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Permalink

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Journal

JAMA Neurology, 72(11)

ISSN

2168-6149

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Publication Date

2015-11-01

DOI

10.1001/jamaneurol.2015.0607

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Peer reviewed

Original Investigation | CLINICAL TRIAL

Targeting Prodromal Alzheimer Disease With Avagacestat

A Randomized Clinical Trial

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IMPORTANCE 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% ($\kappa = 0.68$; 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](https://clinicaltrials.gov/ct2/show/study/NCT00890890)

JAMA Neurol. 2015;72(11):1324-1333. doi:10.1001/jamaneurol.2015.0607
Published online September 28, 2015.

 Supplemental content at jamaneurology.com

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Section Editor: Ira Shoulson, MD.

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 study⁵ 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 (A β) synthesis relative to processing of Notch substrates. Phase 1 studies^{6,7} demonstrated that avagacestat decreased A β 40 and A β 42 levels at dosages expected to be tolerated in patients. Given that A β 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.¹⁰⁻¹⁵ 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 moni-

tored 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 MCI¹⁸ 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 (A β 42 level of <200 pg/mL or total tau to A β 42 ratio of \geq 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 Test²¹ (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 Examination²² score between 24 and 30, and Clinical Dementia Rating²³ 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).

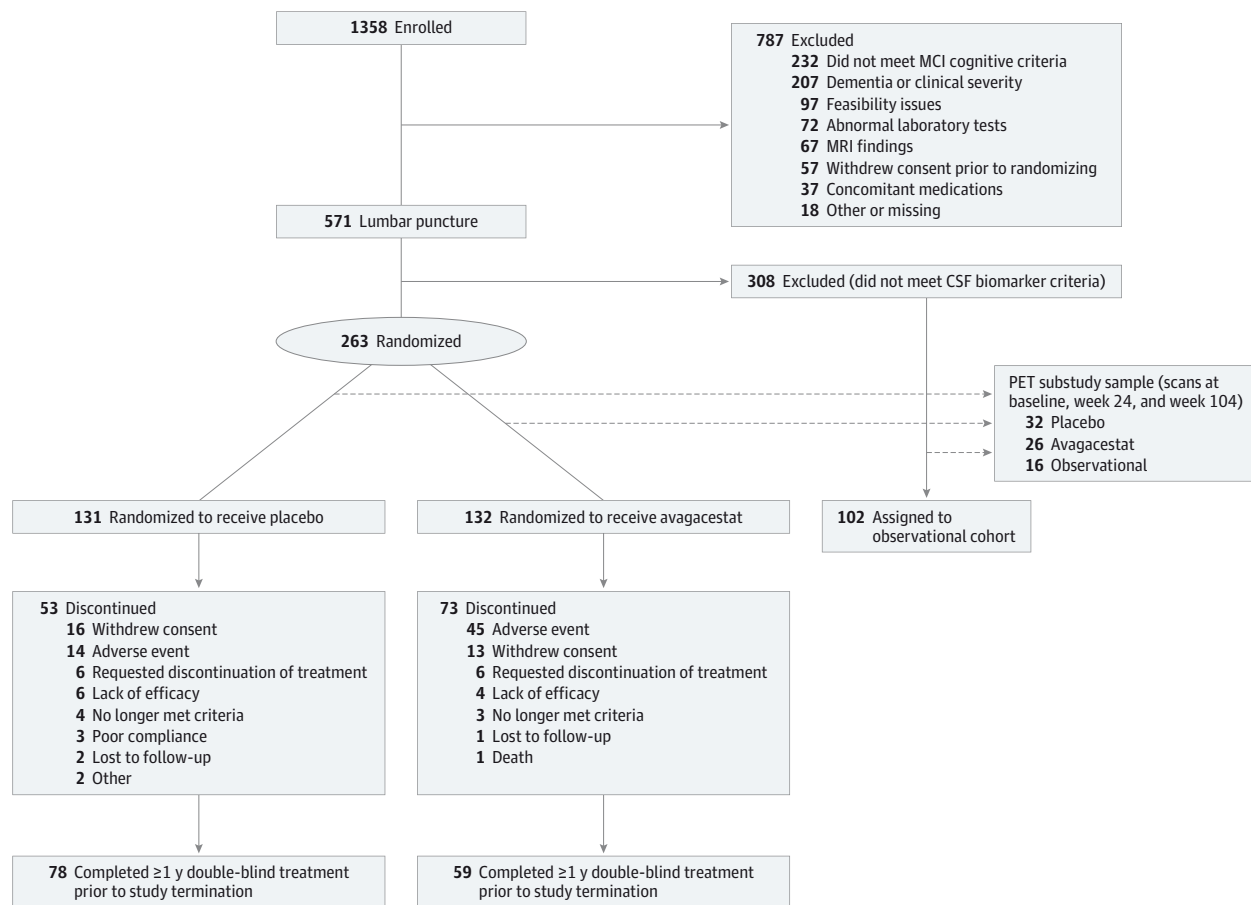
Exclusion criteria were as follows: (1) presence of a condition other than AD to explain the patient's cognitive symptoms, (2) previous stroke, (3) positive fecal test for occult blood at screening, (4) chronic inflammatory bowel disease, (5) frequent diarrhea or loose stools, (6) vitamin B₁₂ or folate deficiency, (7) Geriatric Depression Scale²⁴ score of 6 or higher at screening (suggesting clinical depression), and (8) exposure to an investigational agent related to A β 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-

Figure 1. CONSORT Flow Diagram: Patient Disposition



Patient flow in the randomized treatment phase (avagacestat vs placebo) for cerebrospinal fluid (CSF) biomarker-positive participants and the observational cohort for CSF biomarker-negative participants. After all participants in the treatment phase had the opportunity to receive double-blind treatment for at

least 1 year, the study was terminated early after an interim analysis suggested a lack of efficacy on key clinical outcome measures. MCI indicates mild cognitive impairment; MRI, magnetic resonance imaging; and PET, positron emission tomography.

diagrams, 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 Association²⁹ 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 A β 1-42 were analyzed (Luminex xMap technique, INNO-BIA AlzBio3 kit; Innogenetics) at a central laboratory. Levels of A β 40 and A β 42 were measured using electrochemiluminescence detection technology in multiplex format (Meso Scale Discovery). Cerebrospinal fluid levels of A β 1-42 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.¹⁰ Results were evaluated centrally (BioClinica). Whole-brain and ventricular atrophy rates were computed using tensor-based morphometry,³⁰⁻³² and hippocampal atrophy was calculated using hippocampus boundary shift integral.³³

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^{34,35} 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 ϵ 4 (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 was 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 A β 42 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 A β 42 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

Table 1. Baseline Demographics, Clinical Characteristics, and CSF Biomarker Criteria: Randomized Sample

Characteristic	Placebo (n = 131)	Avagacestat (n = 132)	Total (N = 263)
Age, mean (SD), y	71.6 (7.78)	71.9 (7.63)	71.7 (7.7)
Male sex, %	58	55.3	57
Educational level, mean (SD), y	15.15 (3.482)	14.95 (3.549)	15.05 (3.510)
APOE4 carrier, No. (%)	88 (67.2)	90 (68.2)	178 (67.7)
Cognition evaluation scores, mean (SD)			
ADAS-Cog	11.2 (4.5)	11.4 (4.80)	11.3 (4.65)
ADCS ADL-MCI	45.7 (4.76)	44.6 (5.26)	45.2 (5.04)
CDR-SB	1.93 (0.966)	1.95 (1.027)	1.94 (0.995)
MMSE	27.1 (1.67)	27.0 (1.91)	27.0 (1.79)
Summary of A β 42, tau, and CSF criteria			
A β 42, mean (range), pg/mL ^a	206.7 (44-387)	197.7 (81-441)	202.2 (44-441)
Tau, mean (range), pg/mL ^a	127.7 (36-571)	127.0 (34-414)	127.3 (34-571)
A β 42 <200 pg/mL, No./total No. (%)	61/131 (46.6)	77/132 (58.3)	138/263 (52.5)
Tau/A β 42 \geq 0.39, No./total No. (%)	116/130 (89.2)	119/132 (90.2)	235/262 (89.7)
A β 42 and ratio of A β 42 <200 pg/mL and tau \geq 0.39, No./total No. (%)	48/130 (36.9)	64/132 (48.5)	112/262 (42.7)

Abbreviations:

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; APOE4, apolipoprotein E ϵ 4; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

^a Mean value is based on the geometric mean.

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 NMSC. 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 to creatinine or protein to creatinine ratios were found (eTable 2 in Supplement 2). Laboratory test abnormalities occurring in the avagacestat group at greater than twice the frequency 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 in-

organic 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 A β 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 A β 40

by 10% to 15% was noted for all dose groups. A reduction of 5% to 9% was noted in CSF A β 42, 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^{36,37} 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 (\pm 12 weeks) compared with the randomized cohort.

PET Substudy

The concordance between qualitative amyloid-positive PET and pathologic CSF was 87.7% ($\kappa = 0.68$; 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 A β 42 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.¹⁰ 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 metaplasia³⁸ 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 avagacestat¹⁰ 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

Table 2. Summary of AEs

Characteristic	Placebo (n = 131)	Avagacestat (n = 132)
Any SAE, No. (%)	31 (23.7)	49 (37.1)
Cardiac disorders	1 (0.8)	3 (2.3)
GI tract disorders	1 (0.8)	6 (3.5)
Neoplasms	12 (9.2)	23 (17.4)
Injury, poisoning, and procedural complications	4 (3.1)	7 (5.3)
Any AE leading to treatment discontinuation, No. (%)	13 (9.9)	46 (34.8)
Any GI tract AE	3 (2.3)	19 (14.4)
Any skin AE	1 (0.8)	7 (5.3)
Any nervous system disorder	2 (1.5)	8 (6.1)
Any AE, No. (%)	110 (84.0)	126 (95.5)
Any GI tract AE	48 (36.6)	87 (65.9)
Diarrhea	24 (18.3)	41 (31.1)
Nausea	4 (3.1)	35 (26.5)
Vomiting	2 (1.5)	14 (10.6)
Any skin AE	50 (38.2)	72 (54.5)
Rash	8 (6.1)	27 (20.5)
Any neoplasms	20 (15.3)	25 (18.9)
BCC	5 (3.8)	8 (6.1)
SCC skin	1 (0.8)	8 (6.1)
SCC	0	8 (6.1)
Malignant melanoma	1 (0.8)	0
Other AEs		
Fatigue	9 (6.8)	24 (18.2)
Weight decreased	2 (1.5)	14 (10.6)
Appetite decreased	3 (2.3)	14 (10.6)
Dizziness	13 (9.9)	20 (15.2)
Depression	11 (8.4)	7 (5.3)
Anxiety	12 (9.2)	4 (3.0)
Cerebral microbleed	2 (1.5)	4 (3.0)
Vasogenic edema	1 (0.8)	3 (2.3)

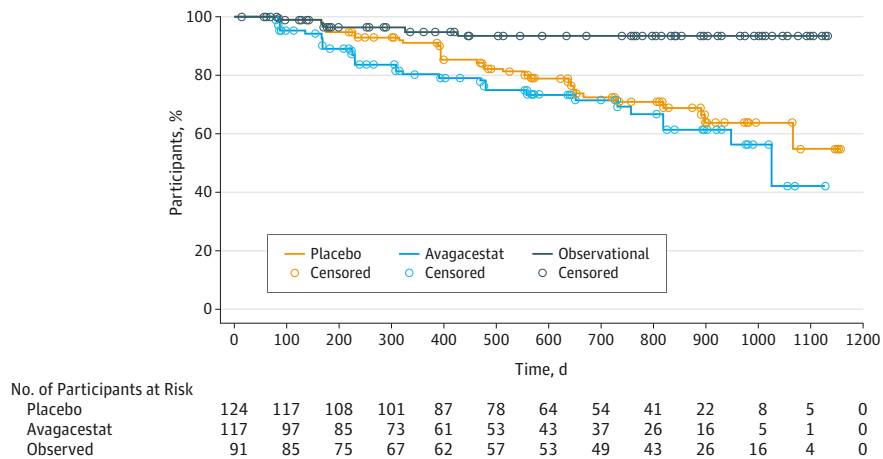
Abbreviations: AE, adverse event; BCC, basal cell carcinoma; GI, gastrointestinal; SAE, serious AE; SCC, squamous cell carcinoma.

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 studies⁴¹ 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 A β 40 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

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



Number of study participants at risk at each time point who had not progressed to dementia. All participants met clinical criteria for mild cognitive impairment but only those in the randomized arms (avagacestat and placebo) met pathologic CSF biomarker criteria cutoff values of Aβ42 level of less than 200 pg/mL or total tau [T-tau]:Aβ42 ratio of 0.39 or greater. Observational

cohort participants did not meet pathologic CSF criteria at study entry. Progression from prodromal AD to dementia was confirmed by an independent adjudication committee. At 2 years, rates of progression to dementia were 30.7% in avagacestat participants, 29.0% in the placebo group, and 6.5% in the observational cohort.

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

Characteristic	Placebo (n = 131)			Avagacestat (n = 132)		
	Week 24	Week 56	Week 104	Week 24	Week 56	Week 104
ADAS-Cog score						
No. of patients	114	102	66	100	77	45
Mean change (SE)	1.02 (0.38)	1.15 (0.46)	2.52 (0.72)	1.14 (0.41)	1.52 (0.52)	3.15 (0.83)
Difference vs placebo				0.12	-0.36	-0.63
P value				.83	.59	.57
ADCS ADL-MCI score						
No. of patients	107	101	64	98	75	45
Mean change (SE)	0.09 (0.42)	-1.36 (0.52)	-3.57 (0.83)	-1.28 (0.45)	-2.10 (0.57)	-4.41 (0.97)
Difference vs placebo				-1.28	-0.74	-0.84
P value				.02	.33	.51
CDR-SB						
No. of patients	111	103	66	100	76	45
Mean change (SE)	0.13 (0.12)	0.76 (0.13)	1.65 (0.25)	0.35 (0.13)	0.74 (0.15)	1.12 (0.29)
Difference vs placebo				0.24	-0.02	-0.20
P value				.20	.90	.16
MMSE score						
No. of patients	114	103	67	99	77	46
Mean change (SE)	-1.20 (0.23)	-1.48 (0.32)	-2.24 (0.42)	-1.60 (0.25)	-2.39 (0.36)	-2.95 (0.49)
Difference vs placebo				-0.39	-0.83	-0.71
P value				.23	.08	.27

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.

^a 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.

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 AN1792³⁶ and bapineuzumab.³⁷ Although amyloid level lowering would be expected to provide a clinical benefit, it remains uncertain what degree of amy-

loid 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 observations⁴² 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 intraindividual 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 individuals with PDAD who had a specific hippocampal pattern of memory im-

pairment, 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 predefined 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.

ARTICLE INFORMATION

Accepted for Publication: March 20, 2015.

Published Online: September 28, 2015.
doi:10.1001/jamaneurol.2015.0607.

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University Langone Medical Center, New York (Ferris); BioClinica Inc, Newtown, Pennsylvania (Pachai, Bracoud); Avid Radiopharmaceuticals, Philadelphia, Pennsylvania (Mintun); Mary S. Easton Center for Alzheimer’s Disease Research, University of California at Los Angeles (Grill); Institute for Neurodegenerative Disorders, New Haven, Connecticut (Marek, Seibyl); University of British Columbia, Vancouver, British Columbia, Canada (Feldman).

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Obtained funding: Coric, Berman.

Administrative, technical, or material support: Coric, van Dyck, Andreasen, Brody, Soininen, Ferris, Colby, Soares, Marek, Seibyl, Cedarbaum, Berman.

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Conflict of Interest Disclosures: Drs Coric, Pilcher, Dockens, Soares, Luo, Cedarbaum, Albright, Feldman, and Berman; Mss Colby and Kerselaers; and Mr Kaplita were or are employees of Bristol-Myers Squibb and own or have owned stock in the company. Dr Salloway was a site principal investigator and consulted with Bristol-Myers Squibb on the design and analysis of the present study; has received grants and personal fees from Janssen Alzheimer Immunotherapy, Pfizer, Biogen, Merck, Eli Lilly and Company, Roche, and Genentech; has received grants from GE Healthcare, Avid Radiopharmaceuticals, and Functional Neuromodulation; and has received

personal fees from Astra Zeneca and Piramal, outside the submitted work. Dr van Dyck has served as a consultant to Elan, Janssen, Pfizer, Bristol-Myers Squibb, Roche, and Abbvie, and has received research support from Elan, Bristol-Myers Squibb, Eli Lilly and Company, Wyeth, Pfizer, Janssen, Medivation, Baxter, Eisai, Biogen Idec, Merck, Roche, Genentech, TauRx, Forum, Toyama, and grants from the National Institutes of Health (National Center for Advancing Translational Sciences UH3 TR000967-02 [principal investigator], National Institute of Neurological Disorders and Stroke R01 NS087568 [coinvestigator], and National Institute on Aging R01 AG046543 [coinvestigator]). Mr Dubois has served as a paid consultant to Bristol-Myers Squibb. Dr Andreasen has served as a paid consultant for Lundbeck, Axon, Eli Lilly and Company, and Resverlogix. Dr Soininen has served as a consultant for ACImmune and Orion Pharma. Dr Thein owns and operates a for-profit clinical trials research clinic and has conducted trials and/or consulted for Bristol-Myers Squibb, Merck, Genentech, Pfizer, Eli Lilly and Company, Takeda, Novartis, Biogen, Osmotica, Accera, Tau Rx, Forum, Roche, Astra-Zeneca, Avanir, Lundbeck, Janssen, Novo Nordisk, Baxter, Eisai, Aerial, and other companies. Dr Mintun is an employee of Avid Radiopharmaceuticals. Dr Grill serves as site investigator for clinical trials sponsored by Avanir, Biogen Idec, Eli Lilly and Company, Genentech, Janssen Alzheimer Immunotherapy, Bristol-Myers Squibb, and the Alzheimer's Disease Cooperative Study. Drs Marek and Seibyl have equity interest in Molecular Neuroimaging LLC and have served as consultants to Bristol-Myers Squibb. Dr Marek has also served as a consultant to GE Healthcare, Eli Lilly and Company, Merck, Navidea, Piramal, Pfizer, Sanofi, Roche, and Lysosomal Therapeutics Incorporated. During this clinical trial, Dr Feldman was a full-time employee at Bristol-Meyers Squibb (2009-2011) on leave from University of British Columbia (UBC). In this role, he received salary and stocks/stock options from Bristol-Meyers Squibb. In the past 3 years, he has provided consultative services through UBC with Eli Lilly and Company, Kyowa Hakko Kirin, General Electric Health Care, Biogen Idec, Eisai, Genentech, and Arena Pharmaceuticals, with no personal funds being received for these services. In the past 3 years, his UBC research group has participated in or continues to participate in clinical trials sponsored by Roche, Eli Lilly and Company, Genentech, and Baxter. No other disclosures were reported.

Funding/Support: This study was funded by Bristol-Myers Squibb.

Role of the Funder/Sponsor: Employees of Bristol-Myers Squibb participated in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We acknowledge with deep appreciation all the patients, study partners, and investigative teams who participated in the CN156-018 trial. We recognize the efforts of the principal investigators and their clinical staff, including Niels Andreasen, MD, PhD, Piero G. Antuono, MD, Jeffrey Apter, MD, Serge Belliard, MD, Charles B. Bernick, MD, Michael J. Borrie, MD, John Brockington, MD, Mark Brody, MD, Craig

Curtis, MD, Paul Dautzenberg, MD, P. Murali Doraiswamy, MD, Eugene Duboff, Martin Farlow, MD, Mildred Farmer, MD, Steven Ferris, PhD, Stephen Flitman, MD, Tamas Fulop, MD, Gary Gerard, MD, Nupur Ghoshal, MD, PhD, Joshua Grill, PhD, George Grossberg, MD, Danilo Antonio Guzman, MD, John M. Heath, MD, Lawrence Honig, MD, PhD, Ging-Yuek Robin Hsiung, MD, M. Saleem Ismail, MD, Peter Johannsen, MD, Beverly Jones, MD, Michael Jonsson, MD, Ron Keren, MD, Bruce Kohrman, MD, David Margolin, MD, PhD, Michael Mega, MD, Lennart Minthon, MD, Trenton Moyer, MD, Patricia Naslund, MD, Ziad Nasreddine, MD, Mahmoud Okasha, MD, Omid Omidvar, MD, Jean Marc Orgogozo, MD, Nader Oskooilar, MD, PhD, Florence Pasquier, PhD, David G. Patry, MD, Joseph Pittard, MD, Steven G. Potkin, MD, Joseph Quinn, MD, Michael S. Rafii, MD, PhD, Ralph Richter, MD, Juha Rinne, MD, PhD, Joel Ross, MD, Olivier Rouaud, PhD, Marwan Sabbagh, MD, Stephen Salloway, MD, MS, Douglas Scharre, MD, Sanjiv Sharma, MD, Thomas Shiovitz, MD, Hilikka Soininen, MD, PhD, Reisa A. Sperling, MD, Louise Taber, MD, Pierre Tariot, MD, Leslie Taylor, MD, Stephen Thein, PhD, Christopher van Dyck, Nick G. Vatakis, MD, Bruno Vellas, MD, Martine Verclletto, PhD, Franklin Watkins, MD, Myron Weiner, MD, Richard Weisler, MD, John Wherrett, MD, Kerri Louise Wilks, MD, and Jaron L. Winston, MD. We also thank the Avagacestat Development Team for their outstanding implementation of this study protocol, including Caroline Clairmont, PhD, Kimberly Gentile, BS, James Hazel, BSN, RN, Laura Ruggiero, BS, Stacey Prince, BA, Judith Braga, MPH, Olive Watson-Coleman, RN, MPH, Kimberly Marmor, BA, Timothy McCormack, BS, Jaclyn Marin, BA, Katherine Lears, BS, Tamara Bratt, MHS, Randy Slemmon, PhD, Sue Behling, BS, MT, Christina Smith, PhD, Kathleen Szymczak, BS, Christine Lesczczynski, RMA, and Kevin Ruddy, BS (all Bristol-Myers Squibb). We acknowledge the efforts of the Data Monitoring Committee (Serge Gauthier, MD, F Loren A. Laine, MD, and Daniel Zelterman, PhD) and Diagnosis Adjudication Committee (Norman Foster, MD, DAC, Howard Chertkow, MD, Ranjan Dua, MD, and Matthew Gabel, PhD), Elliot Sigal, MD, PhD, Brian Daniels, MD, Doug Manion, MD, and Jane Tiller, MD, provided scientific guidance and insight (Bristol-Myers Squibb). Editorial and writing assistance was provided by Brian Atkinson, PhD (Bristol-Myers Squibb), and Kate Jesien, PhD (Caudex Medical Inc). None of these individuals received financial compensation outside of their usual salaries.

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