HHS Public Access

Author manuscript

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Alzheimer Dis Assoc Disord. 2017 ; 31(1): 19–26. doi:10.1097/WAD.0000000000000150.

Optimizing effect sizes with imaging enrichment and outcome choices for mild Alzheimer's disease clinical trials

Timothy S. Chang[a], **Edmond Teng**[a,b], **David Elashoff**[c], and **Joshua D. Grill**[d] **for the Alzheimer's Disease Neuroimaging Initiative***

[a]University of California, Los Angeles, Department of Neurology, David Geffen School of Medicine, 710 Westwood Plaza, Los Angeles, CA, USA, 90095

[b]Veterans Affairs Greater Los Angeles Healthcare System, 11301 Wilshire Blvd, Los Angeles, CA 90073

[c]Department of Biostatistics, David Geffen School of Medicine, 710 Westwood Plaza, Los Angeles, CA, USA, 90095

[d]University of California Irvine, Institute for Memory Impairments and Neurological Disorders, 3206 Biological Sciences III, Irvine CA 92697-4545

Abstract

Recent clinical trials in mild Alzheimer's disease (AD) have enriched for amyloid-specific positron emission tomography imaging and used extended versions of the AD Assessment Scale-Cognitive Subscale (ADAS-Cog) in an effort to increase the sensitivity to detect treatment effects. We used data from mild AD participants in the AD Neuroimaging Initiative to model trial effect sizes for 12- and 24-month trials using three versions of the ADAS-Cog and increased standardized uptake value ratio (SUVR) cutoffs for amyloid imaging inclusion criteria. For 12-month trials, extended ADAS-Cog versions improved effect sizes. The ADAS-Cog11 elicited larger effect sizes when enriching for SUVR 1.1 only, while the ADAS-Cog12 and ADAS-Cog13 were associated with larger effect sizes with higher SUVR thresholds. For 24-month trials, extended ADAS-Cog versions increased effect sizes for trials not enriched for amyloid and trials enriched for SUVR 1.1. Only enriching for higher SUVR thresholds (1.3 and 1.4, not 1.1) increased trial power. We conclude that extended versions of the ADAS-Cog improve mild AD trial effect sizes for both 12- and 24-month long studies while amyloid imaging criteria may be most valuable for 12-month trials.

Keywords

Alzheimer's disease; cognitive decline; clinical trial; enrichment; ADAS-Cog

Corresponding Author: Joshua D. Grill, University of California Irvine, Institute for Memory Impairments and Neurological Disorders, 3206 Biological Sciences III, Irvine CA 92697-4545. Phone: 949-824-5905. Fax: 949-824-0885. jgrill@uci.edu.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

1. Introduction

The “amyloid hypothesis” postulates that beta-amyloid (Aβ) accumulation represents an early and critical mechanistic step in the pathogenesis of Alzheimer’s disease (AD)[1]. Recent clinical trials of anti-Aβ immunotherapies in mild-to-moderate AD (Mini-Mental State Examination [MMSE] 16–26), however, have failed to demonstrate clinical benefit on the 11-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog11)[2–4]. Although these negative results may represent evidence against the amyloid hypothesis[5], an alternative interpretation is that the absence of positive findings reflects relative weaknesses in trial design. For example, post-hoc analyses of some recent mild-to-moderate AD trials of immunotherapies suggested efficacy when data were limited to participants with mild AD (MMSE 20–26) and scores on extended ADAS-Cog versions were examined[3,4]. Furthermore, a sizeable proportion of participants in these trials had negative amyloid PET imaging, suggesting that they did not have underlying Aβ pathology[6]. Together, these findings have contributed to a paradigm shift in AD dementia trials, whereby studies are targeting earlier stages of AD, requiring demonstration of amyloid pathology, and measuring efficacy with extended versions of the ADAS-Cog[7].

Though the ADAS-Cog11 was used in the clinical trials that demonstrated the efficacy of acetylcholinesterase inhibitors in mild-to-moderate AD[8], extended ADAS-Cog versions may offer increased sensitivity at earlier stages of disease. In particular, adding a delayed recall subtest (ADAS-Cog12)[9] captured greater annual decline in Mild Cognitive Impairment (MCI)[10] and may require smaller sample sizes for MCI treatment trials[11], compared to the ADAS-Cog11. Increased sensitivity with the ADAS-Cog12 was not seen in participants with dementia due to AD, likely due to floor effects on delayed recall items[10]. The ADAS-Cog13 includes an additional cancellation task, which demonstrated disease worsening over time without ceiling or floor effects in mild and severe AD[12]. Current interventional clinical trials for mild AD are using the ADAS-Cog11[13], ADAS-Cog12[14], and ADAS-Cog13[15] as primary cognitive outcome measures.

Trials of anti-Aβ interventions are also implementing amyloid imaging inclusion criteria[16] to confirm the presence of underlying AD pathology[17,18], thereby limiting trial samples to participants who express the therapeutic target[6]. AD trials using positive 18F-Florbetapir amyloid imaging as an inclusion criterion have implemented a minimum standardized uptake value ratio (SUVR) cutoff of 1.1[7]. This cutoff represents the upper 95% confidence interval for young cognitively normal controls[19] and in autopsy samples yielded 97% sensitivity and 99% specificity for the presence of moderate to frequent senile plaques[20]. The optimal SUVR cutoff for entry into AD clinical trials remains uncertain, however, as different SUVR cutoffs may be associated with varying degrees of longitudinal change on the ADAS-Cog[21].

There is a relative dearth of available data regarding the impact of ADAS-Cog versions and amyloid imaging SUVR cutoffs on trial efficiency. The aim of this study was to model the impact of these design choices on calculated effect sizes in mild AD treatment trials lasting 12 or 24 months using longitudinal data from the Alzheimer’s Disease Neuroimaging

Initiative (ADNI). We hypothesized that larger effect sizes would emerge with higher SUVR cutoffs for positive amyloid imaging and the use of extended ADAS-Cog versions.

2. Methods

2.1 ADNI

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org. Data was downloaded on December 9, 2014 from http://adni.loni.usc.edu/data-samples/access-data/.

All ADNI participants had a modified Hachinski scale score of ≤4, a Geriatric Depression Scale (abbreviated 15-item version) scores of ≤6, were fluent in English or Spanish, had a suitable study partner who could accompany them to study visits, and lived at home. They had no significant neurologic or psychiatric disease; no history of alcohol or substance abuse; no clinically significant laboratory abnormalities on vitamin B12, rapid plasma reagin, or thyroid function tests; and no contraindication to neuroimaging. They did not take psychoactive drugs, including antidepressants with anticholinergic properties, or warfarin. They had not participated in a clinical trial of an investigational medication within 1 month of baseline or for the duration of their participation in ADNI, and they were not involved in other studies that included neuropsychological testing that could interfere with the ADNI-related testing[22].

2.2 Study Participants

This study included ADNI1 and ADNI2 participants. We examined data from AD participants who had MMSE scores between 20–26 (inclusive), global Clinical Dementia Rating scale scores of 0.5 or 1.0, and who met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD[17] at baseline.

2.3 ADAS-Cog

The version of the ADAS-cog included in ADNI can be scored in three manners. The ADAS-Cog11 has a range of 0 to 70 and incorporates tests of memory, language, attention, and praxis in addition to other cognitive abilities[23]. This version has traditionally been incorporated in mild-to-moderate dementia trials. Extended versions include a delayed recall item (ADAS-Cog12), increasing the maximum score to 80[9], and a number cancellation task (ADAS-Cog13), increasing the maximum score to 85[12]. Higher scores indicate poorer performance for the ADAS-cog.

2.4 Amyloid Imaging

18F-Florbetapir amyloid signal[24] was quantified using SUVR, the ratio of cortical to whole cerebellum 18F-Florbetapir uptake[25]. Regions of interest included the frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices. SUVR values were calculated by ADNI investigators and downloaded from www.loni.usc.edu. Baseline 18F-Florbetapir data were available for 100 ADNI participants.

An SUVR cutoff of 1.1, which has been used as an inclusion criterion for a recent Phase III study in mild AD[7], was used as our lowest boundary for amyloid positivity. The other examined SUVR cutoffs utilized in this study (1.3 and 1.4) were chosen *a priori*.

2.5 Data Analysis

We examined how trial design variables impacted study power as measured by modeled trial effect sizes. Effect sizes were calculated as /, where was the ADAS-Cog score at time *i* minus ADAS-Cog score at baseline. was the standard deviation of . Time *i* was 12 or 24 months. Since a higher ADAS-Cog score indicates poorer performance, positive represented cognitive decline.

We calculated 95% confidence intervals (CI) for effect size using 10,000 iteration bootstrap resampling. Throughout the text, we report the effect size and the 95% confidence intervals. We also calculated the 95% CIs of effect size difference between ADAS-Cog and SUVR pairs using 10,000 iteration bootstrap resampling in order to determine if the CIs of this difference overlapped with zero. All analyses were performed using R v3.1.2 (http://www.R-project.org).

3. Results

3.1 Demographics

Table 1 shows demographic information for ADNI participants used in the current analyses, with and without SUVR enrichment. Participants were highly educated, mostly Caucasian, and were a mean age of 75. Minimal differences were observed between the groups, based on amyloid enrichment. For increasing SUVR cutoffs, a higher frequency of APOE ε4 carriers was observed.

3.2 ADAS-Cog versions

Effect sizes were larger for 24-month trials relative to 12-month trials, regardless of which version of the ADAS-Cog was used (Table 2). For both 12- and 24-month trials, increased effect sizes were observed for ADAS-Cog versions that included additional items (i.e., ADAS-Cog12 and 13). Using the ADAS-Cog13 increased effect sizes by 7% for 12-month trials (effect size=0.69 [95% CI: 0.59–0.80] ADAS-Cog11 vs. 0.74 [0.63–0.85] ADAS-Cog13) and 10% for 24-month trials (1.04 [0.92–1.19] ADAS-Cog11 vs. 1.14 [1.01–1.30] ADAS-Cog13), relative to the ADAS-Cog11 (Table 2).

Tables 3 and 4 display the bootstrapping results for the differences in effect sizes between all possible pairs within the 12- and 24-month time points, respectively. All of the comparisons at 12-months without amyloid enrichment overlapped with zero. At 24-months, the 95% CIs for the effect size difference of ADAS-Cog11 versus ADAS-Cog12 and ADAS-Cog11 versus ADAS-Cog13 did not overlap with zero.

3.3 Amyloid Imaging Enrichment

The median 18F-Florbetapir SUVR was 1.43. SUVRs of 1.1, 1.3 and 1.4 represented the 8^{th}, 25^{th} and 43^{rd} percentiles. Of the 100 participants with amyloid imaging, 91% met the SUVR 1.1 criteria; 76% of participants met the SUVR 1.3 criteria, and 58% met the SUVR 1.4 criteria (Table 1).

Modeled twelve-month trials using the ADAS-Cog11, 12 and 13 demonstrated 13% (0.69 [0.59–0.80] no SUVR enrichment vs. 0.78 [0.59–1.01] SUVR≥1.1), 8% (0.73 [0.62–0.84] no SUVR enrichment vs. 0.79 [0.59–1.03] SUVR≥1.1), and 13% (0.74 [0.63–0.85] no SUVR enrichment vs. 0.84 [0.64–1.09] SUVR≥1.1) improvements in effect sizes, respectively, when enriching for SUVR≥1.1 (Table 2). Only the 95% CI effect size difference for ADAS-Cog13 and ADAS-Cog12 did not overlap zero (Table 3). Compared to SUVR≥1.1, there was little or no additional increase in effect sizes for 12-month trials using ADAS-Cog11 when enriching for SUVR≥1.3 or≥1.4. Higher SUVR cutoffs, however, did improve effect sizes for ADAS-Cog12 and 13. For example, the ADAS-Cog13 effect size for SUVR≥1.4 was 29% (0.74 [0.63–0.85] no SUVR enrichment vs. 0.96 [0.74–1.26] SUVR≥1.4) greater than without amyloid imaging enrichment.

Amyloid enrichment for SUVR 1.1 did not improve effect sizes for modeled 24-month trials (Tables 2 and 4). Enrichment for SUVR≥1.3 or ≥1.4 increased effect sizes by as much as 15% (1.04 [0.92–1.19] no SUVR enrichment, ADAS-Cog11 vs. 1.20 [0.73–2.18]

SUVR≥1.4, ADAS-Cog11), although the effect size difference 95% CI overlapped zero. Nevertheless, increased effect sizes at these higher SUVR cutoffs were observed for all versions of the ADAS-Cog (Table 2).

The graphical trends illustrated in Figure 1 complement the observations made when analyzing the SUVR cutoffs of 1.1, 1.3 and 1.4. For 12-month trials, the ADAS-Cog13 yielded larger effect sizes relative to the ADAS-Cog11, with more pronounced increases seen at higher SUVR thresholds. In contrast, for 24-month trials, the ADAS-Cog versions incorporating the additional items offered increased effect sizes only when the lower SUVR thresholds were used.

4. Discussion

This study examined how protocol decisions related to amyloid enrichment criteria and ADAS-Cog version affect AD clinical trial power. Our findings demonstrate that these aspects of trial design, in conjunction with trial length, can significantly modulate expected detectable effect sizes and, in turn, the statistical power for detecting treatment benefit on clinical trials for mild AD.

Ninety-two percent of AD participants met amyloid imaging criteria of SUVR greater than 1.1, similar to observed rates in prior studies[26]. This cutoff has been shown to discriminate AD participants from healthy controls with a sensitivity of 92% and specificity of 90%[27]. Mean SUVRs in AD study participants are often higher than 1.1, however[28], leading us to examine whether varying SUVR criteria would impact AD trial power. Similarly, the recent use of extended versions of the ADAS-Cog, particularly in registration trials, raises the question of whether the choice of ADAS-Cog version might interact with other trial design choices to impact statistical power.

For 12-month trials, the use of extended ADAS-Cog versions and amyloid enrichment increased effect sizes. In trials using the standard 11-item ADAS-Cog, enriching for amyloid SUVR 1.1 afforded an effect size that would reduce trial sample sizes by 22%. Interestingly, increasing the minimum SUVR criteria did not further increase trial power when using this version of the ADAS-Cog, but trials using extended versions of ADAS-Cog appeared to benefit from higher minimum amyloid burden requirements. These results suggest that Phase Ib and Phase IIa proof-of-principle trials that limit to participants with higher amyloid burden and implement ADAS-Cog versions with additional items may require smaller sample sizes.

For 24-month trials, extended ADAS-Cog versions yielded increased trial effect sizes when including all eligible mild AD patients. Differences between ADAS-Cog versions were no longer apparent when higher amyloid PET SUVR criteria were implemented. Nevertheless, irrespective of which ADAS-Cog version was used, higher amyloid PET SUVR thresholds yielded more robust gains in effect size with longer trials. These findings are consistent with prior studies that correlated higher degrees of amyloid positivity with lower cognitive performance[18,29] and greater cognitive decline[30]. Therefore, the benefit of amyloid enrichment in longer trial designs, such as those typically used in Phase III registration

studies, may be enhanced in trials that use more stringent biomarker criteria. These potential benefits must be carefully weighed against the expected increased screen failure rates and amyloid imaging costs that would be associated with implementing such criteria.

The differences observed between the trial lengths may also be an important consideration for those designing AD trials. While shorter proof-of-concept trials may be appropriate in early Phase studies, these results suggest an additional complication may be introduced if ADAS-cog results from those studies are used to power larger, longer Phase III studies. Study inclusion criteria may also be used by regulatory agencies when considering approval indications.

4.1 Limitations

Some limitations to this study should be pointed out. Data were drawn from a single convenience sample (ADNI) whose participants were mostly Caucasian and highly educated. As such, our findings may not be representative of the larger AD population. This convenience sampling, however, may be more representative of interventional clinical trials than would be random sampling of a population-based study. Few AD participants with higher SUVRs and 24-month cognitive outcomes were available for analysis. Thus, the results for these particular analyses should be considered less robust. Similarly, we did not have sufficient data to examine AD patients with lower MMSE scores (16–20), who are often included in mild-to-moderate AD trials.

As in other studies that examine clinical trial power, our experiments assume that interventions tested in trials will have generalized effects on cognition, if beneficial. If, however, a drug had benefits on executive function but not delayed recall, for example, the generalizability of our results would be reduced. Similarly, our study does not account for the possibility of differential drug effects based on SUVR level, APOE genotype, or other demographic or disease-related characteristics. Furthermore, if greater amyloid burden is the result of greater disease severity, the enrichment strategy of limiting to those with greatest amyloid burden may directly contradict a trial design enrolling only those with mild disease.

Our analyses did not include other techniques to optimize selection of AD trial participants, including enrichment for AD risk genes[31] such as APOE and other AD biomarkers, such as volumetric measures of atrophy[32], cerebral metabolic measures[33] or CSF markers of Aβ or tau[34]. Nevertheless, CSF Aβ measures correlate closely with 18F-Florbetapir PET results[35].

Though enrichment strategies can be useful in decreasing sample sizes, these design choices must be weighed against their larger implications on screening efficiency, imaging costs, and the generalizability of trial results. In our dataset, the screen failure rates for using SUVR≥1.4 as enrichment may be as high as 43% based on the amyloid PET criteria alone.

4.2 Conclusions

Extended ADAS-Cog versions and amyloid imaging enrichment may offer improved AD trial statistical power, but design choices must be made with caution. Our observations suggest that enriching for mild AD patients with higher brain amyloid burden and implementing extended versions of the ADAS-Cog can help optimize trial power in 12-

month more so than 24-month clinical trials. Such advantages may be mitigated by expected parallel increases in screen failure rates and amyloid imaging costs. Nevertheless, these approaches should be considered when designing future clinical trials of novel therapeutics in mild AD and the current findings may aid in that process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Joshua Grill and Edmond Teng were supported by NIA AG016570. Dr. Grill is currently supported by NIA AG016573. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare;;IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
MCI	Mild Cognitive Impairment
SUVR	standardized uptake value ratio
ADNI	Alzheimer's Disease Neuroimaging Initiative
PET	positron emission tomography

References

1. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297(5580):353–356. DOI: 10.1126/science.1072994 [PubMed: 12130773]
2. Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014; 370(4):322–333. DOI: 10.1056/NEJMoa1304839 [PubMed: 24450891]
3. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014; 370(4):311–321. DOI: 10.1056/NEJMoa1312889 [PubMed: 24450890]

4. Cummings J, Cho W, Ward M, et al. A randomized, double-blind, placebo-controlled phase 2 study to evaluate the efficacy and safety of crenezumab in patients with mild to moderate Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2014; 10(4):P275.
5. Castellani RJ, Lee H, Siedlak SL, et al. Reexamining Alzheimer's disease: evidence for a protective role for amyloid-beta protein precursor and amyloid-beta. J Alzheimers Dis. 2009; 18(2):447–452. DOI: 10.3233/JAD-2009-1151 [PubMed: 19584435]
6. Selkoe DJ. The therapeutics of Alzheimer's disease: Where we stand and where we are heading. Ann Neurol. 2013; 74(3):328–336. DOI: 10.1002/ana.24001 [PubMed: 25813842]
7. Eli Lilly and Company. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000–2015. Progress of Mild Alzheimer's Disease in Participants on Solanezumab Versus Placebo (EXPEDITION 3). http://ClinicalTrials.gov/show/NCT01900665. NLM Identifier: NCT01900665. ; NCT01900665 [Accessed February 18, 2015]
8. Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. Dementia. 1996; 7(6):293–303. [PubMed: 8915035]
9. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. Lancet. 2006; 367(9518): 1262–1270. DOI: 10.1016/S0140-6736(06)68542-5 [PubMed: 16631882]
10. Sano M, Raman R, Emond J, et al. Adding delayed recall to the Alzheimer Disease Assessment Scale is useful in studies of mild cognitive impairment but not Alzheimer disease. Alzheimer Dis Assoc Disord. 2011; 25(2):122–127. DOI: 10.1097/WAD.0b013e3181f883b7 [PubMed: 20921876]
11. Grill JD, Di L, Lu PH, et al. Estimating sample sizes for predementia Alzheimer's trials based on the Alzheimer's Disease Neuroimaging Initiative. Neurobiol Aging. 2013; 34(1):62–72. DOI: 10.1016/j.neurobiolaging.2012.03.006 [PubMed: 22503160]
12. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997; 11(Suppl 2):S13–S21. [PubMed: 9236948]
13. Merck Sharp & Dohme Corp. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000–2015. An Efficacy and Safety Trial of MK-8931 in Mild to Moderate Alzheimer's Disease (P07738). http://ClinicalTrials.gov/show/NCT01739348. NLM Identifier: NCT01739348. ; NCT01739348 [Accessed February 18, 2015]
14. Prof Brian Lawlor, University of Dublin, Trinity College, Molecular Medicine Ireland LBG;, Alzheimer Europe; Archer Pharmaceuticals, Inc.; E–Search Limited; University College Dublin;King's College London;Istituto Di Ricerche Farmacologiche Mario Negri; University Hospital, Lille;University of Ulm;Szeged University;Goeteborgs Universitet;University College Cork;Aristotle University Of Thessaloniki;Stichting Katholieke Universiteit;St. James's Hospital, Ireland. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000–2015. A Phase III Trial of Nilvadipine to Treat Alzheimer's Disease. NCT02017340 [Accessed February 18, 2015]
15. Hoffmann-La Roche. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000–2015. A Study of Gantenerumab in Patients With Mild Alzheimer Disease. http://ClinicalTrials.gov/show/NCT02051608. NLM Identifier: NCT02051608. ; NCT02051608. http://ClinicalTrials.gov/show/NCT02051608 [Accessed February 18, 2015]
16. The Cleveland Clinic. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000–2015. Rasagiline Rescue in Alzheimer's Disease Clinical Trial (R2). NCT02054208. http://ClinicalTrials.gov/show/NCT02359552 [Accessed February 18, 2015]
17. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263–269. DOI: 10.1016/j.jalz.2011.03.005 [PubMed: 21514250]
18. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. AnnNeurol. 2004; 55(3):306–319.

19. Joshi AD, Pontecorvo MJ, Clark CM, et al. Performance characteristics of amyloid PET with florbetapir F 18 in patients with alzheimer's disease and cognitively normal subjects. J Nucl Med. 2012; 53(3):378–384. DOI: 10.2967/jnumed.111.090340 [PubMed: 22331215]
20. Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. Lancet Neurol. 2012; 11(8):669–678. DOI: 10.1016/S1474-4422(12)70142-4 [PubMed: 22749065]
21. Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. Brain. May. 2015 doi: 10.1093/brain/awv112
22. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI). Neurology. 2010; 74(3):201–209. DOI: 10.1212/WNL.0b013e3181cb3e25 [PubMed: 20042704]
23. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984; 141(11):1356–1364. [PubMed: 6496779]
24. Wong DF, Rosenberg PB, Zhou Y, et al. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (flobetapir F 18). Journal of Nuclear Medicine. 2010; 51(6):913–920. [PubMed: 20501908]
25. Landau, Susan, Jagust, William. [Accessed February 18, 2015] Florbetapir processing methods. Apr. 2014 ADNI_AV45_Methods_JagustLab_04-29-14.pdf
26. Johnson KA, Sperling RA, Gidicsin CM, et al. Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. Alzheimers Dement. 2013; 9(5 Suppl):S72–S83. DOI: 10.1016/j.jalz.2012.10.007 [PubMed: 23375563]
27. Mattsson N, Insel PS, Landau S, et al. Diagnostic accuracy of CSF Ab42 and florbetapir PET for Alzheimer's disease. Ann Clin Transl Neurol. 2014; 1(8):534–543. DOI: 10.1002/acn3.81 [PubMed: 25356425]
28. Fleisher AS, Chen K, Liu X, et al. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol. 2011; 68(11):1404–1411. DOI: 10.1001/archneurol.2011.150 [PubMed: 21747008]
29. Tolboom N, van der Flier WM, Yaqub M, et al. Differential association of [11C]PIB and [18F]FDDNP binding with cognitive impairment. Neurology. 2009; 73(24):2079–2085. DOI: 10.1212/WNL.0b013e3181c679cc [PubMed: 20018636]
30. Tateno A, Sakayori T, Kawashima Y, et al. Comparison of imaging biomarkers for Alzheimer's disease: amyloid imaging with [(18) F]florbetapir positron emission tomography and magnetic resonance imaging voxel-based analysis for entorhinal cortex atrophy. Int J Geriatr Psychiatry. Jul. 2014 doi: 10.1002/gps.4173
31. Kohannim O, Hua X, Rajagopalan P, et al. Multilocus genetic profiling to empower drug trials and predict brain atrophy. Neuroimage Clin. 2013; 2:827–835. DOI: 10.1016/j.nicl.2013.05.007 [PubMed: 24179834]
32. Hua X, Leow AD, Parikshak N, et al. Tensor-Based Morphometry as a Neuroimaging Biomarker for Alzheimer's Disease: An MRI Study of 676 AD, MCI, and Normal Subjects. Neuroimage. 2008; 43(3):458–469. DOI: 10.1016/j.neuroimage.2008.07.013 [PubMed: 18691658]
33. Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. Eur J Nucl Med Mol Imaging. 2005; 32(4):486–510. DOI: 10.1007/s00259-005-1762-7 [PubMed: 15747152]
34. Barnes J, Bartlett JW, Fox NC, Schott JM. Targeted recruitment using cerebrospinal fluid biomarkers: implications for Alzheimer's disease therapeutic trials. J Alzheimers Dis. 2013; 34(2): 431–437. DOI: 10.3233/JAD-121936 [PubMed: 23229078]
35. Landau SM, Lu M, Joshi AD, et al. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of β-amyloid. Ann Neurol. 2013; 74(6):826–836. DOI: 10.1002/ana.23908 [PubMed: 23536396]

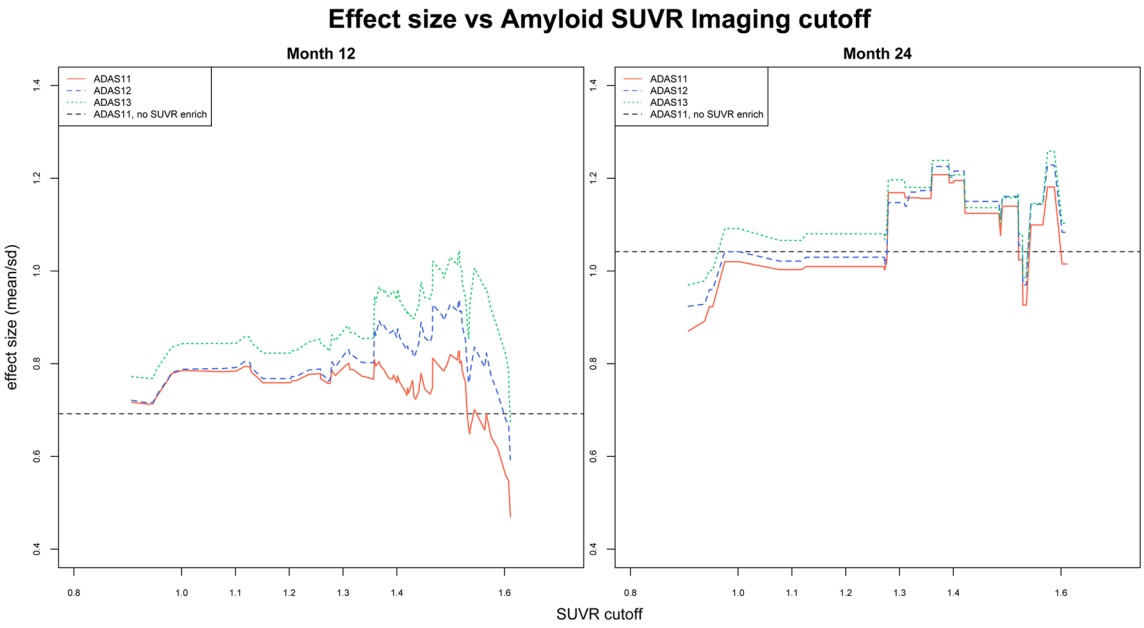

Figure 1.

Table 1

Demographics for all patients

Variable	No SUVR enrichment	SUVR 1.1	SUVR 1.3	SUVR 1.4
Total, n (%*)	258	91 (91)	76 (76)	58 (58)
Age, years (SD)	75.1 (7.6)	74.4 (7.8)	74.1 (7.9)	74.3(8.1)
Gender, % male	45%	43%	49%	50%
Education, years (SD)	15.2 (2.9)	15.7 (2.5)	15.7(2.7)	15.7(2.7)
APOEε4, %				
0	33%	26%	21%	23%
1	46%	50%	51%	51%
2	21%	24%	27%	26%
Non-Latino ethnicity, %	98%	97%	96%	95%
Race, %				
Asian	2%	3%	4%	5%
Black	4%	4%	4%	3%
More than one	1%	2%	3%	2%
White	93%	91%	89%	90%
MMSE, mean (SD)	23.3 (2.0)	23.0 (2.0)	23.0 (2.0)	23.1 (2.0)

Values correspond to percentage or mean (standard deviation [SD]) for discrete or continuous values. MMSE = mini-mental status exam.

*For SUVR groups, the reported percent is calculated based on the number of ADNI participants for whom 18F-Florbetapir imaging was available (n=100).

Table 2

Effect sizes for ADAS-Cog versions at 12 and 24 months with and without amyloid imaging enrichment

	ES	95% CI	Δμ	σ	n	ES	95% CI	Δμ	σ	n
	Month 12					Month 24				
	No SUVR enrichment									
ADAS-Cog11	0.69	0.59–0.80	4.4	6.4	258	1.04	0.92–1.19	9.4	9	162
ADAS-Cog12	0.73	0.62–0.84	4.7	6.5	249	1.13	1.00–1.29	9.5	8.4	150
ADAS-Cog13	0.74	0.63–0.85	5.1	6.9	249	1.14	1.01–1.30	10.3	9.1	148
	SUVR ≥ 1.1									
ADAS-Cog11	0.78	0.59–1.01	4.8	6.1	91	1	0.67–1.57	8.4	8.4	24
ADAS-Cog12	0.79	0.59–1.03	5.1	6.4	89	1.02	0.73–1.54	8.9	8.7	26
ADAS-Cog13	0.84	0.64–1.09	5.7	6.7	89	1.07	0.78–1.56	10.1	9.5	24
	SUVR ≥ 1.3									
ADAS-Cog11	0.8	0.59–1.05	4.9	6.2	76	1.17	0.80–1.87	9.7	8.3	20
ADAS-Cog12	0.83	0.62–1.09	5.2	6.3	74	1.15	0.82–1.75	10.1	8.8	22
ADAS-Cog13	0.88	0.65–1.16	5.9	6.7	74	1.2	0.87–1.83	11.5	9.6	20
	SUVR ≥ 1.4									
ADAS-Cog11	0.77	0.55–1.06	5	6.4	58	1.2	0.73–2.18	11	9.2	15
ADAS-Cog12	0.88	0.66–1.16	5.5	6.3	56	1.22	0.78–2.12	11.8	9.7	16
ADAS-Cog13	0.96	0.74–1.26	6.3	6.6	56	1.21	0.80–2.03	12.9	10.7	15

Caption: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, ES = effect size, CI = confidence interval, Δμ = mean change in ADAS-Cog, σ = standard deviation, n=sample size, SUVR = standardized uptake value ratio.

Table 3

10,000 iteration bootstrap resampling point estimates and 95% CIs for the difference in estimated effect sizes between all 12-month trial design pairs.

	SUVR no enrich, ADAS12	**SUVR no enrich, ADAS13**	**SUVR 1.10, ADAS11**	**SUVR 1.10, ADAS12**	**SUVR 1.10, ADAS13**	**SUVR 1.30, ADAS11**	**SUVR 1.30, ADAS12**	**SUVR 1.30, ADAS13**	**SUVR 1.40, ADAS11**	**SUVR 1.40, ADAS12**	**SUVR 1.40, ADAS13**
SUVR no enrich, ADAS11	−0.04 (−0.08–0.01)	−0.05 (−0.1–0)	−0.09 (−0.28–0.06)	−0.1 (−0.31–0.07)	−0.15 (−0.37–0.02)	−0.11 (−0.32–0.06)	−0.14 (−0.37–0.05)	−0.19 (−0.45–0.02)	−0.08 (−0.33–0.12)	−0.18 (−0.44–0.01)	−0.27 (−0.55–-0.07)
SUVR no enrich, ADAS12		−0.01 (−0.04–0.02)	−0.06 (−0.24–0.09)	−0.06 (−0.26–0.09)	−0.12 (−0.32–0.05)	−0.07 (−0.29–0.1)	−0.1 (−0.33–0.08)	−0.15 (−0.41–0.04)	−0.05 (−0.3–0.16)	−0.15 (−0.41–0.05)	−0.23 (−0.51–-0.03)
SUVR no enrich, ADAS13			−0.05 (−0.23–0.11)	−0.05 (−0.25–0.11)	−0.11 (−0.31–0.05)	−0.06 (−0.28–0.11)	−0.09 (−0.32–0.09)	−0.14 (−0.4–0.04)	−0.04 (−0.3–0.17)	−0.14 (−0.4–0.07)	−0.22 (−0.5–-0.02)
SUVR 1.10, ADAS11				−0.01 (−0.09–0.07)	−0.06 (−0.17–0.04)	−0.01 (−0.13–0.08)	−0.04 (−0.19–0.08)	−0.1 (−0.27–0.05)	0.01 (−0.16–0.16)	−0.09 (−0.29–0.06)	−0.18 (−0.39–-0.02)
SUVR 1.10, ADAS12					−0.05 (−0.11–-0.01)	−0.01 (−0.16–0.13)	−0.04 (−0.17–0.07)	−0.09 (−0.25–0.03)	0.02 (−0.21–0.21)	−0.08 (−0.31–0.1)	−0.17 (−0.41–0.01)
SUVR 1.10, ADAS13						0.05 (−0.11–0.2)	0.02 (−0.11–0.13)	−0.04 (−0.17–0.07)	0.07 (−0.17–0.28)	−0.03 (−0.27–0.17)	−0.12 (−0.36–0.07)
SUVR 1.30, ADAS11							−0.03 (−0.13–0.06)	−0.08 (−0.22–0.04)	0.02 (−0.11–0.13)	−0.08 (−0.24–0.05)	−0.16 (−0.35–-0.02)
SUVR 1.30, ADAS12								−0.05 (−0.12–-0.01)	0.05 (−0.15–0.22)	−0.05 (−0.25–0.1)	−0.13 (−0.35–0.02)
SUVR 1.30, ADAS13									0.11 (−0.13–0.31)	0.01 (−0.22–0.18)	−0.08 (−0.31–0.08)
SUVR 1.40, ADAS11										−0.1 (−0.2–-0.02)	−0.19 (−0.32–-0.08)
SUVR 1.40, ADAS12											−0.08 (−0.16–-0.03)

Caption: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, SUVR = standardized uptake value ratio

Table 4

10,000 iteration bootstrap resampling point estimates and 95% CIs for the difference in estimated effect sizes between all 24-month trial design pairs.

	SUVR no enrich, ADAS12	**SUVR no enrich, ADAS13**	**SUVR 1.10, ADAS11**	**SUVR 1.10, ADAS12**	**SUVR 1.10, ADAS13**	**SUVR 1.30, ADAS11**	**SUVR 1.30, ADAS12**	**SUVR 1.30, ADAS13**	**SUVR 1.40, ADAS11**	**SUVR 1.40, ADAS12**	**SUVR 1.40, ADAS13**
SUVR no enrich, ADAS11	−0.09 (−0.18--0.02)	−0.1 (−0.19--0.02)	0.04 (−0.5–0.35)	0.02 (−0.47–0.3)	−0.02 (−0.5–0.25)	−0.13 (−0.81–0.23)	−0.11 (−0.69–0.21)	−0.16 (−0.76–0.17)	−0.15 (−1.17–0.3)	−0.17 (−1.11–0.25)	−0.17 (−0.99–0.23)
SUVR no enrich, ADAS12		−0.01 (−0.04–0.03)	0.13 (−0.39–0.43)	0.11 (−0.36–0.38)	0.07 (−0.38–0.33)	−0.03 (−0.71–0.31)	−0.01 (−0.59–0.29)	−0.06 (−0.66–0.25)	−0.06 (−1.07–0.39)	−0.08 (−1.02–0.33)	−0.07 (−0.89–0.32)
SUVR no enrich, ADAS13			0.14 (−0.39–0.45)	0.12 (−0.36–0.4)	0.07 (−0.38–0.34)	−0.03 (−0.71–0.33)	−0.01 (−0.59–0.31)	−0.06 (−0.66–0.26)	−0.05 (−1.06–0.4)	−0.08 (−1.02–0.35)	−0.07 (−0.88–0.33)
SUVR 1.10, ADAS11				−0.02 (−0.13–0.1)	−0.06 (−0.18–0.07)	−0.17 (−0.64–0.02)	−0.14 (−0.56–0.08)	−0.19 (−0.62–0.02)	−0.19 (−0.95–0.12)	−0.21 (−0.9–0.08)	−0.2 (−0.82–0.08)
SUVR 1.10, ADAS12					−0.04 (−0.14–0.07)	−0.15 (−0.6–0.07)	−0.13 (−0.5–0.04)	−0.18 (−0.58–0.03)	−0.17 (−0.94–0.17)	−0.19 (−0.87–0.1)	−0.19 (−0.8–0.11)
SUVR 1.10, ADAS13						−0.1 (−0.54–0.11)	−0.08 (−0.45–0.12)	−0.13 (−0.49–0.02)	−0.13 (−0.89–0.22)	−0.15 (−0.83–0.16)	−0.14 (−0.73–0.14)
SUVR 1.30, ADAS11							0.02 (−0.1–0.2)	−0.03 (−0.14–0.13)	−0.03 (−0.48–0.16)	−0.05 (−0.43–0.12)	−0.04 (−0.36–0.16)
SUVR 1.30, ADAS12								−0.05 (−0.2–0.09)	−0.05 (−0.63–0.21)	−0.07 (−0.55–0.12)	−0.06 (−0.47–0.18)
SUVR 1.30, ADAS13									0 (−0.55–0.28)	−0.02 (−0.49–0.21)	−0.01 (−0.38–0.2)
SUVR 1.40, ADAS11										−0.02 (−0.15–0.12)	−0.01 (−0.12–0.26)
SUVR 1.40, ADAS12											0.01 (−0.1–0.22)

Caption: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, SUVR = standardized uptake value ratio