (degrees)	[20]	[15]	[90]	[12]	[90]	[111]	[142]	[160]	[12]	[111]