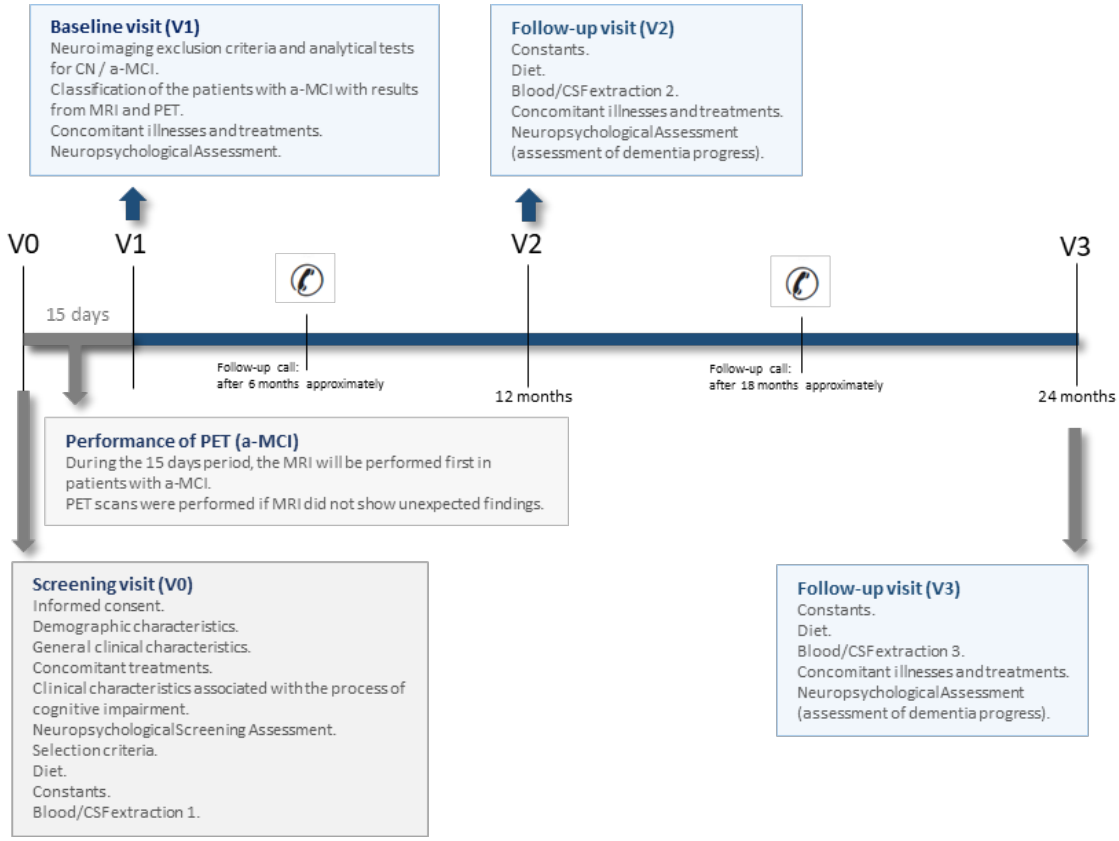
Appendix

Study design



Supplementary figure S1. Schematic description of the AB255 study.

Methods: neuropsychological tests

Protocol for neuropsychological assessment (1).

A neuropsychological assessment was carried out during the screening visit:

- MMSE(2).
- Learning and deferred memory test of a list of words on the Weschler memory scale, WMS-III(3),.
- Buschke Free and Cued Selective Reminding Test(4).
- Vocabulary Test (WAIS-III).
- Word accentuation test.
- Hachinski ischemic scale(5).
- Geriatric Depression Scale (Sheikh and Yesavage)(6).
- Clinical Dementia Rating (CDR).
- Questionnaire of Functional Activities, IDDD Scale (Interview for Deterioration in Daily Activities in Dementia, IDDD) (7).

In the baseline visit and the later follow-up visits (12 and 24 months), the following neuropsychological protocol was administered, which contains tests sensitive to the following cognitive functions: orientation to reality, attention, capacity for learning and verbal memory, visual memory, language, visual gnosis, praxis and executive functions.

- MMSE.
- ADAS-Cog.
- Boston Naming Test.
- Rey Auditory-Verbal Learning Test.
- Rey Copy and Deferred Recall of Complex Figures Test.
- 15 objects test.
- Trail making test (parts A and B).
- Category fluency test (animals), key phonetic fluency (words with “p”).
- Digits and Symbols test (WAIS).
- Cubes test (WAIS).
- CDR.
- Questionnaire of Functional Activities, IDDD Scale (Interview for Deterioration in Daily Activities in Dementia, IDDD).

Magnetic Resonance Imaging Protocol

Sequence / parameters	Sagittal T1	Axial T2 flair	Axial T2	Sagittal MPR	Axial T2*
TR	500 ms	9280 ms	4540 ms	2060 ms	800 ms
TE	14 ms	108 ms	115 ms	3.93 ms	26 ms
No. SLICES	20	20	20	192	20
WIDTH	5	5	5	1	5
SPACING	30%	30%	30%	30%	30%
FOV	230 mm	230 mm	230 mm	255 mm	230 mm
ORIENTATION	sagittal	axial	axial	sagittal	axial
PHASE	A-P	R-L	R-L	A-P	R-L
AVERAGES	2	2	2	1	2
CONCATENATIONS	1	1	1	1	1
ANTENNA	Head Coil	Head Coil	Head Coil	Head Coil	Head Coil
TI	-----	2500	-----	1100	-----
INCLINATION ANGLE	90	180	150	15	20
BASE RESOLUTION	256	256	512	256	256
PHASE RESOLUTION	75%	100%	82%	100%	75%
TIME	3:14	3:54	3:06	8:47	3:52

Methods: PET acquisition and reconstruction

The acquisition of images by PET was only performed in patients with a-MCI. The protocol for the preparation, acquisition and reconstruction of the PET images was the same for all cases carried out in each PET center.
PET acquisition was performed after a 4-hour fasting and after confirmation of blood glucose levels below 110 mg/dL.
The dose of 18FDG was established according to weight (150 microCi/kg), being the standard adult dose 10 mCi (370 MBq) in a volume of 1-10ml with normal saline.
Dosimetry was established in accordance with ICRP 53. For Adults, critical organ dose (bladder) was 0.16 mGy/MBq and effective dose was 0.019 mSv/MBq. 18FDG was administered through a vein in one of the patient's upper arms and, once the dose has been administered, the patients were let to rest for 40 minutes while the radiopharmaceutical is taken up.
Acquisition started 40 minutes after the administration of 18FDG and lasted for 20 minutes until the 60th minute after it was administered. A 3D acquisition mode was used where available.
Depending on the scanner availability, transmission was carried out with either a) Ge-Ga68 sources in special PET machines, or b) with X-ray sources in PET-CT machines. In dedicated PET equipment, the acquisition of the transmission studies was preferably carried out 5-10 minutes after the emission study using segmentation methods in the post processing.
Images were reconstructed using specific parameters for each PET scanner according to ADNI project suggestions for image normalization.