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Targeting Prodromal Alzheimer Disease With Avagacestat: A Randomized Clinical Trial

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IMPORTANT: Early identification of Alzheimer disease (AD) is important for clinical management and affords the opportunity to assess potential disease-modifying agents in clinical trials. To our knowledge, this is the first report of a randomized trial to prospectively enrich a study population with prodromal AD (PDAD) defined by cerebrospinal fluid (CSF) biomarker criteria and mild cognitive impairment (MCI) symptoms.

OBJECTIVES: To assess the safety of the γ-secretase inhibitor avagacestat in PDAD and to determine whether CSF biomarkers can identify this patient population prior to clinical diagnosis of dementia.

DESIGN, SETTING, AND PARTICIPANTS: A randomized, placebo-controlled phase 2 clinical trial with a parallel, untreated, nonrandomized observational cohort of CSF biomarker-negative participants was conducted May 26, 2009, to July 9, 2013, in a multicenter global population. Of 1358 outpatients screened, 263 met MCI and CSF biomarker criteria for randomization into the treatment phase. One hundred two observational cohort participants who met MCI criteria but were CSF biomarker-negative were observed during the same study period to evaluate biomarker assay sensitivity.

INTERVENTIONS: Oral avagacestat or placebo daily.

MAIN OUTCOMES AND MEASURE: Safety and tolerability of avagacestat.

RESULTS: Of the 263 participants in the treatment phase, 132 were randomized to avagacestat and 131 to placebo; an additional 102 participants were observed in an untreated observational cohort. Avagacestat was relatively well tolerated with low discontinuation rates (19.6%) at a dose of 50 mg/d, whereas the dose of 125 mg/d had higher discontinuation rates (43%), primarily attributable to gastrointestinal tract adverse events. Increases in nonmelanoma skin cancer and nonprogressive, reversible renal tubule effects were observed with avagacestat. Serious adverse event rates were higher with avagacestat (49 participants [37.1%]) vs placebo (31 [23.7%]), attributable to the higher incidence of nonmelanoma skin cancer. At 2 years, progression to dementia was more frequent in the PDAD cohort (30.7%) vs the observational cohort (6.5%). Brain atrophy rate in PDAD participants was approximately double that of the observational cohort. Concordance between abnormal amyloid burden on positron emission tomography and pathologic CSF was approximately 87% (κ = 0.68; 95% CI, 0.48-0.87). No significant treatment differences were observed in the avagacestat vs placebo arm in key clinical outcome measures.

CONCLUSIONS AND RELEVANCE: Avagacestat did not demonstrate efficacy and was associated with adverse dose-limiting effects. This PDAD population receiving avagacestat or placebo had higher rates of clinical progression to dementia and greater brain atrophy compared with CSF biomarker-negative participants. The CSF biomarkers and amyloid positron emission tomography imaging were correlated, suggesting that either modality could be used to confirm the presence of cerebral amyloidopathy and identify PDAD.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00890890

Published online September 28, 2015.
Identifying Alzheimer disease (AD) before patients meet criteria for dementia may be critical to effectively evaluate whether potential disease-modifying agents can alter the neurodegenerative process and long-term course of this illness. Defining prodromal AD (PDAD) using biomarkers associated with amyloidopathy and clinical criteria for mild cognitive impairment (MCI) has been proposed\(^1\,^2\) as a way of identifying incipient AD dementia. Advances in cerebrospinal fluid (CSF) and neuroimaging biomarkers offer increasing sensitivity in identifying AD before the onset of dementia.\(^3\,^4\) Enriching clinical trials with patients who have both the clinical phenotype and underlying biomarker signature of AD will help ensure diagnostic accuracy, minimize exposure of individuals without AD to investigational agents, and increase the chances of detecting efficacy signals. A recent study\(^5\) in patients with dominantly inherited AD found that structural and biochemical changes associated with AD begin years before the onset of clinically evident symptoms, supporting the notion that early intervention with a disease-modifying agent will be required to optimally affect symptom emergence and disease progression. Nonetheless, it remains to be established if fulfilling criteria for PDAD predetermines eventual development of dementia or simply represents a risk factor.

Avagacestat (BMS-708163) is an oral γ-secretase inhibitor designed for the selective inhibition of β-amyloid (Aβ) synthesis relative to processing of Notch substrates. Phase 1 studies\(^6\,^7\) demonstrated that avagacestat decreased Aβ40 and Aβ42 levels at dosages expected to be tolerated in patients. Given that Aβ abnormality is an early marker of AD pathology and seems to change substantially throughout the course of MCI,\(^8\,^9\) avagacestat was advanced into a phase 2 PDAD clinical trial.\(^10\) We present the methods and results from this prospective, double-blind, placebo-controlled, randomized clinical trial designed to enrich for a study population at increased risk of progressing to dementia. In addition, we present data on patients meeting the clinical criteria for MCI but who were biomarker-negative in an observational cohort to assess the predictive value of using PDAD criteria to select patients at risk of progressing to dementia during the trial.

Methods

The treatment period of this multicenter, global, randomized, double-blind, 2-arm, placebo-controlled, parallel-group, randomized clinical trial was planned to extend until at least 2 years after the last patient was randomized. Individuals who met clinical criteria for MCI, but not for PDAD (because of the absence of CSF biomarker evidence of AD pathology) were eligible to be monitored longitudinally in an observational cohort.

Written informed consent was obtained from outpatients aged 45 to 90 years with MCI. The study was approved by an institutional review board designated by each site and was conducted in accordance with ethical principles and applicable regulatory requirements.\(^16\)\(^,^17\) The full study protocol can be found in Supplement 1. An independent data-monitoring committee had access to all study data and monitored the safety of participants on a quarterly basis throughout the trial. Patients at US sites and where allowed by local country regulations outside the United States received financial compensation for study visits and travel.

Inclusion and Exclusion Criteria

Randomized patients with PDAD met the following criteria: (1) clinical symptoms of MCI\(^18\) but not Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)\(^19\) criteria for dementia and (2) CSF biomarker results consistent with the presence of amyloidopathy (Aβ42 level of <200 pg/mL or total tau to Aβ42 ratio of ≥0.39) (Figure 1). Clinical MCI criteria required a subjective memory problem verified by a study partner, as well as demonstration of abnormal memory functioning as documented by at least 1 of the 4 following criteria: (1) scoring below the educational level-adjusted cutoff (1.5 SDs below the mean) on the Logical Memory II subscale from the Wechsler Memory Scale–Revised,\(^20\) (2) Free and Cued Selective Reminding Test\(^21\) (word list version) Total Recall score of 39 or less, (3) Free and Cued Selective Reminding Test Free Recall score of 24 or less, or (4) Free and Cued Selective Reminding Test Delayed Free Recall score of 8 or less. Other inclusion criteria included Mini–Mental State Examination\(^22\) score between 24 and 30, and Clinical Dementia Rating\(^23\) global score of 0.5 with a memory box score of 0.5 or less. In addition, screening magnetic resonance imaging (MRI) had to meet all of the following criteria: (1) provide a qualitative assessment showing either a normal MRI commensurate with age or atrophy consistent with an AD diagnosis, (2) reveal no focal asymmetric lobar atrophy or other findings suggesting that the primary cause of dementia was better attributed to a cause other than AD, (3) reveal no more than mild to moderate white matter disease (1-2 lacunar infarcts were acceptable, but no lacunes were permitted in the anterior thalamus, genu of internal capsule, or basal forebrain; no cortical infarcts), (4) reveal no more than 4 cerebral microhemorrhages, and (5) reveal no current or prior evidence of macrohemorrhages (>10 mm).

Exclusion criteria were as follows: (1) presence of a condition other than AD to explain the patient’s cognitive symptoms, (2) previous stroke, (3) positive fecal test for occult blood at screening, (4) chronic inflammatory bowel disease, (5) frequent diarrhea or loose stools, (6) vitamin B12 or folate deficiency, (7) Geriatric Depression Scale\(^24\) score of 6 or higher at screening (suggesting clinical depression), and (8) exposure to an investigational agent related to Aβ modulation within 12 months before screening. Patients who received stable doses of approved AD medications for at least 2 months prior to screening or who remained free of such medications throughout the trial were also excluded (Figure 1).

After being informed that their CSF biomarker results did not qualify for randomization to the treatment arms of the study, individuals who met all other inclusion criteria were invited to consent and to be followed up longitudinally in the observational cohort.

Safety Assessments

Safety and tolerability were evaluated by reports of adverse events (AEs) and clinically meaningful changes in electrocar-
diograms, vital signs, physical examination findings, laboratory test results, and MRIs tabulated by treatment arm. Adverse events were identified for up to 30 days after the study, and serious AEs (SAEs) were monitored until resolution.

**Clinical Outcome Assessments**

Key clinical outcome measures, including the 11-item Alzheimer’s Disease Assessment Scale–cognitive subscale,25 Clinical Dementia Rating Sum of Boxes,26 and Alzheimer’s Disease Cooperative Study Activities of Daily Living MCI version27 were performed at screening, baseline, and approximately every 12 weeks thereafter. Other outcome measures (Mini-Mental State Examination and Free and Cued Selective Reminding Test)21,22,28 were performed at screening and/or baseline and approximately every 24 weeks thereafter.

Progression to dementia was assessed at each visit. Assessment included review of Clinical Dementia Rating scores, Geriatric Depression Scale scores, and neuropsychological test information. Diagnoses of progression to dementia of the AD type were based on fulfilling both *DSM-IV-R*19 and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria. A diagnostic adjudication committee reviewed all investigator reports of progression, but results were not revealed to the sites.

**CSF Biomarker Assessments**

Lumbar punctures were performed at screening and optionally for randomized patients at week 2, week 24, and the end of treatment. The CSF levels of total tau, phosphorylated tau, and Aβ42 were analyzed (Luminex xMap technique, INNO-BIA AlzBio3 kit; Innogenetics) at a central laboratory. Levels of Aβ40 and Aβ42 were measured using electrochemiluminescence detection technology in multiplex format (Meso Scale Discovery). Cerebrospinal fluid levels of Aβ1-42 and total tau used for inclusion criteria were prospectively analyzed as patients were screened each week. In assessing changes in CSF biomarkers over time, baseline and on-treatment CSF samples from each patient were analyzed in the same analytical run to avoid any batch-to-batch assay variation.
MRI Assessments
Magnetic resonance imaging scans were performed on 1.5-T scanners at baseline and every 12 weeks thereafter. Volumetric MRI assessment techniques have been described. Results were evaluated centrally (BioClinica). Whole-brain and ventricular atrophy rates were computed using tensor-based morphometry, and hippocampal atrophy was calculated using hippocampus boundary shift integral.

PET Amyloid Assessments
Imaging using florbetapir F 18 positron emission tomography (PET) was performed in a subset of patients at baseline, week 24, and week 104 at selected sites. The florbetapir F 18 PET methods were performed blinded to patient assignment and analyzed as described previously under the direction of a central laboratory (Molecular Neuroimaging). Neocortical amyloid burden was expressed visually as either positive (consistent with an AD pattern of amyloidopathy) or negative (not consistent with an AD pattern of amyloidopathy), and quantitatively as the mean standard uptake value ratio for specific brain regions (posterior cingulate, parietal, lateral temporal, and frontal). The ratio was calculated as the target region standard uptake value divided by the brain tissue reference region, with the cerebellar cortex used as the reference region.

Randomization and Interventions
Patients with PDAD were randomly assigned (1:1) across the 2 blinded treatment groups: placebo or avagacestat once daily (Figure 1). Patients assigned to the avagacestat group initially received 50 mg/d for the first 2 weeks and then 125 mg/d. An amendment to the protocol reduced the dose to 50 mg/d and allowed for down-titration to 25 mg/d owing to high treatment discontinuation rates at 125 mg/d. Treatment allocation was stratified based on concomitant cholinesterase inhibitor use (yes/no), apolipoprotein E ε4 (APOE4) carrier status (carrier/noncarrier), and consent for PET scanning. Patient safety visits occurred every 2 weeks during the first 8 weeks of treatment, with telephone assessments occurring on alternating weeks. Follow-up visits were every 4 weeks until week 24 and every 12 weeks thereafter. On study termination, patients were monitored for 12 weeks after the last interim analysis to assess AEs and laboratory findings. A follow-up dermatologic examination was performed 6 months after treatment with the study drug was discontinued.

Statistical Analysis
The sample size of 135 participants per randomization arm was chosen empirically and estimated to be associated with a 98% probability of observing a specific AE if the true incidence was 3%. The incidence of AEs and SAEs was tabulated by treatment group and summarized descriptively. The incidence of potentially clinically relevant changes or events in laboratory test values was tabulated by status at baseline (normal vs abnormal). An intent-to-treat approach was taken for the analysis of time to progression to dementia, while all evaluable patients were included in the analyses related to outcome measures requiring baseline and at least 1 treatment assessment.

For each cognition assessment, the change from baseline was analyzed using a mixed-effects, repeated-measures model with a restricted maximum likelihood estimation. Time was treated as a categorical variable. An unstructured covariance matrix was used to represent the correlation of the repeated-measures within-patient errors. The adjusted mean change score from baseline and the 95% CI for the treatment difference between avagacestat and placebo were calculated for each visit. For CSF biomarkers, the geometric mean over baseline of Aβ42 was analyzed. The mean change from baseline of total tau, phosphorylated tau, and volumetric MRI (hippocampal, ventricular, and whole brain) were also analyzed. No adjustments were made for multiple comparisons. Nominal P values were provided for descriptive purposes.

The PET substudy assessed the correlation between standard uptake values (mean of 4 assessed regions) and CSF Aβ42 concentrations. In addition, concordance was determined between PET-determined assessment of pathologic amyloid burden (using qualitative scale) and pathologic CSF at baseline.

Results
Demographic variables across the study groups are summarized in Table 1. A total of 1358 patients were enrolled. Of these, 787 individuals (58.0%) were excluded prior to CSF testing. Of 571 patients who met the clinical inclusion criteria and completed the lumbar puncture, 263 participants (46.1%) met the CSF biomarker criteria for study entry and were randomized (Figure 1). Median treatment duration was approximately 22 months with a maximum of 41 months over both arms. After all participants had the opportunity to receive study treatment for at least 1 year, an interim analysis revealed minimal reductions in CSF amyloid and no significant treatment differences in the avagacestat arm vs placebo. The sponsor, in consultation with the DMC and external experts in the field, terminated the trial given the lack of apparent efficacy and unfavorable risk-benefit profile evident from the interim analysis.

Safety and Tolerability
Avagacestat doses of 50 mg/d were well tolerated with low treatment discontinuation rates, whereas the 125-mg/d dose had greater rates of discontinuation than placebo owing to gastrointestinal tract and skin AEs. Following this observation, the protocol was amended so that the highest dose was 50 mg/d with the ability to allow for down-titration to 25 mg/d. Forty-six patients in the avagacestat group and 44 patients in the placebo group down-titrated to doses of 25 mg/d for tolerability reasons. Discontinuation rates were similar between groups (19.6% at a dose of 50 mg/d and 43% at a dose of 125 mg/d). Common AEs in avagacestat patients included diarrhea, nausea, vomiting, fatigue, weight loss, decreased appetite, dizziness, and nonmelanoma skin cancer (NMSC) (Table 2 and eTable 1 in Supplement 2). Incident cerebral microbleeds were observed in both the avagacestat (3.0%) and placebo (1.5%) groups, but none were considered symptomatic. Vasogenic edema occurred in 3 participants in the avagacestat arm and 1 in the placebo arm (none was considered symptomatic). No
trends were observed in either treatment group for the incidence of cerebral microhemorrhages.

Most SAEs occurred in participants randomized before the protocol-specified avagacestat dose reduction from 125 mg/d to 50 mg/d. The SAE rates were higher with avagacestat (49 participants [37.1%]) compared with placebo (31 [23.7%]), attributable to a higher incidence of NMSCs. Of these SAEs, 8 (6.1%) were squamous cell carcinoma (avagacestat group) and 5 (3.8%) were basal cell carcinoma (placebo group). Although NMSCs were considered SAEs, none were life-threatening, and all were readily managed with conventional excision methods without recurrence or evidence of metastasis.

Among patients who received 125 mg/d of avagacestat throughout the study, 3 cases of gastrointestinal tract-related AEs were observed, ranging in severity from mild microcolitis to serious pancolitis.

**Treatment-Emergent AEs and Laboratory Findings**

Participants who received avagacestat demonstrated greater weight loss than did those who received placebo (mild, 6.1% vs 1.5%; moderate, 4.5% vs 0% weight loss). No significant differences in vital signs were observed between the groups. Treatment-emergent glycosuria, defined by any single positive urine glucose test result, was observed in 58.0% of avagacestat-treated patients but was not associated with treatment discontinuation, serum glucose changes, or evidence of glomerular injury. No decreases in glomerular filtration rate, cystatin C level, or clinically meaningful changes in albumin or creatinine levels were observed in the placebo group included uric acid levels less than the lower limit of normal (men: avagacestat, 20 of 72 [27.8%] and placebo, 2 of 76; women: avagacestat, 7 of 59 [11.9%] and placebo, 0), low calcium levels (avagacestat, 18 of 131 [13.7%] and placebo, 5 of 130 [3.8%]), glucosuria (avagacestat, 76 of 131 [58.0%] and placebo, 11 of 129 [8.5%]), and inorganic phosphorous (avagacestat, 50 of 116 [43.1%] and placebo, 11 of 125 [8.8%]) (eTable 3 in Supplement 2). Mean effects on renal function and electrolyte values normalized on discontinuation of the drug during follow-up.

**Success of Screening Algorithm: Progression to Dementia Rates**

Patients in the randomized (biomarker-positive) cohort progressed to dementia at a higher rate than did the observational (biomarker-negative) cohort (Figure 2). Time-to-progression analysis did not suggest long-term differences between the randomized groups (hazard ratio, 1.354; 95% CI, 0.825-2.222). In the randomized group, the overall rates of progression were 8.9% and 19.7% for placebo and avagacestat, respectively, after 1 year and 29.0% and 30.7% for placebo and avagacestat, respectively, after 2 years. Longitudinal decline in the randomized groups was greater than in the observational cohort, as were rates of progression (4.9% after 1 year and 6.5% after 2 years).

**Clinical Outcome Measures**

Clinical outcomes across treatment arms are summarized in Table 3. There were no statistically significant differences compared with placebo among treatment groups with regard to the Alzheimer’s Disease Cooperative Study Activities of Daily Living MCI version, Alzheimer’s Disease Assessment Scale–cognitive subscale, Mini-Mental State Examination, and Clinical Dementia Rating Sum of Boxes outcome measures. Differential effects in subgroups based on APOE4 carrier status or background cholinesterase inhibitor use were not apparent. There were no statistically significant treatment differences by geographic region.

**CSF Biomarkers and Volumetric MRI**

The CSF Aβ40 biomarker results provided modest evidence of target engagement at the avagacestat, 50-mg/d, dose (eTable 4 in Supplement 2). At weeks 24 and 104, lowering of CSF Aβ40...
by 10% to 15% was noted for all dose groups. A reduction of 5% to 9% was noted in CSF Aβ42, which was not significantly different from placebo levels.

Higher atrophy rates were observed in the avagacestat arm vs the placebo arm for whole brain, ventricles, and hippocampus as measured by volumetric MRI. The differences were significant at weeks 24 and 56 and were not significant at week 104, probably owing to the lower number of observations (eTable 5 in Supplement 2). This finding was consistent with previously reported brain atrophy results with other amyloid-lowering treatments. The observational cohort (20 participants) demonstrated approximately half the change in volume across all 3 regions at week 104 (±12 weeks) compared with the randomized cohort.

PET Substudy
The concordance between qualitative amyloid-positive PET and pathologic CSF was 87.7% (κ = 0.68; 95% CI, 0.48-0.87) (eFigure in Supplement 2). We found a statistically significant correlation between the mean standard uptake values across 4 areas of interest and the CSF total tau to Aβ42 ratio at baseline. Similar Spearman rank correlation coefficients were also observed with each of the 4 regions: posterior cingulate (0.41; P < .001), lateral temporal (0.53; P < .001), frontal lobe (0.52; P < .001), and parietal lobe (0.47, P < .001) (eTable 6 and eTable 7 in Supplement 2).

Discussion
The aims of this study were to assess the safety of avagacestat and demonstrate the feasibility of prospectively enriching a PDAD clinical trial population using biomarker criteria consistent with AD pathology. The study met its clinical trial enrichment aims but failed to demonstrate clinically meaningful pharmacodynamic effects of avagacestat.

Avagacestat treatment did not demonstrate signals of efficacy and was associated with dose-limiting effects on tolerability and safety. Doses of avagacestat, 50 mg/d, were well tolerated during long-term administration while doses of 125 mg/d were not tolerable and led to unacceptable rates of treatment discontinuation. Safety and tolerability of avagacestat, 50 mg/d, used for up to 46 months in the PDAD population were consistent with those observed in an earlier population with mild to moderate AD who received the drug for 6 months.6 Although avagacestat was developed for its amyloid precursor protein selectivity over Notch, some of the AEs observed were likely related to Notch inhibition. In animal models, Notch inhibition is associated with goblet cell metaplasia and NMSCs.39 In the present study, there were more cases of mild to severe colitis and NMSC among the avagacestat group than in the placebo arm. Similar trends were previously observed with avagacestat and semagacestat.40 The risk of incident NMSC appeared to abate 3 to 6 months after treatment discontinuation.

Functional effects on proximal renal tubule cell function (as measured by asymptomatic laboratory changes in glycosuria, calcium, phosphate, and uric acid) were observed in this study, as described previously.10 These effects included elevated rates of glycosuria accompanied by clinically nonsignificant decreases in serum uric acid, calcium, and potassium levels.

Although phase 1 studies of avagacestat that were 1 month in duration suggested tolerable doses to achieve a mean 60% to 65% reduction in CSF amyloid levels, significant AEs were observed in the present phase 2 trial after longer-term use of the drug and necessitated dose reduction that was associated with only a modest effect on amyloid production. Avagacestat, 50 mg/d, minimally reduced (10%-15%) CSF Aβ40 levels. No diurnal variation was apparent, potentially attributable to the half-life of avagacestat being more than 48 hours.

No significant differences were observed in key clinical outcome measures across treatment groups. The lack of a favorable clinical effect suggested a low likelihood that avagacestat would demonstrate meaningful clinical effects in long-term, large-scale studies. Progression to dementia was not significantly different between the avagacestat and placebo groups.

Table 2. Summary of AEs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 131)</th>
<th>Avagacestat (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE, No. (%)</td>
<td>31 (23.7)</td>
<td>49 (37.1)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1 (0.8)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>GI tract disorders</td>
<td>1 (0.8)</td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>12 (9.2)</td>
<td>23 (17.4)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>4 (3.1)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Any AE leading to treatment discontinuation, No. (%)</td>
<td>13 (9.9)</td>
<td>46 (34.8)</td>
</tr>
<tr>
<td>Any GI tract AE</td>
<td>3 (2.3)</td>
<td>19 (14.4)</td>
</tr>
<tr>
<td>Any skin AE</td>
<td>1 (0.8)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Any nervous system disorder</td>
<td>2 (1.5)</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td>Any AE, No. (%)</td>
<td>110 (84.0)</td>
<td>126 (95.5)</td>
</tr>
<tr>
<td>Any GI tract AE</td>
<td>48 (36.6)</td>
<td>87 (65.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (18.3)</td>
<td>41 (31.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (3.1)</td>
<td>35 (26.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.5)</td>
<td>14 (10.6)</td>
</tr>
<tr>
<td>Any skin AE</td>
<td>50 (38.2)</td>
<td>72 (54.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (6.1)</td>
<td>27 (20.5)</td>
</tr>
<tr>
<td>Any neoplasms</td>
<td>20 (15.3)</td>
<td>25 (18.9)</td>
</tr>
<tr>
<td>BCC</td>
<td>5 (3.8)</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td>SCC skin</td>
<td>1 (0.8)</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td>SCC</td>
<td>0</td>
<td>8 (6.1)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Other AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (6.8)</td>
<td>24 (18.2)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>2 (1.5)</td>
<td>14 (10.6)</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>3 (2.3)</td>
<td>14 (10.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 (9.9)</td>
<td>20 (15.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>11 (8.4)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12 (9.2)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Cerebral microbleed</td>
<td>2 (1.5)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Vasogenic edema</td>
<td>1 (0.8)</td>
<td>3 (2.3)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; GI, gastrointestinal; SAE, serious AE; SCC, squamous cell carcinoma.
groups. However, avagacestat led to higher brain, ventricular, and hippocampal atrophy rates. Similar increases in brain atrophy rates have been reported with other amyloid-lowering treatments, such as AN1792\textsuperscript{36} and bapineuzumab.\textsuperscript{37} Although amyloid level lowering would be expected to provide a clinical benefit, it remains uncertain what degree of amy-

Figure 2. Cerebrospinal Fluid (CSF) Biomarker Entry Criteria on Time to Adjudicated Progression to Dementia

Table 3. Mean Changes From Baseline to Weeks 24, 56, and 104 in Cognitive and Functional Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 131)</th>
<th>Avagacestat (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 24</td>
<td>Week 56</td>
</tr>
<tr>
<td>ADAS-Cog score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>114</td>
<td>102</td>
</tr>
<tr>
<td>Mean change (SE)</td>
<td>1.02 (0.38)</td>
<td>1.15 (0.46)</td>
</tr>
<tr>
<td>Difference vs placebo</td>
<td>0.12</td>
<td>−0.36</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADCS ADL-MCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>107</td>
<td>101</td>
</tr>
<tr>
<td>Mean change (SE)</td>
<td>0.09 (0.42)</td>
<td>−1.36 (0.52)</td>
</tr>
<tr>
<td>Difference vs placebo</td>
<td>−1.28</td>
<td>−0.74</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR-SB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>111</td>
<td>103</td>
</tr>
<tr>
<td>Mean change (SE)</td>
<td>0.13 (0.12)</td>
<td>0.76 (0.13)</td>
</tr>
<tr>
<td>Difference vs placebo</td>
<td>0.24</td>
<td>−0.02</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>114</td>
<td>103</td>
</tr>
<tr>
<td>Mean change (SE)</td>
<td>−1.20 (0.23)</td>
<td>−1.48 (0.32)</td>
</tr>
<tr>
<td>Difference vs placebo</td>
<td>−0.39</td>
<td>−0.83</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
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</table>

Abbreviations: ADCS-MCI-ADL, Alzheimer’s Disease Cooperative Study Mild Cognitive Impairment Activities of Daily Living; ADAS-Cog, Alzheimer’s Disease Assessment Scale–Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination.

* Estimates are based on a repeated-measures model including terms for treatment, assessment time, treatment by time interaction, baseline value, apolipoprotein E ε4 carrier status, and cholinesterase inhibitor use at baseline. For all statistical analyses, no adjustments were made for multiple comparisons. Nominal P values are provided for descriptive purposes and should be interpreted with caution.
lloid reduction would be adequate to achieve positive effects on clinical outcome measures. Participants in the biomarker-positive group exhibited clinical decline, including progression to dementia that was greater than that observed in the biomarker-negative observational cohort, confirming the usefulness of PDAD criteria. Objective MRI measurements further support the clinical differentiation of the biomarker-positive vs biomarker-negative groups. The MRI volume change observed in the biomarker-negative cohort was approximately half that observed in the biomarker-positive group. Finally, we confirmed previous observations\(^2\) that CSF amyloid levels correlated with PET-amyloid imaging. This finding suggests that CSF and amyloid PET biomarkers may be used interchangeably to identify PDAD.

The high screening failure rates among participants in our study suggests that efforts to refine entry criteria are needed to improve recruitment efficiency in clinical trials; however, changes to screening criteria must be carefully considered so as not to negatively affect the rates of cognitive decline or progression to dementia. Limitations of the present study include its small sample size, high screen failure rate in enrollment of participants, use of a research CSF amyloid assay not approved as a diagnostic test, and high intra-individual variability associated with the use of clinical rating scales. Additionally, investigators and study participants were aware of CSF biomarker results, which may have biased cognitive assessments in the biomarker-negative observational cohort. However, objective evidence, including MRI volumes (automated and semi-automated analytic procedures performed by blinded readers) as well as a review of all cases of clinical progression to dementia by an independent adjudication committee, support the observed differences in disease course between the biomarker-positive and -negative groups.

The enrichment strategy of enrolling participants with PDAD who had a specific hippocampal pattern of memory impairment, an MRI pattern consistent with AD, and a supporting molecular diagnostic CSF biomarker pattern was successful in achieving the expected increased rates of dementia progression during the trial. However, not all participants with PDAD progressed to dementia during the study period. Long-term follow-up and additional prospective studies are needed to further validate the construct of PDAD vs simply describing such populations as “CSF-positive patients with MCI.” Additional analyses of this study will add insights on the relative value of various baseline biomarkers (eg, patterns of atrophy on MRI, CSF biomarker profile, and PET radiotracer amyloid imaging) in predicting clinical progression.

Conclusions
This trial failed to demonstrate clinically meaningful effects of avagacestat on CSF amyloid biomarkers or clinical outcome measures. Although avagacestat was relatively well tolerated at 50 mg/d, minimal pharmacodynamic effects on amyloid reduction were observed at that dose. A higher incidence of AEs and untenable discontinuation rates at 125 mg/d precluded evaluation of avagacestat at doses associated with more robust reductions in CSF amyloid.

We believe this to be the first prospective randomized clinical trial in an amyloid biomarker–confirmed PDAD population. The findings provide important validation for the recently evolved nosology of prodromal stages of AD. The trial design was unique in that the biomarker criteria were pre-defined and each patient’s CSF sample was analyzed in real-time prior to randomization. Although our study failed to demonstrate that avagacestat meaningfully affects the course of AD, the results show the feasibility of prospectively identifying PDAD and enriching a clinical trial population with patients at increased risk of progressing to dementia.
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REFERENCES

Targeting Prodromal Alzheimer Disease With Avagacestat

Original Investigation Research

Assessment of Instrumental Activities of Daily Living


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