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Valacyclovir Treatment of Early Symptomatic Alzheimer Disease
The VALAD Randomized Clinical Trial

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IMPORTANCE Neuroscientific, epidemiological, and electronic health record studies implicate herpes simplex virus (HSV) as potentially etiological for Alzheimer disease (AD).

OBJECTIVE To compare the efficacy and adverse effects of valacyclovir vs placebo in participants with early symptomatic AD and HSV seropositivity (HSV-1 or HSV-2).

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial included adults with a clinical diagnosis of probable AD or a clinical diagnosis of mild cognitive impairment with positive biomarkers for AD, a positive serum antibody test (IgG or IgM) for HSV-1 or HSV-2, and a Mini-Mental State Examination score of 18 to 28. The trial was conducted at 3 US outpatient clinics specializing in memory disorders. Recruitment occurred from January 2018 to May 2022; the last follow-up occurred in September 2024.

INTERVENTION Either 4 g/d of valacyclovir (n = 60) or matching placebo (n = 60).

MAIN OUTCOMES AND MEASURES The primary outcome was least-squares mean (LSM) change at 78 weeks in the 11-item Alzheimer's Disease Assessment Scale Cognitive (ADAS-Cognitive) Subscale score (range, 0-70; higher scores indicate greater impairment). The secondary outcomes were LSM change in the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) Scale score; LSM change in the ^{18}F-florbetapir amyloid positron emission tomography (PET) standardized uptake value ratio (SUVR; higher scores indicate higher amyloid levels) for 6 brain regions (medial orbitofrontal, anterior cingulate, parietal lobe, posterior cingulate, temporal lobe, and precuneus); and LSM change in ^{18}F-MK-6240 tau PET medial temporal SUVR (higher scores indicate higher tau levels) for 4 brain regions (amygdala, hippocampus, entorhinal, and parahippocampus). The frequency of adverse events was the safety outcome.

RESULTS Of the 120 participants (mean age, 71.4 [SD, 8.6] years; 55% were female), 93 (77.5%) completed the trial. At 78 weeks, the LSM change in the 11-item ADAS-Cognitive Subscale score was 10.86 (95% CI, 8.80 to 12.91) in the valacyclovir group vs 6.92 (95% CI, 4.88 to 8.97) in the placebo group, indicating greater cognitive worsening with valacyclovir than placebo (between-group difference, 3.93 [95% CI, 1.03 to 6.83]; P = .01). The LSM change in the ADCS-ADL Scale score at 78 weeks was −13.78 (95% CI, −17.00 to −10.56) in the valacyclovir group vs −10.16 (95% CI, −13.37 to −6.96) in the placebo group (between-group difference, −3.62 [95% CI, −8.16 to 0.93]). At 78 weeks, the LSM change in the ^{18}F-florbetapir amyloid PET SUVR was 0.03 (95% CI, −0.04 to 0.10) in the valacyclovir group vs 0.01 (95% CI, −0.06 to 0.08) in the placebo group (between-group difference, 0.02 [95% CI, −0.08 to 0.12]). The LSM change in the ^{18}F-MK-6240 tau PET medial temporal SUVR at 78 weeks was 0.07 (95% CI, −0.06 to 0.19) in the valacyclovir group vs −0.04 (95% CI, −0.15 to 0.07) in the placebo group (between-group difference, 0.11 [95% CI, −0.06 to 0.28]). The most common adverse events were elevated serum creatinine level (5 participants [8.3%] in the valacyclovir group vs 2 participants [3.3%] in the placebo group) and COVID-19 infection (3 [5%] vs 2 [3.3%], respectively).

CONCLUSIONS AND RELEVANCE Valacyclovir was not efficacious with cognitive worsening for the primary outcome and it is not recommended to treat individuals with early symptomatic AD and HSV seropositivity.

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Visual Abstract
Research Summary
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Infectious diseases may be etiologic or contribute to the pathogenesis of Alzheimer disease (AD).[1-3] Among the implicated infectious agents are herpes simplex virus type 1 (HSV-1), which primarily causes oral herpes, and to a lesser extent HSV type 2 (HSV-2), which primarily causes genital herpes. After an initial oral infection, HSV-1 becomes latent in the trigeminal ganglion and can enter the brain via retrograde axonal transport, infiltrating the locus coeruleus and migrating to the temporal lobe, potentially contributing to neurodegeneration and AD pathology.[2,4] Among individuals infected with HSV, DNA containing HSV has been detected in postmortem brain tissue samples of trigeminal and olfactory ganglia.[5]

β-Amyloid plaques and tau neurofibrillary tangles are neuropathological features of AD. In animal models, HSV-1 infection of neuronal and glial cells triggers a decrease in amyloid precursor protein, an increase in intracellular levels of amyloid β-protein, and phosphorylation of tau protein.[6-8] An autopsy study of patients with AD demonstrated that 90% of amyloid plaques contained HSV-1 DNA, and 72% of the total HSV-1 DNA in the brain was associated with these plaques.[6] The effects of HSV-2 and HSV-1 are similar on amyloid and tau proteins.[9] The HSV-1 proteins were present in hippocampal neurons of mice infected intraperitoneally with HSV-1, indicating that blood-borne transmission may occur with both HSV-1 and HSV-2, and explain the 10% of herpes simplex encephalitis cases caused by HSV-2.[10] In cell cultures, the antiviral medications acyclovir, penciclovir, and foscarnet reduced HSV-1 particles and the accumulation of both amyloid β-protein and phosphorylated tau.[11]

The majority of older adults have had HSV infections.[12] Compared with individuals seronegative to HSV, individuals seropositive to HSV showed odds ratios for AD ranging from 1 to 3 in clinical and epidemiological studies[13-15]; this association was not found in patients with autosomal-dominant AD.[16] In a study conducted in Taiwan based on the electronic health records for 8262 people, medication treatment for HSV infection was associated with decreased risk of dementia (hazard ratio, 0.09) compared with no treatment.[17] In contrast, the association of medication treatment for HSV infection with decreased dementia risk was not found consistently across 4 European countries that contributed 2.5-million electronic health records.[18]

In an 18-week pilot trial studying schizophrenia, the widely used drug valacyclovir for HSV infection was superior vs placebo on tests of memory.[19] In a 4-week, open-label, pilot study including 33 participants with AD and HSV IgG seropositivity, which indicates old infection, 3 g/d of valacyclovir was administered safely with measurable concentrations of acyclovir (main metabolite of valacyclovir) in cerebrospinal fluid but without significant changes in total tau and neurofilament light levels in cerebrospinal fluid.[20] Placebo-controlled clinical trials of antiviral medications for HSV infection repurposed to treat AD have not been conducted.

We conducted a phase 2, randomized clinical trial (Valacyclovir Treatment of Alzheimer's Disease; VALAD) to determine the efficacy and safety of valacyclovir in participants with early symptomatic AD and HSV seropositivity.

Key Points

Question Can valacyclovir, an antiviral medication effective against herpes simplex virus, which has been implicated in the pathogenesis of Alzheimer disease, be repurposed to provide clinical benefit in patients with early symptomatic Alzheimer disease?

Findings In this randomized clinical trial that included 120 participants with early symptomatic Alzheimer disease and herpes simplex seropositivity, the least-squares mean change in the 11-item Alzheimer's Disease Assessment Scale Cognitive Subscale score (range, 0-70; higher scores indicate greater impairment) at 78 weeks was 10.86 in the valacyclovir group vs 6.92 in the placebo group, which was a significant difference favoring placebo.

Meaning Valacyclovir was not efficacious with cognitive worsening for the primary outcome and it is not recommended to treat individuals with early symptomatic Alzheimer disease and herpes simplex virus seropositivity.

Methods

Trial Design and Oversight

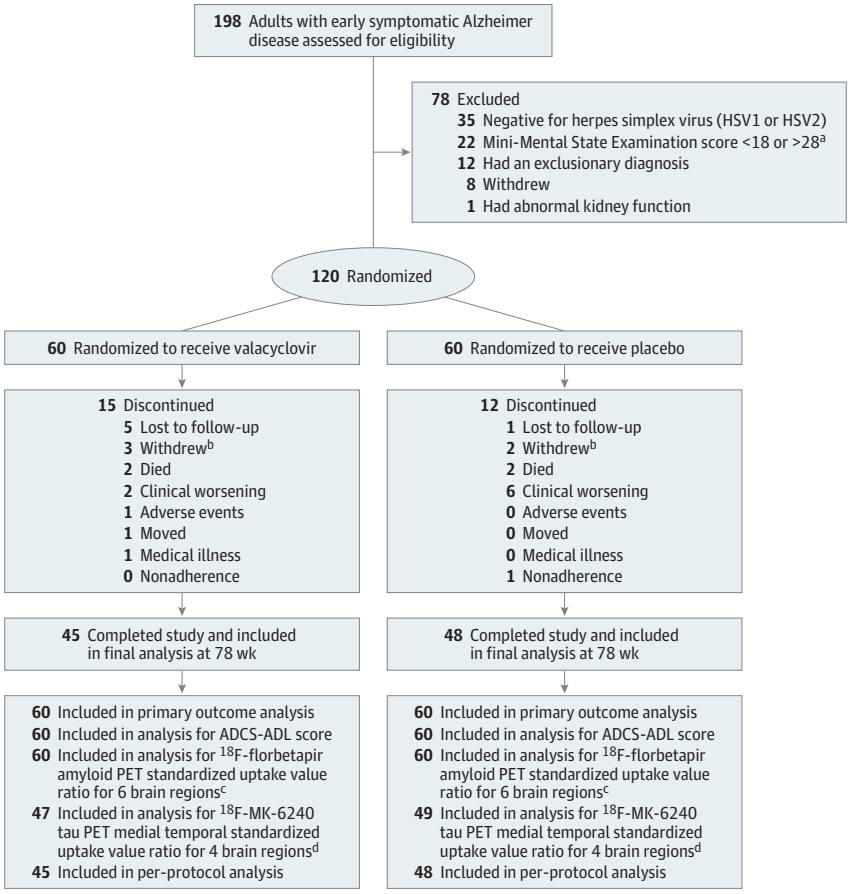
This study was a 3-site, 18-month, double-blind, placebo-controlled, parallel-group treatment, randomized clinical trial including participants with early symptomatic AD and positive serum antibodies (IgG or IgM) to HSV-1 or HSV-2. The trial protocol was published[21] and appears in Supplement 1 along with a summary of changes from the initial to the final. Valacyclovir was chosen because it is a widely used medication for HSV infection with an excellent safety profile.[22]

Valacyclovir (a prodrug of acyclovir) is converted to acyclovir via first-pass hepatic metabolism, leading to plasma acyclovir levels 3 to 5 times that of corresponding doses of oral acyclovir.[23] Acyclovir levels in plasma and cerebrospinal fluid (optional procedure) were assessed at 12 and 78 weeks by investigators who were blinded to treatment assignment. Structural magnetic resonance imaging (MRI), ^{18}F-florbetapir amyloid positron emission tomography (PET), and ^{18}F-MK-6240 tau PET were conducted at baseline and week 78. The ^{18}F-MK-6240 tau PET was conducted because tau pathology is a feature of AD and HSV can induce tau pathology in animal models.[7] Apolipoprotein E (ε2, ε3, or ε4 allele) was genotyped by LGC Genomics using single-nucleotide variations rs429358 and rs7412.

The study was conducted between January 2018 and September 2024 using the Good Clinical Practice and International Council of Harmonization standards and in accordance with the Declaration of Helsinki ethical principles.[24] The trial protocol was approved by the institutional review boards (IRBs) at the 3 participating sites (Columbia University Medical Center/New York State Psychiatric Institute, the New York University Medical Center, and Banner Health).

Late in the study, the initial IRB approval for the New York State Psychiatric Institute became restricted because of an unrelated institutional research pause and IRB approval was transferred to the Columbia University Medical Center, which used

Figure 1. Flow of Participants With Early Symptomatic Alzheimer Disease in VALAD Trial



ADCS-ADL indicates Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale; PET, positron emission tomography; VALAD, Valacyclovir Treatment of Alzheimer's Disease.

[a]The score range is 0 to 30; higher scores indicate better cognitive function.

[b]None asked to have their data removed from the study.

[c]The 6 brain regions were medial orbitofrontal, anterior cingulate, parietal lobe, posterior cingulate, temporal lobe, and precuneus.

[d]The 4 brain regions were amygdala, hippocampus, entorhinal, and parahippocampus.

a reliance agreement for this 3-site study with an external IRB (WIRB-Copernicus Group). There were 6 participants from the Columbia University Medical Center who completed their final visit at the New York University Medical Center site after IRB approval was received.

Participants and their representatives provided written informed consent. An independent data and safety monitoring board provided trial oversight. The Consolidated Standards of Reporting Trials (CONSORT) reporting guideline[25] was used. Race and ethnicity information was collected by open-ended questioning of the participant to ascertain sample representation of the early symptomatic AD population in the US.

Eligibility Criteria

The detailed eligibility criteria and study procedures were published.[21] Eligible adults met National Institute on Aging clinical diagnostic criteria for probable AD[26] or diagnostic criteria for mild cognitive impairment (MCI) with at least 1 of the following biomarkers: prior PET results positive for amyloid pathology (based on a clinical radiology reading or a standardized uptake value ratio [SUVR] ≥1.15), a ^{18}F-fludeoxyglucose PET scan (clinical radiology reading of reduced parietotemporal metabolism), or an AD profile based on cerebrospinal fluid (amyloid tau index). A Mini-Mental State Examination score of 18 to 28 was required (score range, 0-30; higher scores indicate better cognitive function). The National Alzheimer's Coordinating Centers uniform dataset (version 3), which included neuropsychological testing, was administered at baseline, week 52, and week 78.[27] Use of cholinesterase inhibitors or memantine at stable doses for at least 1 month was permitted.

The exclusion criteria were major psychiatric and neurological disorders, modified Hachinski Ischemic Score for Vascular Dementia greater than 4, suicidal ideation or plan, low serum levels of vitamin B_{12}, abnormal thyroid function test results, benzodiazepine use (equivalent to ≥2 mg/d of lorazepam), and severe visual or hearing impairment. Because valacyclovir can cause kidney toxic effects, patients with an estimated glomerular filtration rate less than 44 mL/min/1.73 m^2 were excluded.[28]

Randomization and Treatment Regimen

Computer-generated numbers were used to randomize participants in block sizes of 2 and 4 to valacyclovir or placebo 1:1 (**Figure 1**) without stratification factors and with separate randomization tables for each site. The central research pharmacy and data manager had access to the randomization code; all research raters and clinical staff remained blinded throughout the trial. The research pharmacy made

identical-looking 0.5-g capsules of valacyclovir and placebo. During the COVID-19 pandemic, the research pharmacy sent the prescribed study medications to participants. The level of reported adherence was corroborated by participant pill counts.

The recommended oral dose of valacyclovir is 1 g/d to 3 g/d for acute HSV infection and 4 g/d for recurrent HSV infection. Safety has been demonstrated up to 8 g/d.[12,29] A dosage of 3 g/d orally of valacyclovir provides steady-state cerebrospinal fluid concentrations equivalent to 0.72 to 1.66 µg/mL of acyclovir, which reaches or exceeds the in vitro 50% minimum inhibitory concentration (0.02-0.90 µg/mL) for HSV-1.[23,30] At an oral dose of 4 g/d of valacyclovir, the concentration of acyclovir in cerebrospinal fluid would be higher. The target valacyclovir dose was 4 g/d. Valacyclovir was initially dosed at 2 g/d (1 g twice daily) and then increased to 3 g/d at 2 weeks and 4 g/d at 4 weeks or when the maximum tolerated dose was reached. The dose of 4 g/d was maintained for the remainder of the trial. During the trial, dose reduction to a minimum 2 g/d was permitted. Participants who could not continue 2 g/d were discontinued from the study medication and were followed up at all remaining protocol time points based on the intent-to-treat study design.

Safety monitoring included vital signs, physical examination, and clinical laboratory tests. The adverse events and safety end points were prespecified. The occurrence of adverse events was determined via participant and representative report and review of medical records and clinical laboratory results. The adverse events were rated as serious and mild or moderate and by the likelihood of being caused by valacyclovir. During the trial, the blinding process was broken for 2 participants. One participant was admitted to the hospital with dehydration and delirium (subsequently exited study per the trial protocol) and the other participant because of poststudy discovery that the initial HSV seropositivity result was in fact seronegative (incorrectly recorded by a research rater). The latter participant's data were included in the analyses.

Brain Imaging

The structural MRI acquisition sequences followed the protocol of the Alzheimer's Disease Neuroimaging Initiative for GE scanners (3.0 T).[31] The brain imaging analyses used FreeSurfer software (Laboratories for Computational Neuroimaging). A bolus injection of tracer (10 mCi) was used for ^{18}F-florbetapir amyloid PET; the PET scan was acquired 50 to 70 minutes after the bolus injection was administered. A bolus injection of tracer (5 mCi) was used for ^{18}F-MK-6240 tau PET; the PET scan was acquired 80 to 120 minutes after the bolus injection was administered.

Primary and Secondary Outcomes

The prespecified primary outcome was least-squares mean (LSM) change at 78 weeks in the 11-item Alzheimer's Disease Assessment Scale Cognitive (ADAS-Cognitive) Subscale score (range, 0-70; higher scores indicate greater impairment; minimal clinically important difference is 3 points).[32] The 11-item ADAS-Cognitive Subscale score was chosen because significant change was shown in trials of cholinesterase inhibitors and it was being widely used in AD trials at the time of study inception.

The prespecified secondary outcomes were LSM change at 78 weeks in the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Scale score (range, 0-78; higher scores indicate better functioning)[33]; LSM change in ^{18}F-florbetapir amyloid PET SUVR (higher scores indicate higher amyloid levels)[34] for 6 brain regions (mean of medial orbitofrontal, anterior cingulate, parietal lobe, posterior cingulate, temporal lobe, and precuneus regions normalized to cerebellar gray matter); and LSM change in ^{18}F-MK-6240 tau PET medial temporal SUVR (tau PET was added as a later component; higher scores indicate higher tau levels) for 4 brain regions (mean of amygdala, hippocampus, entorhinal, and parahippocampus regions normalized to cerebellar gray matter).

Cerebrospinal fluid measures were prespecified secondary outcome measures, but data were very limited and statistical analyses could not be performed. The prespecified exploratory outcomes were the ^{18}F-MK-6240 tau PET medial temporal global score for the 4 brain regions (mean of amygdala, hippocampus, entorhinal, and parahippocampus regions) normalized to cerebellar gray matter; the hippocampal volume measured with MRI; and cortical thickness measured with MRI ("AD signature"[35] of 9 brain regions).

The post hoc cognitive outcomes were the Montreal Cognitive Assessment score (range, 0-30; higher scores indicate better global cognition) and the Craft story verbatim delayed recall score from the National Alzheimer's Coordinating Centers test battery (range, 0-44; higher scores indicate better verbal memory). Diagnostic group (AD vs MCI) was examined post hoc as a modifier of treatment group effect on the primary outcome. The frequency of adverse events was the safety outcome. The definition of each outcome did not change from study initiation to reporting of results.

Sample Size Calculation

A power analysis was conducted for the primary outcome (LSM change in 11-item ADAS-Cognitive Subscale score from baseline to 78 weeks) using the RMASS software program (Gibbons, Roy, Kapur, and Jercan) for longitudinal studies. Assuming a within-subject correlation coefficient of $r = 0.3$ (moderate correlation) for repeated measures and dropout uniformly distributed over time to reach 15% by 78 weeks, a total sample size of 130 participants (65 per group) was originally projected to detect a Cohen d of 0.50 with 80% power at a significance level of $P = .05$. After receiving approval from the National Institute on Aging (study sponsor) and the data and safety monitoring board, the recruitment target was reduced to 120 participants due to pandemic-related recruitment delays and required study completion within the extended funding timeline.

For a study size of 120 participants, the minimum detectable effect size increased slightly to a Cohen d of 0.52. A medium effect size, however, has not been demonstrated for any intervention in AD and was unlikely to be demonstrated in this phase 2 treatment trial of patients with early

symptomatic AD. We required a small effect size (Cohen d = 0.20) for valacyclovir compared with placebo to justify proceeding to a phase 3 trial.

Statistical Analysis

The baseline variables were summarized by treatment group using means and SDs for continuous variables and counts and percentages for categorical variables. The primary analyses included all participants according to the assigned treatment.

Linear mixed-effects models were used to assess the treatment effects on the cognitive and functional outcomes with the change score from baseline as the dependent variable and treatment, study time point (categorical), and their interaction as predictors, adjusting for baseline value of the outcome. The models were then further adjusted for age, sex, and apolipoprotein E e4 genotype. Each model included all available follow-up assessments at 12, 26, 52, and 78 weeks for the 11-item ADAS-Cognitive Subscale score and the ADCS-ADL Scale score and at 52 and 78 weeks for the Craft story verbatim delayed recall score and the Montreal Cognitive Assessment score. The primary end point was 78 weeks.

Missing data were handled by linear mixed-effects models under the missing at random assumption. The sensitivity analyses were conducted for study completers (per-protocol analysis), participants who were taking cholinesterase inhibitors or memantine, and participants with a baseline ^{18}F-florbetapir amyloid PET SUVR of 1.15 or greater (positive amyloid level for AD).

Linear regression analyses were conducted to evaluate treatment effects on change in imaging outcomes from baseline to 78 weeks, adjusting for baseline value of the imaging measure. The model was then further adjusted for age, sex, and apolipoprotein E e4 genotype. Sensitivity analyses using weighted linear regression were performed to address potential bias from missing data, with weights calculated as the inverse probability of completion (estimated via logistic regression with Ridge regularization). The adverse events by treatment group were summarized by occurrence frequency. The plasma and cerebrospinal fluid acyclovir concentrations obtained at 12 weeks and 78 weeks were summarized using means and SDs.

All statistical analyses were conducted using R version 4.3.3 (R Foundation for Statistical Computing). The significance level was a 2-sided α = .05. For the secondary, exploratory, and post hoc outcomes, the point estimates with 95% CIs are reported without adjustment for multiple comparisons. The statistical analysis plan (initial and final with a summary of changes) appears in Supplement 2.

Results

Participants

Of the 198 participants screened in person, 120 were enrolled (60 randomized to valacyclovir and 60 to placebo) and, of these, 93 (77.5%) completed the trial. There were 90 participants enrolled at Columbia University Medical Center/New York State Psychiatric Institute, 27 at New York University Medical Center, and 3 at Banner Health. The mean age of the participants was 71.4 years (SD, 8.6 years), 55% were female, 75% were diagnosed with AD, and 25% were diagnosed with MCI (**Table 1**).[36-39]

Of the 90 participants with a clinical diagnosis of AD, 54 had positive biomarkers for AD prior to enrollment, 22 had positive biomarkers for AD at the baseline evaluation (^{18}F-florbetapir amyloid PET SUVR ≥1.15), and 14 untested for AD biomarkers prior to enrollment had a negative ^{18}F-florbetapir amyloid PET scan at the baseline evaluation. All 30 participants with MCI were positive for AD biomarkers prior to enrollment. Therefore, in the total sample of 120 participants, 106 (88.3%) tested positive for AD biomarkers and 14 (11.7%) tested negative for AD biomarkers.

There was no randomization imbalance for age, sex, years of education, seropositivity for HSV-1 or HSV-2, or baseline values for the outcome measures (Table 1). The presence of old HSV infection is indicated by IgG antibody positivity. In the valacyclovir group, 80% were positive for HSV-1 IgG antibodies and 31.7% were positive for HSV-2 IgG antibodies. In the placebo group, 86.7% were positive for HSV-1 IgG antibodies and 33.3% were positive for HSV-2 IgG antibodies (Table 1). Eighty-three participants (69.2%) were taking cholinesterase inhibitors or memantine. Enrollment was completed before either lecanemab or donanemab was approved by the US Food and Drug Administration.

Clinical Outcomes

Primary Outcome

The LSM change in the 11-item ADAS-Cognitive Subscale score at 78 weeks was 10.86 (95% CI, 8.80-12.91) in the valacyclovir group vs 6.92 (95% CI, 4.88-8.97) in the placebo group, indicating greater cognitive worsening with valacyclovir than with placebo (between-group difference, 3.93 [95% CI, 1.03-6.83]; P = .01) (**Table 2** and **Figure 2**A). Additional adjustment for age, sex, and apolipoprotein E ε4 genotype did not materially change the results (eTable 1 in Supplement 3).

Secondary Outcomes

The LSM change in ADCS-ADL Scale score at 78 weeks was −13.78 (95% CI, −17.00 to −10.56) in the valacyclovir group vs −10.16 (95% CI, −13.37 to −6.96) in the placebo group (between-group difference, −3.62 [95% CI, −8.16 to 0.93]), which was not significantly different (Table 2 and Figure 2B). The LSM change in the ^{18}F-florbetapir amyloid PET SUVR for 6 brain regions at 78 weeks was 0.03 (95% CI, −0.04 to 0.10) in the valacyclovir group vs 0.01 (95% CI, −0.06 to 0.08) in the placebo group (between-group difference, 0.02 [95% CI, −0.08 to 0.12]), which was not significantly different (Table 2). The LSM change in the ^{18}F-MK-6240 tau PET medial temporal SUVR for 4 brain regions at 78 weeks was 0.07 (95% CI, −0.06 to 0.19) in the valacyclovir group vs −0.04 (95% CI, −0.15 to 0.07) in the placebo group (between-group difference, 0.11 [95% CI, −0.06 to 0.28]), which was not significantly different (Table 2).

Exploratory Outcomes

The LSM change in hippocampal volume (measured with MRI) was −209.91 (95% CI, −257.84 to −161.98) in the valacyclovir

Table 1. Baseline Demographics and Health Characteristics of Participants With Early Symptomatic Alzheimer Disease (AD)

	Valacyclovir (n = 60)	Placebo (n = 60)
Demographics		
Sex, No. (%)		
Female	35 (58.3)	31 (51.7)
Male	25 (41.7)	29 (48.3)
Age, mean (SD), y	71.3 (8.8)	71.6 (8.6)
Race and ethnicity, No. (%)[a]		
American Indian or Alaska Native	0	1 (1.7)
Asian	3 (5.0)	0
Black or African American	8 (13.3)	7 (11.7)
Hispanic or Latino	9 (15.0)	10 (16.7)
White	46 (76.7)	46 (76.7)
Other	3 (5.0)	6 (10.0)
Length of education, mean (SD), y	15.8 (3.9)	16.5 (3.7)
Health characteristics		
11-Item Alzheimer's Disease Assessment Scale Cognitive Subscale score, mean (SD)[b]	20.6 (6.6)	19.2 (7.6)
Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale score, mean (SD)[c]	65.8 (10.5)	65.6 (11.4)
Craft story verbatim delayed recall score, mean (SD)[d]	4.39 (5.59)	4.77 (5.31)
Clinical Dementia Rating (CDR) Scale Sum of Boxes score, mean (SD)[e]	4.2 (1.7)	4.2 (1.9)
Mini-Mental State Examination score, mean (SD)[f]	21.9 (2.6)	22.4 (3.0)
Montreal Cognitive Assessment score, mean (SD)[g]	16.6 (4.3)	16.9 (5.0)
Clinical subgroup, No. (%)		
Mild cognitive impairment (CDR score of 0.5)	15 (25.0)	15 (25.0)
Mild dementia (CDR score of 1)	45 (75.0)	43 (71.7)
Moderate dementia (CDR score of 2)	0	2 (3.3)
Cholinesterase inhibitor use, No. (%)	39 (65.0)	40 (66.7)
Memantine use, No. (%)	17 (28.3)	20 (33.3)
Positive for herpes simplex virus type 1, No. (%)		
IgG antibodies	48 (80.0)	52 (86.7)
IgM antibodies	1 (1.7)	0
Positive for herpes simplex virus type 2, No. (%)		
IgG antibodies	19 (31.7)	20 (33.3)
IgM antibodies	1 (1.7)	0
Positive for apolipoprotein E e4, No. (%)	29 (48.3)	38 (63.3)
Creatinine level, mean (SD), mg/dL	0.90 (0.21)	0.90 (0.20)
^{18}F-florbetapir amyloid PET SUVR for 6 brain regions, mean (SD)[h]	1.57 (0.37)	1.57 (0.41)
Hippocampal volume measured by MRI, mean (SD), cu mm	3170 (524)	3220 (591)
Cortical thickness measured by MRI, mean (SD), mm	2.41 (0.17)	2.41 (0.16)
^{18}F-MK-6240 tau PET medial temporal measures for 4 brain regions, mean (SD) [No.][i]		
SUVR	2.18 (1.29) [47]	1.91 (1.53) [49]
Global score	1.53 (1.59) [47]	1.48 (1.92) [49]

Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standardized uptake value ratio.

SI conversion factor: To convert creatinine to µmol/L, multiply by 88.4.

[a] Collected via open-ended questioning of participants. For "Other," 7 reported more than 1 race; 1, Middle Eastern; and 1, did not specify.

[b] Score range, 0 to 70; higher scores indicate worse cognition. The scores were similar to North American studies of mild to moderate AD.[36] The minimal clinically important difference (MCID) is 3 points.

[c] Score range, 0 to 78; higher scores indicate better daily function. The scores were similar to North American studies of mild to moderate AD.[36] The proposed MCID range is 2 to 8 points.

[d] Score range, 0 to 44; higher scores indicate better verbal memory for delayed recall. The MCID has not been established.

[e] Score range, 0 to 18; higher scores indicate worse global cognition and function. The scores were in between those from a trial of early AD[37] and North American studies.[36] The MCID is 2 points.[38]

[f] Score range, 0 to 30; higher scores indicate better cognitive function. The scores were similar to North American studies.[36] The MCID is 2 points.[38]

[g] Score range, 0 to 30; higher scores indicate better global cognition. The scores were similar to studies of mild AD. The MCID is 2 points.[39]

[h] Across 6 brain regions normalized to cerebellar gray matter (higher scores = higher amyloid levels). The MCID has not been established.

[i] Across 4 brain regions normalized to cerebellar gray matter (higher scores = higher tau levels). The MCID has not been established.

Table 2. Primary, Secondary, Exploratory, and Post Hoc Outcomes

	Valacyclovir					Placebo					
	At baseline		At 78 wk		Least-squares mean change (95% CI)[a]	At baseline		At 78 wk		Least-squares mean change (95% CI)[a]	Between-group difference (95% CI)
	Mean (SD)	No.	Mean (SD)	No.		Mean (SD)	No.	Mean (SD)	No.		
Primary outcome											
11-Item ADAS Cognitive Subscale score[b]	20.55 (6.57)	60	30.36 (14.04)	42	10.86 (8.80 to 12.91)	19.15 (7.60)	60	25.29 (11.76)	42	6.92 (4.88 to 8.97)	3.93 (1.03 to 6.83)[c]
Secondary outcomes											
ADCS-ADL Scale score[b]	65.82 (10.46)	60	53.02 (20.79)	43	−13.78 (−17.00 to −10.56)	65.55 (11.43)	60	54.35 (18.79)	43	−10.16 (−13.37 to −6.96)	−3.62 (−8.16 to 0.93)
^{18}F-florbetapir amyloid PET SUVR for 6 brain regions[d,e]	1.57 (0.37)	60	1.63 (0.35)	41	0.03 (−0.04 to 0.10)	1.57 (0.41)	60	1.60 (0.41)	40	0.01 (−0.06 to 0.08)	0.02 (−0.08 to 0.12)
^{18}F-MK-6240 tau PET medial temporal SUVR for 4 brain regions[d,f]	2.18 (0.82)	47	2.32 (0.79)	24	0.07 (−0.06 to 0.19)	1.91 (0.88)	49	1.90 (0.89)	31	−0.04 (−0.15 to 0.07)	0.11 (−0.06 to 0.28)
Exploratory outcomes[d]											
Hippocampal volume assessed by MRI, cu mm	3165.06 (523.55)	59	2987.99 (615.33)	33	−209.91 (−257.84 to −161.98)	3220.51 (590.99)	59	3022.87 (650.22)	43	−159.59 (−201.58 to −117.61)	−50.32 (−114.04 to 13.40)
Cortical thickness assessed by MRI, mm	2.41 (0.17)	59	2.37 (0.17)	33	−0.09 (−0.11 to −0.07)	2.41 (0.16)	59	2.35 (0.18)	43	−0.07 (−0.09 to −0.05)	−0.01 (−0.05 to 0.02)
^{18}F-MK-6240 tau PET medial temporal global score for 4 brain regions[f]	1.99 (1.14)	46	2.14 (1.14)	24	0.19 (0.07 to 0.31)	1.91 (1.09)	49	1.98 (1.16)	31	0.09 (−0.01 to 0.20)	0.10 (−0.05 to 0.26)
Post hoc outcomes											
MoCA score[b]	16.64 (4.33)	55	13.72 (7.34)	36	−3.92 (−5.26 to −2.57)	16.90 (5.03)	59	14.16 (6.77)	43	−3.51 (−4.72 to −2.29)	−0.41 (−2.22 to 1.40)
Craft story verbatim delayed recall score[b]	4.39 (5.59)	56	3.20 (5.89)	35	−1.45 (−2.59 to −0.31)	4.77 (5.31)	56	3.27 (5.52)	41	−1.89 (−2.94 to −0.84)	0.44 (−1.11 to 2.00)

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standardized uptake value ratio.

[a] Follow-up minus baseline (week 0) values.

[b] This is a cognitive or functional outcome. The linear mixed-effects repeated-measures analyses were adjusted for the baseline value.

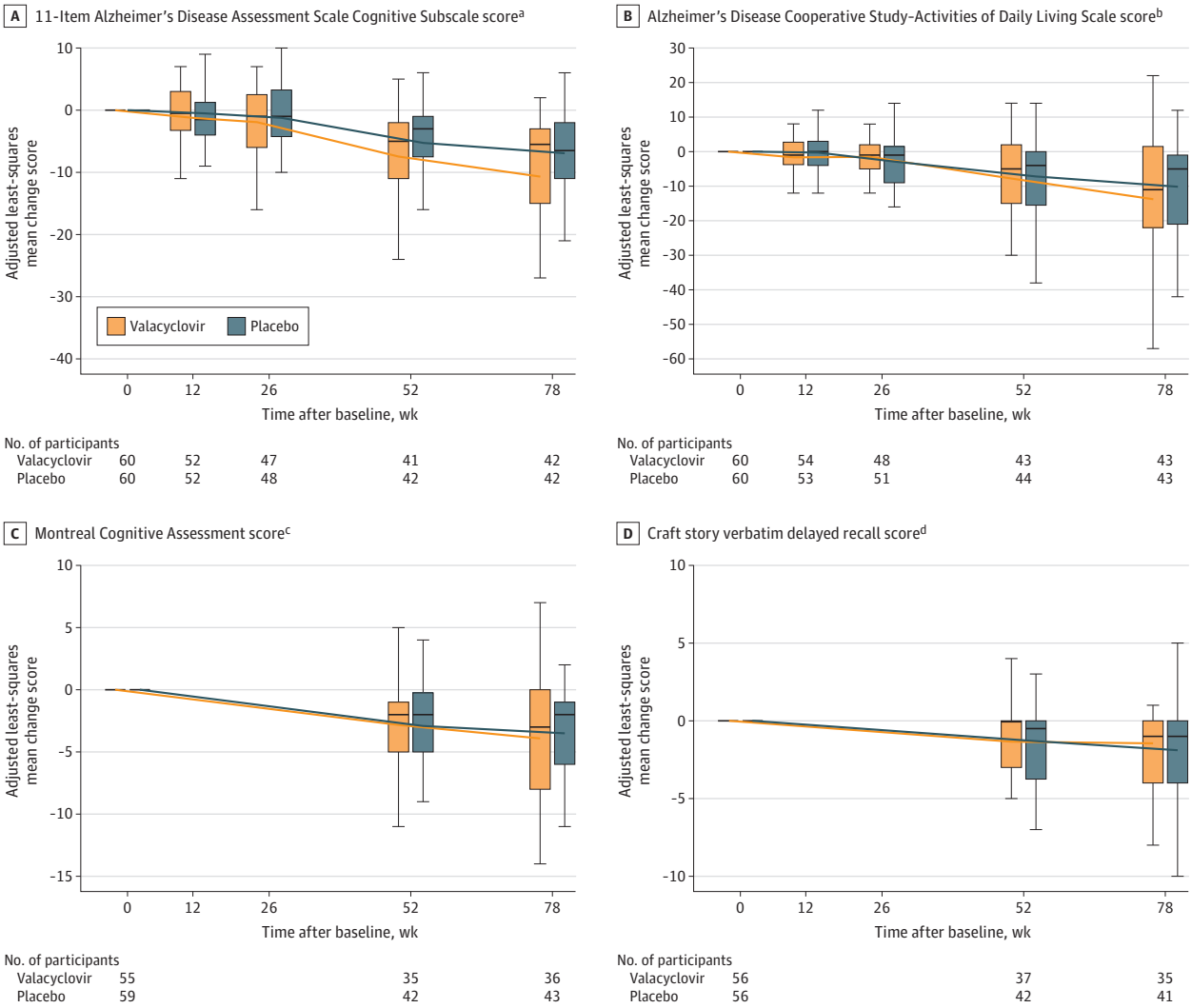
[c] $P = .01$.

[d] The linear regression analyses were adjusted for the baseline value.

[e] The 6 brain regions were medial orbitofrontal, anterior cingulate, parietal lobe, posterior cingulate, temporal lobe, and precuneus. Higher scores indicate presence of higher amyloid levels.

[f] The 4 brain regions were amygdala, hippocampus, entorhinal, and parahippocampus. Higher scores indicate presence of higher tau levels.

Figure 2. Change in Cognitive and Functional Outcomes Over Time



Linear mixed-effects models were used and were adjusted for baseline values. The boxes represent the IQRs; the black lines inside the boxes represent the means; and the whiskers represent the minimum or maximum values.

[a]The score range is 0 to 70; higher scores indicate worse cognition (minimal clinically important difference, 3 points).

[b]The score range is 0 to 78; higher scores indicates better daily function (proposed minimal clinically important difference, 2-8 points).

[c]The score range is 0 to 30; higher scores indicate better global cognition (minimal clinically important difference, 2 points).

[d]The score range is 0 to 44; higher scores indicate better verbal memory for delayed recall (minimal clinically important difference, not established).

group vs −159.59 (95% CI, −201.58 to −117.61) in the placebo group (between-group difference, −50.32 [95% CI, −114.04 to 13.40]), which was not significantly different (Table 2). The LSM change in cortical thickness (measured with MRI) was −0.09 (95% CI, −0.11 to −0.07) in the valacyclovir group vs −0.07 (95% CI, −0.09 to −0.05) in the placebo group (between-group difference, −0.01 [95% CI, −0.05 to 0.02]), which was not significantly different (Table 2). The LSM change in the ^{18}F-MK-6240 tau PET medial temporal global score for 4 brain regions was 0.19 (95% CI, 0.07 to 0.31) in the valacyclovir group vs 0.09 (95% CI, −0.01 to 0.20) in the placebo group (between-group difference, 0.10 [95% CI, −0.05 to 0.26]), which was not significantly different (Table 2).

Post Hoc Outcomes

The LSM change in Montreal Cognitive Assessment score was −3.92 (95% CI, −5.26 to −2.57) in the valacyclovir group vs −3.51 (95% CI, −4.72 to −2.29) in the placebo group (between-group difference, −0.41 [95% CI, −2.22 to 1.40]), which was not significantly different (Table 2 and Figure 2C). The LSM change in the Craft story verbatim delayed recall score was −1.45 (95% CI, −2.59 to −0.31) in the valacyclovir group vs −1.89

Table 3. Adverse Events

	Adverse events, No. (%)[a]	
	Valacyclovir (n = 60)[b]	Placebo (n = 60)
Serious adverse events[c]		
COVID-19	3 (5.0)	2 (3.3)
Other kidney	3 (5.0)	0
Died[d]	2 (3.3)	2 (3.3)
Other infections	2 (3.3)	2 (3.3)
Pneumonia	1 (1.7)	2 (3.3)
Falls	0	2 (3.3)
Mild or moderate adverse events		
Serum creatinine level ≥1.5 mg/dL	5 (8.3)	2 (3.3)
Diarrhea	4 (6.7)	1 (1.7)
Nausea	3 (5.0)	2 (3.3)
Appetite change	2 (3.3)	0
Abdominal pain	2 (3.3)	0
Muscle tendon aches and pain	2 (3.3)	0
Confusion	2 (3.3)	0
Dizziness	1 (1.7)	2 (3.3)
Hypertension	0	3 (5.0)

SI conversion factor: To convert creatinine to µmol/L, multiply by 88.4

[a] Based on participant and representative report, medical records, or clinical laboratory results. All included events occurred in at least 2 participants in either treatment group.

[b] The likelihood of being caused by valacyclovir was determined by the study physician with review by the site principal investigator.

[c] Resulted in inpatient hospitalization, significant disability or incapacity, or death.

[d] All were rated as unrelated to valacyclovir or placebo.

(95% CI, −2.94 to −0.84) in the placebo group (between-group difference, 0.44 [95% CI, −1.11 to 2.00]), which was not significantly different (Table 2 and Figure 2D).

Sensitivity Analyses

Ninety-three participants were included in per-protocol analyses. Similar to the results in primary analysis, the LSM change in the 11-item ADAS-Cognitive Subscale score at 78 weeks was 10.80 (95% CI, 8.58 to 13.01) in the valacyclovir group vs 7.06 (95% CI, 4.84 to 9.28) in the placebo group (between-group difference, 3.73 [95% CI, 0.60 to 6.87]; $P = .02$), which indicates greater cognitive worsening with valacyclovir than with placebo (eTable 2 in Supplement 3). Diagnostic group (75% with AD vs 25% with MCI) was not a significant modifier of treatment group effect on the 11-item ADAS-Cognitive Subscale score (eTable 3 in Supplement 3). For the imaging outcomes, using weighted linear regression to account for the effect of missing data did not change the significance of between-group comparisons (eTable 4 in Supplement 3). Restricting the sample to the 98 participants (81.7%) with a baseline ^{18}F-florbetapir amyloid PET SUVR of 1.15 or greater (positive amyloid level for AD) did not materially alter the results (eTable 5 in Supplement 3), and neither did restriction to participants who were taking cholinesterase inhibitors or memantine during the trial.

Plasma and Cerebrospinal Fluid Measures

Among participants in the valacyclovir group, the mean plasma acyclovir concentration was 7140 ng/mL (SD, 5780 ng/mL) with a 4-g/d dose of valacyclovir (66 samples in the valacyclovir group after combining weeks 12 and 78). The plasma acyclovir levels were consistent with concentrations reported at comparable oral valacyclovir doses in other populations.[30] The mean cerebrospinal fluid acyclovir concentration was 1260 ng/mL (SD, 460 ng/mL) at week 12 (n = 6) and was 1270 ng/mL (SD, 1100 ng/mL) at week 78 (n = 3).

Adverse Events

There was not a significant between-group difference in the number of serious adverse events and mild or moderate adverse events (**Table 3**). The most common serious adverse event was COVID-19 (3 [5%] participants in the valacyclovir group vs 2 [3.3%] participants in the placebo group) and the most common mild or moderate adverse event was elevated serum creatinine level (5 participants [8.3%] in the valacyclovir group vs 2 participants [3.3%] in the placebo group). There were 2 deaths (3.3%) in both groups that were rated as unrelated to the study treatments. When elevated level of serum creatinine occurred, the study physician lowered the oral dose of study medication to 2 g/d and the creatinine level decreased without unblinding of the research raters.

Discussion

Valacyclovir did not demonstrate efficacy vs placebo for the primary outcome of LSM change in the 11-item ADAS-Cognitive Subscale score at week 78. The reason for the effect is unclear. A difference of 3 or more points on the 11-item ADAS-Cognitive Subscale is clinically meaningful for treatment with a cholinesterase inhibitor.[32] Valacyclovir at a high dose (eg, 8 g/d) has been associated with agitation, confusion, and delirium.[29] Neurotoxicity as an adverse event for acyclovir and valacyclovir at therapeutic doses has been described in case reports.[29] Adverse events indicating neurotoxicity were infrequent in both the valacyclovir and placebo groups. It is possible that some participants experienced subtle neurotoxicity without an adverse event that was detectable with cognitive

testing. Another possibility is prolonged exposure during this 78-week trial to valacyclovir at 4 g/d may increase the risk of cognitive worsening in patients with early symptomatic AD.

The secondary outcome measure of daily functioning (LSM change in ADCS-ADL Scale score) and the post hoc measures of verbal memory and global cognition did not show significant between-group differences. Cognitive and functional changes were not assessed with rating instruments in placebo-controlled trials of valacyclovir for patients with multiple sclerosis (an autoimmune disease for which valacyclovir treatment has been studied).[40,41] In the sensitivity analyses for the current trial, which included participants from the per-protocol analysis who completed the trial, restricting the analyses to participants positive for amyloid pathology or who were taking cholinesterase inhibitors or memantine did not materially alter the results. Between-group comparisons by the covariates of age, sex, and apolipoprotein E e4 genotype were not significant.

Valacyclovir did not significantly change the characteristic brain imaging indices of amyloid, tau, and neurodegeneration in AD. These findings weaken the case for HSV as a modifiable factor affecting AD neuropathology. These results are consistent with the lack of change in total tau and neurofilament light in cerebrospinal fluid in an open-label pilot trial of valacyclovir in patients with AD.[20] In the current trial, plasma levels of acyclovir indicated effective gastrointestinal absorption and metabolism of valacyclovir. Cerebrospinal fluid levels of acyclovir were similar at 12 weeks and 78 weeks, indicating that sustained penetration of the central nervous system was achieved,[23] and were similar to results from 4- and 6-month trials of valacyclovir in patients with multiple sclerosis.[40,41] The types of adverse events were consistent with the extensive clinical data available for valacyclovir and with the prevalence of COVID-19 infections during the trial.[12,22]

Anti-HSV medications typically are prescribed short-term for acute HSV infection and long-term maintenance treatment is efficacious in reducing recurrent HSV infection.[42] The current trial addressed medium-term treatment for patients with early symptomatic AD and HSV seropositivity. The utility of long-term anti-HSV treatment in decreasing dementia risk in individuals with HSV seropositivity but without cognitive impairment is unknown.

Among other herpesviruses, initial demonstration of increased human herpesviruses 6A and 7 in autopsied brains with AD has not been replicated.[43,44] Herpes zoster infection, particularly severe infection, has been associated with increased dementia risk.[45] In a 1930s British cohort (when shingles vaccination against herpes zoster was introduced), vaccination decreased dementia risk by 20% compared with a nonvaccinated cohort.[46] A similar result was observed in an Australian cohort.[47] A caveat is that individuals who agree to vaccination or long-term antiviral treatment may be more likely to exhibit healthier lifestyle behaviors associated with decreased dementia risk.[48,49] Prospective controlled trials of long-term antiviral medication treatment after herpes zoster infection as a strategy to prevent cognitive decline and AD have not been conducted. Antiviral drugs in other classes were evaluated in a phase 2a, double-blind, placebo-controlled, randomized clinical trial including 69 patients with AD.[50] A combination of pleconaril (active against enteroviruses) and ribavirin (active against several viruses) was linked to increased frequency and severity of drug-related adverse events, but the trial had a high dropout rate of 46% and inconclusive results.[50] The current study is the first double-blind, placebo-controlled, randomized clinical trial of an antiherpetic, antiviral medication in patients with AD.

The strengths of this trial included its use of rigorous clinical trial methods, assessment of clinical and neuroimaging outcomes, PET amyloid imaging in all participants, and long study duration to examine persistent effects. The participant characteristics were well-balanced in the study treatment groups and among the trial completers. Of the entire sample, 28% were racial and ethnic minority individuals, which supports generalizability to the US population.

Limitations

This study has several limitations. First, the study had a small sample size. Second, the number of recruited participants was low at 1 of the 3 study sites. Third, the COVID-19 pandemic contributed to a moderately high dropout rate of 22.5%; however, this rate is similar to the dropout rate of 23% in a recent 18-month trial of donanemab in patients with early symptomatic AD.[51] Fourth, PET imaging for tau pathology was limited to a subsample. Fifth, plasma biomarkers were not assessed because these biomarkers had not been established at the time of study inception.

Conclusions

Valacyclovir was not efficacious with cognitive worsening for the primary outcome and it is not recommended to treat individuals with early symptomatic AD and HSV seropositivity.

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