Amyloid PET Screening for Enrichment of Early-Stage Alzheimer Disease Clinical Trials

Experience in a Phase 1b Clinical Trial

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Abstract: Amyloid positron emission tomography (PET) imaging is being investigated as a screening tool to identify amyloid-positive patients as an enrichment strategy for Alzheimer disease (AD) clinical trial enrollment. In a multicenter, phase 1b trial, patients meeting clinical criteria for prodromal or mild AD underwent florbetapir PET scanning at screening. PET, magnetic resonance imaging, and co-registered PET/magnetic resonance imaging scans were reviewed by 2 independent readers and binary visual readings tabulated. Semi-quantitative values of cortical to whole cerebellar standard uptake value ratios were computed (threshold 1.10). Of 278 patients with an evaluable PET scan, 170 (61%) and 185 (67%) were amyloid-positive by visual reading and quantitative analysis, respectively; 39% were excluded from the study due to an amyloid-negative scan based on visual readings. More ApoE ϵ4 carriers than noncarriers were amyloid-positive (80% vs. 43%). Comparison of visual readings with quantitative results identified 21 discordant cases (92% agreement). Interreader and intrareader agreements from visual readings were 98% and 100%, respectively. Amyloid PET imaging is an effective and feasible screening tool for enrollment of amyloid-positive patients with early stages of AD into clinical trials.

Key Words: Alzheimer disease, amyloid PET imaging, monoclonal antibody, clinical trial

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Alzheimer disease (AD) is an insidious, progressive disease both pathologically and clinically. The defining pathology [β-amyloid (Aβ) plaques and tau-containing neurofibrillary tangles] accumulates and spreads over many years, starting a decade or more before the onset of overt clinical manifestations.[1] When symptoms (ie, cognitive or behavioral changes) first manifest, they are *ipso facto* subtle and progress for approximately 3 to 5 years before onset of dementia.[1,2]

Cognitive changes associated with AD, particularly in the early asymptomatic stage, are not necessarily specific to AD, which poses a challenge to a clinician when trying to assign a cause and resultantly leads to diagnostic misclassification. Misclassification is detrimental, especially in the research setting, in that patients are exposed to a drug or drug candidate from which they are unlikely to benefit, and clinical studies are more likely to be misinterpreted, underpowered, or potentially fail.

Amyloid positron emission tomography (PET) substudy observations from recent AD phase 3 trials of bapineuzumab and solanezumab have illuminated the extent of misclassification: 16% to 22% of enrolled subjects diagnosed with mild to moderate AD based on clinical criteria did not have evidence of abnormal Aβ pathology on retrospective analyses of PET imaging.[3,4] The issue was worse in ApoE ϵ4 noncarriers, who were more likely than carriers to have had a negative PET scan (36.1% vs. 6.5%).[3] Similar observations have been reported in AD populations followed at memory clinic or academic research centers.[5] In another study, 37% of ApoE ϵ4 noncarriers and 13% of ApoE ϵ4 carriers diagnosed with mild to moderate AD had minimal amyloid plaques on autopsy.[6] These observations underscore the need to implement as part of the screening process an adjunct (to clinical assessments) biomarker to confirm the presence of AD pathology, particularly one to assess for the pathology that the drug candidate targets, to mitigate misclassification.

Florbetapir is a radiopharmaceutical with a high binding affinity and specificity to Aβ plaques in the brain[7] approved by the US Food and Drug Administration and the European Medicines Agency for PET imaging of the brain in adults who are being evaluated for AD and other causes of cognitive decline.[8,9] Visual interpretation of florbetapir-PET images was shown to accurately predict the presence of Aβ pathology at autopsy.[10] Thus, florbetapir would appear to be useful as an adjunct diagnostic marker to select patients with amyloid pathology and also to assess the effect of treatment on amyloid plaque reduction.

Aducanumab (BIIB037), a human immunoglobulin γ1 (IgG1) monoclonal antibody selective for aggregated forms of Aβ, is being investigated as a disease-modifying treatment for AD. In this multiple-dose phase 1b clinical study of aducanumab, patients with prodromal AD or mild AD were enrolled. Here, we report our experience in the phase 1b study of aducanumab of using amyloid PET imaging with florbetapir as an adjunct diagnostic tool to identify and select for enrollment patients demonstrating Aβ pathology from those who first met clinical criteria for prodromal or mild AD.

METHODS

Study Design

This was a multicenter, randomized, 12-month, double-blind, placebo-controlled, multiple-dose study of aducanumab

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followed by a dose-blinded long-term extension in patients with either prodromal or mild AD (ClinicalTrials.gov identifier NCT01677572). The primary objective of the study was to evaluate the safety and tolerability of multiple doses of aducanumab in subjects with prodromal or mild AD.

During the 12-month, double-blind, placebo-controlled phase, patients received aducanumab or placebo by intravenous infusion once every 4 weeks for 52 weeks.

The study was performed at 33 sites in the United States and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation and Good Clinical Practice guidelines, and ethics committee approval at each participating site. All patients provided written informed consent.

Screening Process

The study enrolled subjects with prodromal AD[11] or mild AD.[12] Screening occurred in 3 general stages. First, subjects were evaluated on demographic, and clinical and laboratory criteria, including being between the age of 50 to 90 years, and assigned a diagnosis of presumed prodromal AD or mild AD by the investigator. The clinical criteria for prodromal AD were Mini Mental State Examination (MMSE) score between 24 and 30 (inclusive), a spontaneous memory complaint, objective memory loss defined as a free recall of score of ≤ 27 on the Free and Cued Selective Reminding Test (picture version), absence of significant levels of impairment in other cognitive domains, a global Clinical Dementia Rating of 0.5, essentially preserved activities of daily living, and absence of dementia. The criteria for mild AD were MMSE 20 to 26 (inclusive) and a global Clinical Dementia Rating of 0.5 or 1.0. Subjects who remained eligible then underwent magnetic resonance imaging (MRI) to exclude subjects with confounding pathology or >4 microhemorrhages. Remaining eligible subjects then underwent florbetapir PET scan, and those with a positive scan as determined by a qualified reader were enrolled (Fig. 1). Subjects were excluded from the study if they had a medical condition that might be a contributing cause of cognitive impairment.

Florbetapir PET Imaging

Florbetapir PET imaging was used to provide qualitative assessment (ie, visual interpretation) of brain Aβ plaque at screening and to provide quantitative assessment of the effect of repeated doses of aducanumab on brain Aβ plaque. Florbetapir scans were scheduled at screening and at weeks 26 and 54.

Florbetapir PET data were acquired from 25 imaging centers using 18 different scanner models manufactured by GE, Philips, and Siemens. Before imaging patients at each site, Hoffman phantom data were acquired to assess scanner quality and to calibrate spatial resolution properties of each camera.

For each florbetapir scan, a dose of 370 MBq was injected intravenously, with PET scanning starting approximately 50 minutes later. To allow motion correction during the 20-minute acquisition, scans were acquired as a 4×5-minute sequence for scanners supporting dynamic acquisitions or as a 2×10-minute static sequence on scanners that could not support dynamic acquisition. All patient image datasets were reconstructed using scanner software, generally with iterative techniques, and smoothed using postprocessing Gaussian filtering to achieve an effective uniform spatial resolution of 6.5 mm in-plane and 7.5 mm axially.[13] PET and MRI T1 data were coregistered using rigid transformations to a standard $91 \times 109 \times 91$ voxel, $2 \times 2 \times 2$ mm template space.

Visual Reading

Visual reads were based primarily upon PET image data, with the registered MRI and fused PET/MRI data providing supplemental anatomic information. Scans were interpreted by 1 of 2 board-certified neuroradiologists who, in accordance with the Amyvid™ Prescribing Information (Eli Lilly and Company, Indianapolis, IN),[14] had successfully completed a training program (provided by the manufacturer using either an in-person tutorial or an electronic process). MRI data were made available as part of the dataset submitted for interpretation. This included both the MRI (sagittal T1, 3-dimensional volume T1, FLAIR, T2,

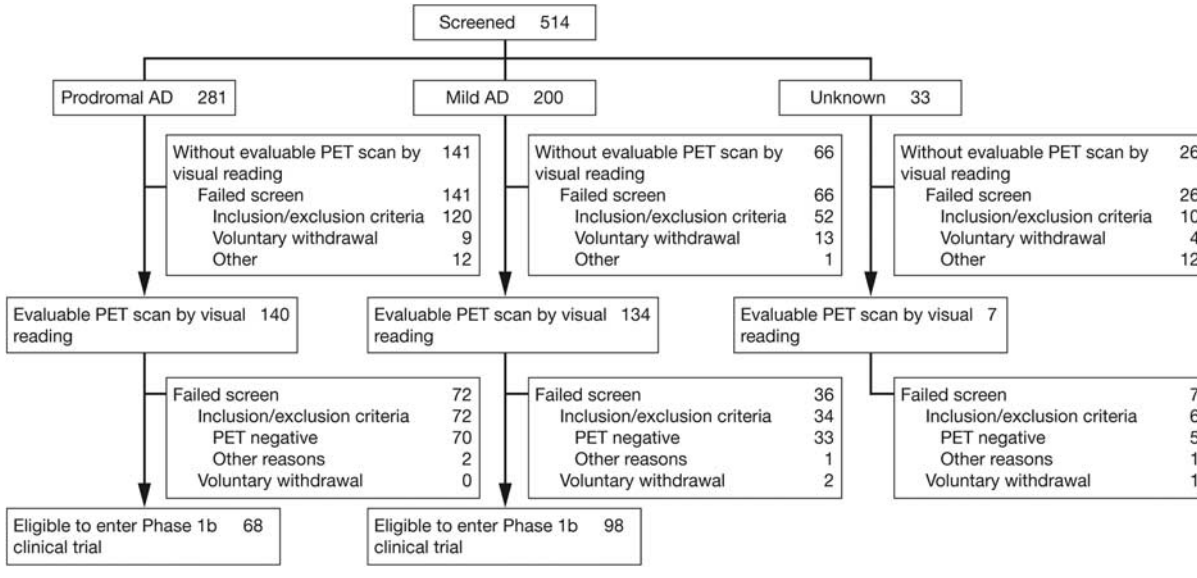

FIGURE 1. Selection of patients. AD indicates Alzheimer disease; PET, positron emission tomography.

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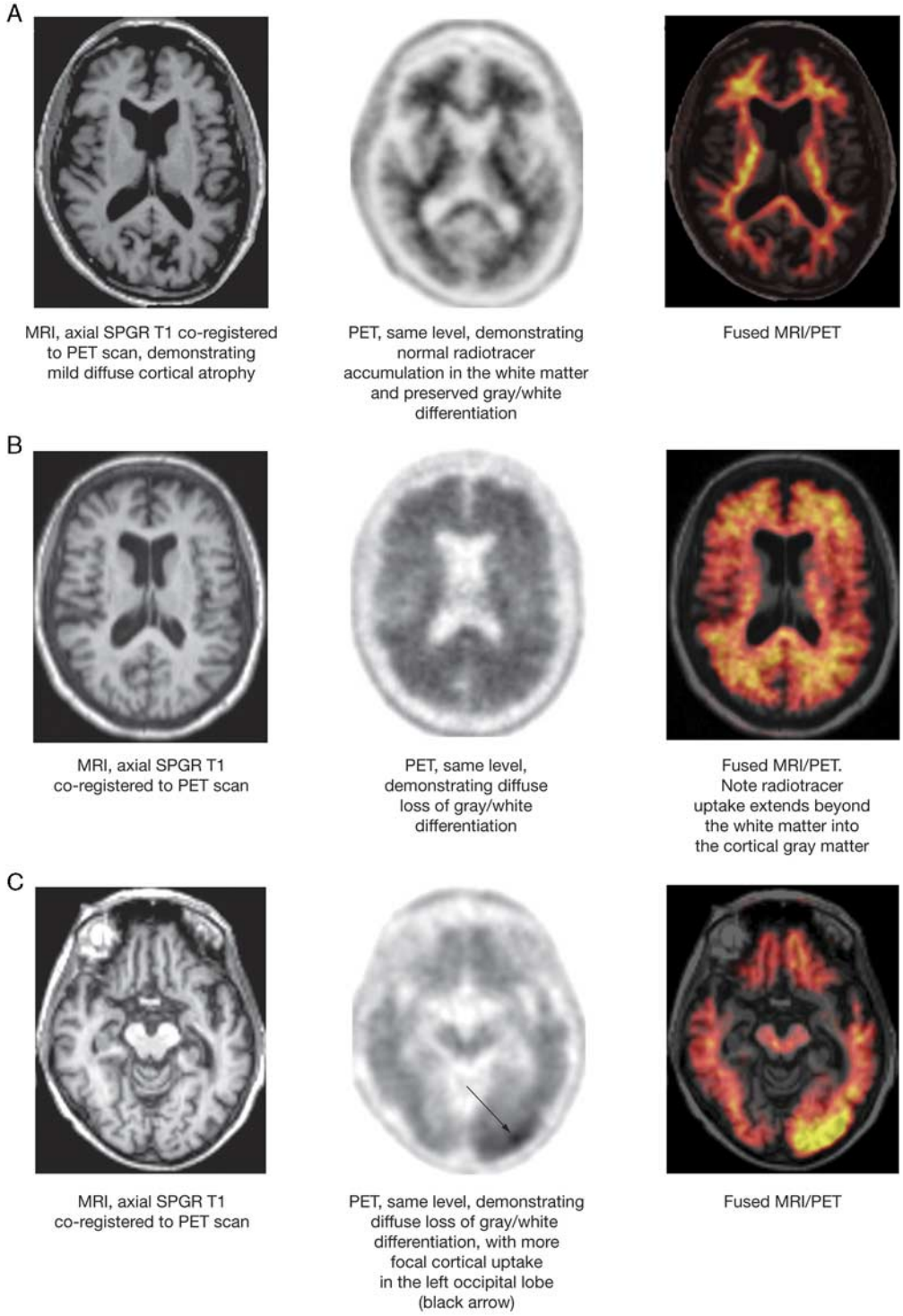

FIGURE 2. Representative amyloid PET scans. A, negative/normal. B, Positive—diffuse cortical uptake. C, Positive—diffuse and focal cortical uptake. MRI indicates magnetic resonance imaging; PET, positron emission tomography; SPGR, spoiled gradient.

and DWI-EPI sequences) and PET data as well as coregistered MRI and PET scans (Fig. 2). Readers had the ability to interrogate and review all the datasets, including the coregistered MRI/PET data in all 3 imaging planes. PET data were alternately assigned to 1 of the 2 readers, and the read of the assigned single reader was used to establish PET amyloid positivity for screening. The binary classification methodology followed guidelines described in the Amyvid Prescribing Information, designating images as either positive or negative by comparing the florbetapir uptake in cortical gray matter with that in the adjacent white matter.[14]

Quantitative Analysis

Semiquantitative values of cortical to whole cerebellar standard uptake value ratios (SUVRs) were computed following the method of Landau et al[15] as a post-hoc analysis to better understand visual/SUVR concordance and overall reader performance. Briefly, data were defined in native patient space using Freesurfer, and a composite cortical SUVR was computed by averaging the ratio of 6 cortical regions normalized to whole cerebellar activity. A SUVR threshold of 1.10 was used to classify amyloid-negative from amyloid-positive subjects.[16]

Interreader/Intrareader Variability Analysis

For the purposes of interreader variability analysis only, the amyloid PET images from the first 250 cases were reviewed by both independent readers and binary visual readings tabulated. Subsequently, 10 cases (pooled from the first 50 clinical cases and from 20 Amyvid training test cases) were presented to the readers allowing for calculation of interreader and intrareader agreement statistics.

RESULTS

Screening

Overall, of 514 subjects who entered the screening period, 348 (68%) ultimately screen failed (Fig. 1). A total of 67% (233/348) of cases screen failed without an evaluable PET scan visual reading due to: inclusion/exclusion criteria [182 subjects (78%)], voluntary withdrawal [26 subjects (11%)], and other [25 subjects (11%)]. Pre-PET screen failure was higher in those with prodromal AD than mild AD [141/281 (50%) vs. 66/200 (33%); 33 subjects were of unknown stage] but similar between ApoE ϵ4 carriers and noncarriers [66/205 (32%) vs. 69/210 (33%); 99 subjects were of unknown stage and/or ApoE ϵ4 carrier status]. Of the 281 who had an evaluable PET scan visual reading, 115 (33%) screen failed: 108 due to a negative PET scan, 3 due to voluntary withdrawal, and 4 due to other reasons.

Patient Demographics

Of the 278 subjects undergoing PET scan, 139 patients (50%) were categorized as prodromal AD, of whom 65 (47%) were ApoE ϵ4 carriers, and 133 (48%) were categorized as mild AD, of whom 71 (53%) were ApoE ϵ4 carriers. AD status was missing for 6 patients. Baseline characteristics are shown in Table 1. Two additional subjects underwent a PET scan but were excluded from the PET population because they were missing quantitative imaging analysis.

PET Imaging

By visual reading (used to screen patients), 61% (n = 170) were deemed amyloid-positive (Table 2). The mean SUVR (range) were 1.45 (1.04 to 2.01) for amyloid-positive subjects and 1.03 (0.85 to 1.37) for amyloid negative-subjects. The mean (SD) MMSE score was 24.4 (3.2) for amyloid-positive and 26.5 (2.7) for amyloid-negative subjects. Subjects categorized as mild AD (75% vs. 50% for prodromal) and ApoE ϵ4 carriers (80% vs. 43% for noncarriers) were more likely to be amyloid-positive. Overall, based on visual reads, PET amyloid positivity was highest among mild AD ApoE ϵ4 carriers (90%), followed by prodromal AD ApoE ϵ4 carriers (71%), mild AD noncarriers (58%), and prodromal AD carriers (31%).

TABLE 1. Screening Data

	Prodromal (n = 139)	Mild (n = 133)	Overall (n = 278)*
Age, mean (y)	72.4	73.0	72.7
Sex (% male)	57	45	52
MMSE score [mean (SD)]	27.4 (1.9)	22.9 (2.5)	25.2 (3.2)
FCSRT score [mean (SD)]	20.3 (7.2)	14.2 (9.3)	17.3 (8.8)†
CDR-SB score [mean (SD)]‡	1.97 (1.07)	3.75 (1.83)	2.85 (1.73)
ApoE ϵ4 status [n (%)]			
Carrier	65 (47)	71 (53)	137 (49)
Noncarrier	74 (53)	62 (47)	141 (51)

*Includes 6 patients with unknown AD stage.

†n = 266 based on subjects with known FCSRT and clinical stage.

‡n = 133, 129, and 265 subjects evaluable for prodromal, mild, and overall, respectively.

AD indicates Alzheimer disease; CDR-SB, Clinical Dementia Rating sum of boxes; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini Mental State Examination.

By quantitative analysis (used to validate visual reading), 67% (185) were amyloid-positive. The mean SUVR were 1.43 (1.10 to 2.01) for amyloid-positive subjects and 0.99 (0.85 to 1.10) for amyloid-negative subjects. The mean MMSE score was 24.6 (3.2) for amyloid-positive and 26.5 (2.8) for amyloid-negative subjects. Similar to the results based on visual reading, subjects categorized as mild AD (78% vs. 57% for prodromal) and ApoE ϵ4 carriers (87% vs. 47% for noncarriers) were more likely to be amyloid-positive. Overall, based on quantitative analysis, PET amyloid positivity was highest among mild AD ApoE ϵ4 carriers (92%), followed by prodromal AD ApoE ϵ4 carriers (82%), mild AD non-carriers (63%), and prodromal AD non-carriers (35%).

There were 21 discordant cases (8%) in which visual interpretation did not match quantitative results: 18 cases had negative visual (thus, were screen failed) but positive quantitative readings (composite SUVRs 1.10 to 1.37) (Fig. 3A), and 3 cases had positive visual but negative quantitative readings (composite SUVRs 1.04, 1.05, and 1.09) (Fig. 3B). Of the discordant cases, 14 were categorized as prodromal AD and 6 as mild AD (1 AD stage missing); 9 were ApoE ϵ4 carriers, and 12 were noncarriers.

The 2 neuroradiologists agreed on amyloid status by visual readings in 98% (246/250) of cases (158/250 amyloid-positive, 92/250 amyloid-negative) (κ score = 0.97). Discordance occurred over 4 cases, which after consensus reading were determined to be 2 positive and 2 negative. Intrareader agreement of amyloid status from visual readings was 100% (κ score = 1; 10 cases, 5 amyloid-positive, 5 amyloid-negative).

DISCUSSION

To our knowledge, this is the first AD study exclusively using PET amyloid imaging as an adjunctive biomarker during screening to mitigate subject misclassification [ie, to exclude subjects without evidence of the pathology (Aβ plaques), which defines the disease]. Overall, of 278 subjects with an evaluable PET scan, 39% were excluded for not having visual evidence of abnormal brain Aβ based on florbetapir PET imaging.

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TABLE 2. Amyloid PET Imaging Results

	Prodromal (n = 139)	Mild (n = 133)	Overall (n = 278)*
Amyloid PET findings by binary visual readings [n (%)]			
Amyloid-positive	69 (50)	100 (75)	170 (61)
Amyloid-negative	70 (50)	33 (25)	108 (39)
Amyloid PET findings via quantitative analysis [n (%)]			
Amyloid-positive	79 (57)	104 (78)	185 (67)
Amyloid-negative	60 (43)	29 (22)	93 (33)
SUVR by amyloid PET findings via binary visual readings			
Amyloid-positive			
Mean SUVR [SD (range)]	1.44 [0.18 (1.04-2.01)]	1.45 [0.15 (1.05-1.96)]	1.45 [0.17 (1.04-2.01)]
Amyloid-negative			
Mean SUVR [SD (range)]	1.03 [0.12 (0.85-1.34)]	1.03 [0.11 (0.85-1.37)]	1.03 [0.12 (0.85-1.37)]
SUVR by amyloid PET findings via quantitative analysis			
Amyloid-positive			
Mean SUVR [SD (range)]	1.42 [0.17 (1.14-2.01)]	1.44 [0.16 (1.10-1.96)]	1.43 [0.16 (1.10-2.01)]
Amyloid-negative			
Mean SUVR [SD (range)]	0.99 [0.06 (0.85-1.09)]	1.00 [0.07 (0.85-1.10)]	0.99 [0.06 (0.85-1.10)]
Amyloid PET findings via binary visual reading by ApoE ϵ4 status [n (%)]			
Carrier			
Amyloid-positive	46 (71)	64 (90)	110 (80)
Amyloid-negative	19 (29)	7 (10)	27 (20)
Noncarrier			
Amyloid-positive	23 (31)	36 (58)	60 (43)
Amyloid-negative	51 (69)	26 (42)	81 (57)
Amyloid PET findings via quantitative analysis by ApoE ϵ4 status [n (%)]			
Carrier			
Amyloid-positive	53 (82)	65 (92)	119 (87)
Amyloid-negative	12 (18)	6 (8)	18 (13)
Noncarrier			
Amyloid-positive	26 (35)	39 (63)	66 (47)
Amyloid-negative	48 (65)	23 (37)	75 (53)

*Includes 6 patients with unknown AD stage.
AD indicates Alzheimer disease; PET, positron emission tomography; SUVR, standard uptake value ratio.

The incidence of amyloid PET negativity observed in this study was higher than that reported in the phase 3 studies of bapineuzumab (16%)[3] and solanezumab (22%).[4] The difference is most likely attributable to the less advanced population screened and enrolled in this study (prodromal and mild AD; MMSE 20 to 30) compared with the solanezumab and bapineuzumab studies (mild to moderate AD; MMSE 16 to 26).[3,17] A substantial difference in PET negativity between the prodromal and mild AD groups was observed: 50% in the prodromal AD compared with 25% in the mild AD group. In the solanezumab studies, a similar PET negativity was reported in the mild AD group (27%), which was nearly twice as high as that observed in the moderate group (13%).[4] A negative (ie, normal) amyloid PET scan is likely to reflect the absence of appreciable amyloid plaques.[10] Together, these results illustrate the problem of misclassification when diagnosis is based on clinical criteria (and MRI) in the earlier stages of disease.

ApoE ϵ4 carriers were far more likely to have a positive amyloid PET scan than were noncarriers. Overall, 80% of ApoE ϵ4 carriers had a positive amyloid PET scan at screening—findings were higher in those with mild AD (90%) than those with prodromal AD (71%). This finding is consistent with findings reported from the bapineuzumab, solanezumab, and other studies,[3,4,18–20] but now it extends to the prodromal AD group as well. ApoE genotyping early in the screening process may improve the economy of enrichment by amyloid PET by lowering the likelihood of negative amyloid findings. However, in designing clinical studies one should consider other important effects that may be attributable to ApoE allelic carriage such as rates of clinical progression—for example, early onset ApoE ϵ4-negative patients can show a more rapid decline than older ApoE ϵ4-positive patients[21]—differential treatment effects, and differential adverse events such as amyloid-related imaging abnormalities.

Other factors may have contributed to the different amyloid PET results between this study and the bapineuzumab and solanezumab studies. The bapineuzumab and solanezumab results were based on analyses of a subset of subjects at a subset of sites; whereas, in this study, PET imaging was performed as part of the screening process in all subjects at all sites. It is, therefore, conceivable that the populations differed in meaningful ways apart from disease severity and ApoE ϵ4 status due to methodological differences. Different PET ligands were used; this study and the solanezumab studies used florbetapir; whereas, the bapineuzumab studies used Pittsburgh compound B. The regions used for analysis and reference might have also affected the results but are unlikely to have changed the overall conclusion.

Agreement between the visual and quantitative readings of amyloid status was very good (92%), with 21 discordant cases of 278. Visual readings appeared to be more conservative than the quantitative reading in assigning a positive amyloid PET scan (61% vs. 67% amyloid-positive). Discordant cases occurred in a higher proportion of patients with prodromal than with mild AD [14/139 (10%)

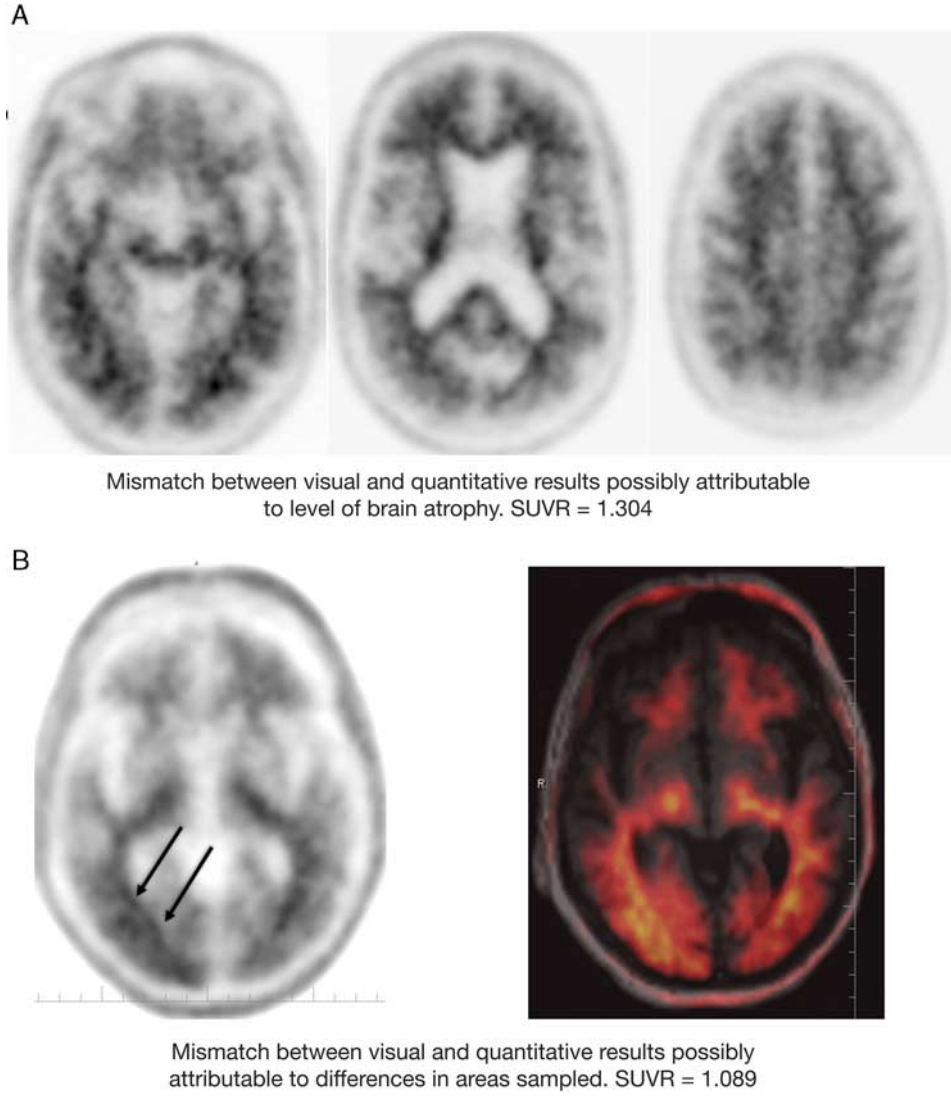

FIGURE 3. Representative PET scans. A, negative PET scan with preserved gray/white differentiation at 3 levels. B, Positive PET scan with loss of gray/white differentiation in the right occipital lobe (black arrows). PET indicates positron emission tomography; SUVR, standard uptake value ratio.

vs. 6/133 (5%)]. Reasons for discordance might include the level of brain atrophy seen and differences in the brain areas sampled. These causes of discordance between visual and quantitative readings warrant further investigation.

In this study, excellent interreader (98% agreement) and intrareader (100% agreement) reliability were achieved, indicating the effectiveness of the visual reading procedure and successful training of the readers. Factors also likely contributing to this high reliability include: use of MRI coregistered PET scans (as opposed to PET/computed tomography or PET alone); uniform spatial resolution, slice thickness, and image orientation, regardless of scanner model or patient position; 20-minute acquisition instead of 10-minute (providing better statistics/less noise in the reconstructed data); and dynamic acquisition providing motion correction during the 20-minute acquisition. Other recommendations for amyloid PET imaging that were adhered to include interpretation by a physician specifically trained in amyloid PET interpretation, as the interpretation process differs markedly from that typically used in nuclear medicine.[8,22] In this study, the physicians who performed the interpretations were neuroradiologists. The increased familiarity of a neuroradiologist with the anatomy of brain versus a nuclear medicine physician was presumably another reason for the high interreader and intrareader agreement. The methodology outlined above enabled standardized imaging to be achieved, which when combined with centralized visual read, demonstrated the feasibility of using amyloid PET for screening in our multicenter trials. Measurement of cerebrospinal fluid levels of Aβ peptides offer another possibility for enriching trials with patients bearing amyloid pathology and the 2 measures may track complimentary aspects of amyloidopathy.[23]

These data from the screening phase of a multicenter phase 1b trial demonstrate that amyloid PET imaging can be an effective and feasible tool to enrich AD clinical trials in amyloid-positive patients. Enrichment by assessing amyloid plaque burden is particularly relevant in earlier stages of AD in which clinical criteria alone appear to result in substantial misclassification.

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