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A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease

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Abstract

Objective
To evaluate the safety and efficacy of crenezumab in patients with mild to moderate Alzheimer disease (AD).

Methods
In this phase 2 trial, 431 patients with mild to moderate AD 50 to 80 years of age were randomized 2:1 (crenezumab:placebo). Patients received low-dose subcutaneous crenezumab 300 mg or placebo every 2 weeks (n = 184) or high-dose intravenous crenezumab 15 mg/kg or placebo every 4 weeks (n = 247) for 68 weeks. Primary outcome measures were change in Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog12) and Clinical Dementia Rating–Sum of Boxes scores from baseline to week 73.

Results
The primary and secondary endpoints were not met. In an exploratory post hoc analysis, a reduction in decline on the ADAS-Cog12 was observed in the high-dose group. Separation from the placebo group on the ADAS-Cog12 was greatest in the milder subsets of AD patients and reached statistical significance in the group with Mini-Mental State Examination scores of 22 to 26. In both groups, there was a significant increase in CSF β-amyloid$_{1-42}$ levels that correlated with crenezumab CSF levels. The overall rate of adverse events was balanced between groups. One case of amyloid-related imaging abnormalities indicative of vasogenic edema or effusions was reported.

Conclusions
Although prespecified criteria for testing treatment effects were not met, these data suggest a potential treatment effect in patients with mild AD treated with high-dose crenezumab. Together with the safety profile for crenezumab, these data support the exploration of crenezumab treatment at even higher doses in patients with early AD.

Clinicaltrials.gov identifier
NCT 01343966.

Classification of evidence
This study provides Class II evidence that, for people with AD, crenezumab does not significantly improve cognition or function at 18 months. The study is rated Class II because <80% of enrolled patients completed the study.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive Subscale; **ADCS-ADL** = Alzheimer's Disease Cooperative Study–Activities of Daily Living; **AE** = adverse event; **ARIA** = amyloid-related imaging abnormalities; **ARIA-E** = amyloid-related imaging abnormalities indicative of vasogenic edema or effusions; **ARIA-H** = amyloid-related imaging abnormalities indicative of microhemorrhage and siderosis; **CDR-SB** = Clinical Dementia Rating–Sum of Boxes; **CREAD** = A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants With Prodromal to Mild Alzheimer's Disease; **FcγR** = Fc-gamma receptor; **MMSE** = Mini-Mental State Examination; **SAE** = serious adverse event.

Alzheimer disease (AD) is the most common form of dementia[1] and is characterized by deposition of amyloid plaques in the brain composed primarily of β-amyloid (Aβ) peptides.[2] Aβ peptides may accumulate as soluble monomers and aggregate as oligomers and insoluble fibrils,[1] but soluble oligomers are suggested to be a major driver of neurotoxicity.[3–5]

Crenezumab, a fully humanized immunoglobulin isotype G4 monoclonal antibody, binds to monomers and aggregated forms of Aβ with a 10-fold–higher affinity for oligomers.[6] The immunoglobulin isotype G4 backbone confers reduced activation of Fc-gamma receptors (FcγRs) and minimizes the FcγR-mediated inflammatory activation of microglia, hypothesized to contribute to neurotoxicity,[7,8] while preserving FcγR-mediated microglial phagocytosis and removal of Aβ oligomers.[6]

Amyloid-related imaging abnormalities (ARIA) indicative of vasogenic edema or effusions (ARIA-E) and microhemorrhage and siderosis (ARIA-H) have been reported recently with monoclonal antibodies that bind aggregated forms of Aβ and have immunoglobulin isotype G1 backbones with fully FcγR-mediated effector function, limiting the dose levels that could be safely administered.[9–11] Crenezumab was designed on the basis of the hypothesis that an antibody with reduced effector function would have a lower risk of inducing ARIA-E/H.[12,13]

Methods

Primary research question

This phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was designed to evaluate the safety and efficacy of crenezumab in patients with mild to moderate AD that was conducted from April 25, 2011, to February 18, 2014, at 72 sites in North America and Europe. Class II evidence is provided here.

Standard protocol approvals, registrations, and participant consents

The study protocol was approved by the local institutional review board at each site. Written informed consent was obtained from each patient (or legally authorized representative) before entry into the study (ClinicalTrials.gov identifier NCT01343966). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guidelines on Good Clinical Practice.

Patients

Eligible patients were 50 to 80 years old, met the criteria for mild to moderate probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria[14] and had a Mini-Mental State Examination (MMSE) score of 18 to 26 points.[15] Additional inclusion criteria were a Geriatric Depression Scale score of <6, a Clinical Dementia Rating–Sum of Boxes (CDR-SB) score of ≥0.5,[16–18] and an Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) Delayed Word Recall score of ≥5.[19] Treatment with approved AD drugs such as acetylcholinesterase inhibitors or memantine was permitted if initiated ≥3 months and stabilized ≥2 months before randomization.

Study design and treatment

The study was conducted in 2 overlapping parts (figure e-1, links.lww.com/WNL/A461). Patients were randomly assigned in a 2:1 ratio to receive crenezumab 300 mg SC every 2 weeks (the low-dose cohort) or placebo in part 1 and to crenezumab 15 mg/kg IV every 4 weeks (the high-dose cohort) or placebo in part 2. Randomization into the 2 parts was independent and sequential. Enrollment in part 2 of the study began only when randomization in part 1 and the safety run-in (described below) were complete. Randomization was managed by a central IxRS vendor using dynamic hierarchical randomization based on 3 factors: *APOE* ε4 genotype, MMSE score (<22 vs ≥22), and study site.

To assess the potential for using a higher dose of crenezumab compared to phase 1, part 2 of the phase 2 study was preceded by a safety run-in period that was conducted in parallel with part 1 and consisted of at least 2 monthly IV administrations of 15 mg/kg crenezumab in 13 patients (11 active: 2 placebo). On the basis of the available safety data, the 15-mg/kg dose was selected for the high-dose IV cohort of the study. Patients from this cohort were not included in the primary efficacy analysis.

Outcomes

The primary efficacy outcome measures were changes in the 12-item ADAS-Cog (ADAS-Cog12) and CDR-SB scores from baseline to week 73.[20,21] The secondary efficacy outcome measure, the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) score, was analyzed in the same manner as the primary efficacy outcome measures.[22]

To assess the exploratory outcome of crenezumab pharmacokinetics, blood samples were collected to measure serum crenezumab concentrations and analyzed with a validated ELISA (limit of detection 50 ng/mL).

CSF collection was conducted as an optional procedure at week 1 (day 1/baseline) and before study drug administration at week 69 (steady state). CSF crenezumab concentrations were analyzed with a validated ELISA (limit of detection 12.5 ng/mL). CSF $A\beta_{1-42}$ was measured with the Elecsys $A\beta_{1-42}$ immunoassay under development by Roche Diagnostics.[23] CSF tau and phosphorylated-tau 181 were measured with INNOTEST ELISAs (Fujirebio, Tokyo, Japan).

MRI assessments were performed by a central imaging reader (NeuroRx, Montreal, Quebec, Canada) and analyzed longitudinally and included the following scans for safety assessments and volumetric measurements: a high-resolution T1-weighted structural scan, a T2-weighted gradient-recalled echo, and a T2-weighted fluid-attenuated inversion recovery. Ventricular, whole-brain, and hippocampal volumes were measured from the T1 MRI.

Safety monitoring

Safety was assessed from reports of adverse events (AEs), serious AEs (SAEs), and AEs of special interest. Safety assessments included clinical laboratory testing, clinical examinations, ECG, and brain MRI. All safety data were assessed by an unblinded Internal Safety Monitoring Committee on a regular basis.

Blood samples were collected to test for the presence of antitherapeutic antibody in serum.

Population and statistical analysis

The study was designed to enroll ≈180 patients each in both the low- and high-dose cohorts; in each part, 60 patients would be enrolled in the placebo arm and 120 patients would be enrolled in the crenezumab arm. Assuming a mean decline of 6 points for change in ADAS-Cog12, an SD of 9 points, and 30% dropout, this sample size would provide 80% power to detect a true treatment delta of 3.6 (60% reduction relative to placebo) when testing at the 2-sided 0.2 level. In addition, assuming a mean decline of 2.4 points for CDR-SB, an SD of 3 points, and 30% dropout, this sample size would provide 80% power to detect a true treatment delta of 1.2 (50% reduction relative to placebo) when testing at the 2-sided 0.2 level.

The efficacy analysis was based on the modified intent-to-treat population, which included all patients who were randomized and had both a baseline measurement and at least 1 post-baseline measurement for that endpoint. Patients were grouped according to the treatment assigned at randomization. In the high-dose 15 mg/kg IV cohort, 2 patients receiving crenezumab were excluded from the safety evaluable population as a result of 2 dosing deviations and 2 patients leaving the study before the first dose, leaving 165 crenezumab and 82 placebo patients.

Cohorts from part 1 (low-dose 300 mg SC cohort) and part 2 (high-dose 15 mg/kg IV cohort) were analyzed separately, reflecting their independent and sequential randomization. Three subpopulations determined by baseline MMSE score were analyzed: MMSE score of 18 to 26 (all patients), MMSE score of 20 to 26 (mild AD), and MMSE score of 22 to 26 (very mild AD). The subpopulations with MMSE scores of 18 to 26 and 20 to 26 were prespecified, while the post hoc subpopulation with MMSE scores of 22 to 26 was based on stratification criteria used at study randomization. Efficacy endpoints with >1 postbaseline outcome measure were analyzed with mixed-effect model repeat measurement for the change scores from the baseline to postbaseline time points. An unstructured variance-covariance matrix for within-patient errors was used.

Efficacy endpoints with 1 postbaseline outcome measure were analyzed with analysis of covariance on the change scores from baseline to the postbaseline time point.

The mixed-effect model repeat measurement and analysis of covariance models for efficacy endpoints were used to estimate mean declines for each treatment group and time point, the least-squares mean treatment difference between the crenezumab and placebo groups at each time point, the 95% CIs for the mean treatment deltas, and the corresponding p values. The CIs and p values were not adjusted for multiplicity in this study.

The safety analysis was performed on all randomized patients who received at least 1 dose of study drug during the study. All analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC). The pharmacokinetics analysis was performed on all patients randomized to active treatment who received at least 1 dose of study drug and provided at least 1 valid pharmacokinetics assessment.

Data availability

We provide qualified researchers access to individual patient-level data through the clinical study data request platform (clincalstudydatarequest.com). Further details of Roche's Data Sharing Policy are available here (clinicalstudydatarequest.com/Study-Sponsors-Roche-Details.aspx).

Results

Participant disposition

The disposition of the enrolled participants is summarized in figure e-2 (links.lww.com/WNL/A461). In total, 431 patients received at least 1 dose of crenezumab or placebo.

The 300 mg SC crenezumab cohort consisted of 184 patients, while 247 patients were allocated to the 15 mg/kg IV cohort. The percentage of patients who had a week 73 assessment was similar across the cohorts and treatment arms. Patients within both parts 1 and 2 of the study had balanced baseline characteristics with no significant differences (table 1).

Efficacy

None of the efficacy outcome measures showed statistically significant differences in any of the prespecified analysis subpopulations.

Changes from baseline over time in scores on the ADAS-Cog12 in patients with mild to moderate AD (MMSE score 18–26) showed no statistically significant difference at week 73 between active treatment and placebo in the 300 mg SC cohort (0.04-point difference; table e-1, links.lww.com/WNL/A462). Similarly, the 15 mg/kg IV crenezumab cohort showed no statistically significant difference on the ADAS-Cog12 between crenezumab treatment and placebo at week 73 (1.78-point difference). In the prespecified subgroup analysis in patients with mild AD (MMSE score 20–26), no effect was observed on the ADAS-Cog12 for the 300 mg SC crenezumab cohort (figure 1B and table e-1). Prespecified subgroup analysis of the 15 mg/kg IV crenezumab cohort (figure 1D and table 2) showed a greater reduction of cognitive decline in patients with a baseline MMSE score of 20 to 26 (2.4-point difference in ADAS-Cog12 score).

At week 73, no statistically significant drug-placebo group separations were seen on the CDR-SB in the patients with mild to moderate (0.69-point difference) and mild (0.71-point difference) AD who received crenezumab in the 300 mg SC cohort (table e-1, links.lww.com/WNL/A462). Likewise, no treatment effect was seen in any prespecified patient population receiving 15 mg/kg IV crenezumab (table 2).

The secondary efficacy endpoint evaluated the change in ADCS-ADL score from baseline to week 73. No statistically significant differences were observed between crenezumab and placebo in the 300 mg SC cohort. At week 73, a difference of −1.42 points for the mild to moderate AD population was observed. A difference of −2.78 points in the prespecified mild AD (MMSE score 20–26) population was also observed (table e-2, links.lww.com/WNL/A462). In the 15 mg/kg IV cohort, there was a reduction of 0.51 points for the mild to moderate (MMSE score 18–26) population and 2.18 points in the mild (MMSE score 20–26) AD population (table 2).

In the exploratory post hoc subgroup analysis of patients with very mild AD (MMSE score 22–26), no effect was observed on the ADAS-Cog12 for the low-dose 300 mg SC crenezumab cohort (figure 1, B and C and table e-1, links.lww.com/WNL/A462). However, patients receiving 15 mg/kg IV crenezumab (figure 1F and table 2) with a baseline MMSE score of 22 to 26 had a 3.44-point difference. No treatment effect on the CDR-SB was seen in patients with very mild AD with a baseline MMSE score of 22 to 26 in either cohort (table e-1 and table 2). No change in ADCS-ADL score was seen from baseline to week 73; patients with MMSE scores of 22 to 26 in the 300 mg SC crenezumab cohort demonstrated a difference of −1.10 points compared with placebo (table e-1). In the 15 mg/kg IV cohort, there was a reduction of 0.12 points in the very mild (MMSE score 22–26) population (table 2).

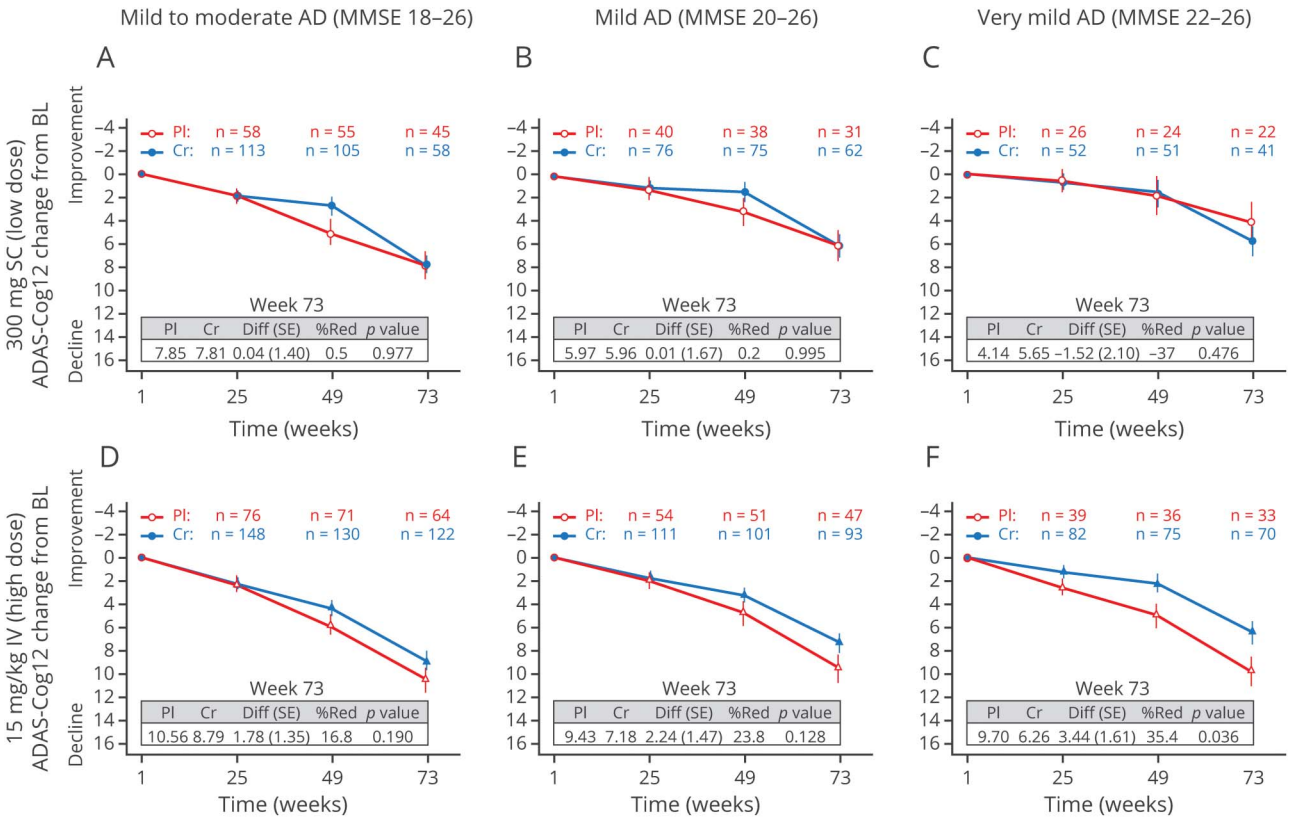
For the 15 mg/kg IV dose cohort, the population with a baseline MMSE score of 22 to 26 was the first post hoc

Table 1 Baseline demographics and disease characteristics

	300 mg SC every 2 wk (low dose)		15 mg/kg IV every 4 wk (low dose)[a]	
	Placebo (n = 62)	Crenezumab (n = 122)	Placebo (n = 84)[b]	Crenezumab (n = 165)[b]
Age (SD), y	70.3 (7.2)	71.2 (6.3)	69.9 (7.1)	70.9 (6.9)
Sex, female (%)	48.4	54.1	57.1	50.9
Weight (SD), kg	72.7 (13.7)	74.3 (15.5)	71.0 (13.0)	71.5 (14.0)
Projected mean dose of crenezumab, mg[c]	0	300	0	1072.5
MMSE mean score (SD)	21.5 (2.6)	21.7 (2.8)	21.6 (2.5)	21.9 (2.7)
MMSE score 20–26, %	71.0	70.5	72.6	73.3
***APOE* ε4 carriers, %**	64.5	63.9	71.4	70.9
ADAS-Cog12 mean score (SD)	28.8 (9.5)	28.2 (8.5)	27.1 (7.5)	28.9 (9.2)
CDR-SB mean score (SD)	4.6 (2.2)	4.7 (1.9)	4.5 (2.1)	4.5 (2.2)
ADCS-ADL mean score (SD)	64.5 (10.5)	64.4 (9.5)	65.0 (10.7)	63.7 (10.9)
Patients using AChEI, memantine, or both, %	87.1	84.4	86.9	88.5

Abbreviations: AChEI = acetylcholinesterase inhibitor; ADAS-Cog12 = 12-point Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR-SB = Clinical Dementia Rating–Sum of Boxes; MMSE = Mini-Mental State Examination.
[a] Safety population; does not include safety run-in cohort.
[b] Randomization population; includes 2 patients who withdrew before the first dose.
[c] Projected mean dose calculated from the mean baseline weight of patients.

Figure 1 ADAS-Cog12 scores



Mean change from baseline to week 73 in (A and D) mild to moderate (MMSE score 18–26), (B and E) mild (MMSE score 20–26), and (C and F) milder (MMSE score 22–26) populations. (A–C) Low-dose 300 mg SC cohort. (D–F) High-dose 15 mg/kg IV cohort. Error bars show SE of the least-squares mean. AD = Alzheimer disease; ADAS-Cog12 = 12-point Alzheimer's Disease Assessment Scale–Cognitive Subscale; BL = baseline; Cr = crenezumab; Diff = difference; MMSE = Mini-Mental State Examination; %Red = percentage reduction; Pl = placebo; SC = subcutaneous; SE = standard error.

subpopulation based on MMSE to be examined. Subsequently, even milder populations defined by an MMSE score of 24 to 26 were also analyzed, as were those with an MMSE score of 26 alone (table e-2, links.lww.com/WNL/A462). These results indicate that the observed percentage reduction relative to placebo consistently increases for ADAS-Cog12 and generally increases for CDR-SB as the subgroups become milder. For ADAS-Cog12, the percentage reduction in the high-dose 15 mg/kg IV cohort ranges from 16.8% for the subgroup with a baseline MMSE score of 18 to 26 to 53.0% for the subgroup with a baseline MMSE score of 26. For CDR-SB, the percent reduction is 3.1% for the subgroup with a baseline MMSE score of 18 to 26 and 54.4% for the subgroup with a baseline MMSE score of 26. No beneficial treatment effects were observed for ADCS-ADL except in the mildest subgroup with a baseline MMSE score of 26, in whom a 42.4% reduction relative to placebo was observed (table e-2).

Crenezumab pharmacokinetics

Crenezumab serum trough concentrations at steady state were 69.2 (29.6) μg/mL after 300 mg SC every 2 weeks dosing and 118 (71.3) μg/mL after 15 mg/kg IV every 4 weeks dosing.

Crenezumab mean steady-state trough concentrations in CSF were 0.19 (SD 0.14) μg/mL and 0.25 (SD 0.12) μg/mL in the 300 mg SC and the 15 mg/kg IV cohort, respectively (figure e-3, links.lww.com/WNL/A461). The proportion of crenezumab detected in the CSF in relation to the serum concentration was similar between doses and routes of administration, with a mean ratio of CSF to serum of 0.28% (SD 0.19%) and 0.29% (SD 0.16%) in the 300 mg SC and 15 mg/kg IV cohorts, respectively.

Biomarker outcomes

No treatment effect was observed in an exploratory volumetric MRI analysis of hippocampal volume, ventricular volume, and whole-brain volume (figure e-4, links.lww.com/WNL/A461).

A statistically significant difference in mean change from baseline in CSF $A\beta_{1-42}$ levels between the crenezumab and placebo groups of −120.16 pg/mL (unadjusted $p = 0.017$) (300 mg SC cohort) and −170.50 pg/mL (unadjusted $p = 0.022$) (15 mg/kg IV cohorts), respectively, was detected (figure e-5A and e-5D, links.lww.com/WNL/A461). No consistent drug-placebo difference was observed in CSF tau or phosphorylated tau levels in either dose group (figure e-5B, e-5C, e-5E, and e-5F). Time-matched CSF crenezumab levels and CSF $A\beta_{1-42}$ changes showed no clear correlation (figure 2).

Table 2 Primary, secondary, and exploratory clinical outcomes in high-dose 15 mg/kg IV cohort at week 73 (placebo vs crenezumab; mITT population)

MMSE range	Placebo, n	Crenezumab, n	Placebo LSM (SE)	Crenezumab LSM (SE)	Difference (SE)	95% CI	*p* Value	Reduction, %[a]	Effect size[b] (SD)
ADAS-Cog12									
18–26	64	122	10.56 (1.09)	8.79 (0.79)	1.78 (1.35)	−0.89 to 4.44	0.190	16.8	0.20 (9.08)
20–26	47	93	9.43 (1.20)	7.18 (0.85)	2.24 (1.47)	−0.66 to 5.15	0.128	23.8	0.27 (8.44)
22–26[c]	33	70	9.70 (1.33)	6.26 (0.91)	3.44 (1.61)	0.24 to 6.64	0.036	35.4	0.44 (7.80)
18–19	17	29	13.82 (2.33)	13.66 (1.84)	0.16 (2.99)	−5.89 to 6.20	0.959	1.1	0.02 (10.2)
18–21	31	52	11.79 (1.77)	11.94 (1.37)	−0.15 (2.25)	−4.62 to 4.32	0.947	−1.3	−0.01 (10.4)
CDR-SB									
18–26	67	126	2.57 (0.35)	2.49 (0.25)	0.08 (0.43)	−0.77 to 0.92	0.853	3.1	0.03 (2.94)
20–26	48	96	2.18 (0.40)	2.21 (0.28)	−0.02 (0.49)	−1.00 to 0.96	0.964	−1.0	−0.01 (2.91)
22–26[c]	34	71	2.24 (0.45)	1.80 (0.31)	0.44 (0.55)	−0.65 to 1.52	0.423	19.6	0.16 (2.75)
18–19	19	30	3.49 (0.65)	3.39 (0.51)	0.10 (0.83)	−1.58 to 1.77	0.908	2.8	0.03 (2.92)
18–21	33	55	2.94 (0.52)	3.38 (0.40)	−0.44 (0.66)	−1.74 to 0.87	0.507	−14.9	−0.14 (3.08)
ADCS-ADL									
18–26	68	125	−9.04 (1.44)	−9.55 (1.06)	0.51 (1.79)	−3.02 to 4.04	0.775	−5.7	0.04 (12.3)
20–26	48	95	−5.96 (1.57)	−8.14 (1.12)	2.18 (1.93)	−1.64 to 6.00	0.260	−37.0	0.19 (11.2)
22–26[c]	34	70	−6.21 (1.71)	−6.34 (1.20)	0.12 (2.10)	−4.04 to 4.29	0.953	−2.0	0.01 (10.3)
18–19	20	30	−16.7 (2.98)	−13.6 (2.37)	−3.15 (3.81)	−10.8 to 4.51	0.413	18.8	−0.23 (13.7)
18–21	34	55	−12.3 (2.32)	−13.5 (1.80)	1.28 (2.93)	−4.55 to 7.11	0.664	−10.4	0.09 (13.8)

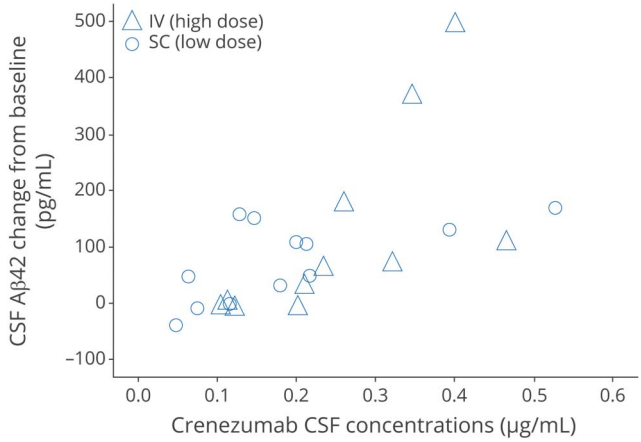
Abbreviations: ADAS-Cog12 = 12-point Alzheimer's Disease Assessment Scale–-Cognitive Subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR-SB = Clinical Dementia Rating–Sum of Boxes; LSM = least-squares mean; mITT = modified intent-to-treat; MMSE = Mini-Mental State Examination; SE = standard error.
[a] Percentage reduction relative to placebo.
[b] Standardized effect size.
[c] Exploratory post hoc analysis.

Safety

The overall rate of AEs was balanced between the active and placebo arms of the study and between the 2 cohorts. The majority of reported AEs were grade 1 or 2 in severity (table 3). An imbalance in the frequency of SAEs was observed that was driven mostly by reports of serious pneumonia, syncope, and Alzheimer-type dementia. An imbalance in the rates of SAEs and non-SAEs of pneumonia was observed; however, there was no evidence of an exposure-response relationship within each cohort. An imbalance in fatal events was observed, with 3 deaths (1.0%) in the crenezumab arms compared with no deaths in the placebo arms. All cases were considered by the investigators to be unrelated to the treatment and were within the expected rates for this population.[24]

The frequency of AEs grade 3 or greater was balanced between the placebo and crenezumab treatment arms across both the 300 mg SC and 15 mg/kg IV cohorts. In the 15 mg/kg IV cohort, more AEs of grade 3 or greater were observed in the crenezumab arm (17.0%, 28 patients) relative to the placebo

Figure 2 CSF $A\beta_{1-42}$ and crenezumab correlation analysis



Correlation analysis of change in CSF $A\beta_{1-42}$ from baseline and crenezumab concentrations in patients receiving low-dose 300 mg SC (circles) and those receiving high-dose 15 mg/kg IV (triangles). Aβ = β-amyloid.

arm (13.4%, 11 patients). This imbalance was driven mainly by cardiovascular events (25% of grade 3 or greater AEs, 7 patients in the crenezumab arm; 18% of grade 3 or greater AEs, 2 patients in the placebo arm), with no clear causal relationship to the study drug, and events (e.g., syncope and atrial fibrillation) were as expected for this patient population.[24] The incidences of AEs leading to discontinuation were balanced between the placebo (4.2%, 6 patients) and crenezumab (3.3%, 10 patients) groups, and no clear pattern for discontinuation was observed.

The incidence of new ARIA-H was balanced between the low-dose and high-dose cohorts (table e-3, links.lww.com/WNL/A462). A single case of asymptomatic ARIA-E was observed in an *APOE* ε4 homozygous female patient in the crenezumab 15 mg/kg IV cohort. A single case of asymptomatic macrohemorrhage was detected in 1 patient receiving crenezumab in the 15 mg/kg IV cohort; the patient was discontinued from study treatment at the time of diagnosis (week 35).

Injection- or infusion-related AEs were balanced across treatment arms, and there was no evidence of clinically relevant immunogenicity in patients receiving crenezumab.

Discussion

This proof-of-concept study in mild to moderate AD found no difference between 2 dose levels of crenezumab and placebo on the coprimary endpoint (ADAS-Cog12 and CDR-SB scores). In post hoc exploratory analysis of patients who received the higher dose of 15 mg/kg IV crenezumab, consistently increasing percentage reductions relative to placebo for the ADAS-Cog12 and CDR-SB endpoints were observed in progressively milder subgroups. These post hoc analyses need confirmation in follow-up studies, but they suggest that earlier treatment and/or higher doses may improve the beneficial effect of crenezumab.

A dose-dependent increase (1.3–1.7 fold) in crenezumab trough concentrations in serum and CSF was observed. The

Table 3 Summary of AEs

	300 mg SC every 2 wk (low dose)		15 mg/kg IV every 4 wk (high dose)[a]	
	Placebo (n = 62)	Crenezumab (n = 122)	Placebo (n = 82)	Crenezumab (n = 165)
Patients with ≥1 AEs, n (%)	57 (91.9)	114 (93.4)	72 (87.8)	146 (88.5)
Death, n (%)	0 (0)	2 (1.6)	0 (0)	1 (0.6)
SAEs, n (%)	6 (9.7)	16 (13.1)	11 (13.4)	32 (19.4)
AEs of grade 3 or greater, n (%)	9 (14.5)	14 (11.5)	11 (13.4)	28 (17.0)
Serious pneumonia, n (%)	0 (0)	1 (0.8)	1 (1.2)	4 (2.4)
Syncope, n (%)	0 (0)	1 (0.8)	1 (1.2)	2 (1.2)
Alzheimer-type dementia, n (%)	0 (0)	1 (0.8)	0 (0)	2 (1.2)
Most frequent AEs, n (%)				
Nasopharyngitis	6 (9.7)	21 (17.2)	8 (9.8)	13 (7.9)
UTI	6 (9.7)	16 (13.1)	10 (12.2)	17 (10.3)
URTI	10 (16.1)	16 (13.1)	4 (4.9)	7 (4.2)
Fall	5 (8.1)	19 (15.6)	5 (6.1)	14 (8.5)
Headache	3 (4.8)	15 (12.3)	7 (8.5)	15 (9.1)

Abbreviations: AE = adverse event; CI = confidence interval; SAE = serious adverse event; UTI = urinary tract infection; URTI = upper respiratory tract infection. NCI CTCAE (Version 4.0).
[a] Safety population; does not include safety run-in cohort.

CSF/serum ratio was ≈0.3% for both cohorts, suggesting dose-proportional penetration into the CNS. The current study does not reveal the exposure driver for efficacy because dose is confounded by route of administration (IV vs SC) and schedule (every 4 vs every 2 weeks). However, the 15 mg/kg IV dose maintains concentrations above the 300 mg SC dose throughout the dosing interval, supporting testing doses that provide higher concentrations.

The increase in CSF $A\beta_{1\text{-}42}$ observed in this study suggests crenezumab achieved target engagement in the brain. There were, however, no changes in CSF total tau or phosphorylated tau. The increase in CSF $A\beta_{1\text{-}42}$ associated with crenezumab treatment could reflect increased input of $A\beta_{1\text{-}42}$ into CSF, decreased clearance of CSF $A\beta_{1\text{-}42}$ out of CSF, or a shift in CSF Aβ content toward more species that are detected by the $A\beta_{1\text{-}42}$ assay. Understanding the relationship between the pharmacodynamic effects on CSF Aβ and amyloid PET and their correlation with cognitive change requires larger follow-up studies.

The incidence of ARIA-E was low with crenezumab and within the background rates of ARIA-E in the mild to moderate AD population (0.2%–0.4%), as observed in similar studies[9,25] and lower than observed with other anti-Aβ monoclonal antibody treatments that showed rates of ARIA-E up to 55% among *APOE* ε4 homozygotes.[9,26–28] In addition, the incidence of ARIA-H was 14.6% in patients receiving placebo and 10.3% in patients receiving crenezumab, suggesting that the drug did not increase the number of new microhemorrhages in this trial.

The overall rate of AEs was balanced in crenezumab- and placebo-treated patients. Although the rate of pneumonia was imbalanced with a higher percentage of cases in crenezumab-treated patients, the frequency in crenezumab-treated patients was within the range that is expected in an elderly population (2.5%–4.4%).[29] In addition, there was a dose-independent imbalance in the rate of urinary tract infections in crenezumab-treated patients. While dose independence does not rule out a causal relationship to treatment, the lower rate of urinary tract infections in the high-dose cohort (10.3%) than in the placebo group (12.2%) suggests that this is unlikely. The higher rate of headaches and falls was also dose independent and, on the basis of individual case assessment, considered unrelated to study drug. The 2 ongoing phase 3 studies will provide more precise and detailed data on the safety profile of crenezumab. Together, these data suggest that crenezumab was generally well tolerated.

Although this trial did not meet the primary endpoints, post hoc analysis of the effects of crenezumab in patients with very mild AD in the high-dose 15 mg/kg IV cohort suggests the utility of treating AD earlier and with higher doses of crenezumab. Because the safety profile observed in this trial suggested generally good tolerability, allowing the evaluation of higher dose levels, two similar crenezumab phase 3 studies (A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants With Prodromal to Mild Alzheimer's Disease [CREAD, NCT02670083; CREAD2, NCT03114657]) are ongoing in patients in the prodromal to mild phase (MMSE score 22–30) using a higher dose of crenezumab intended to drive efficacy while maintaining tolerability.

Author contributions

J.L.C., M.W., D.C., and R.P. designed the study. J.L.C., M.W., M.F., A.Q., R.N.F., and R.P. contributed to the writing of the first draft, Methods section, and background of the report. J.L.C., S.C., M.B., and C.H.v.D. were involved in data collection and study execution. W.C., M.W., M.F., C.R., F.B., A.Q., L.A.H., D.C., D.M., and C.H. provided guidance on and performed statistical analysis and data interpretation. All authors critically reviewed and edited the manuscript.

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FULL-LENGTH ARTICLE NPub.org/u91gru

ABBY

A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease

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Trial registration number
NCT01343966 on ClinicalTrials.gov.

Study question
Is crenezumab effective for patients with mild to moderate Alzheimer disease (AD)?

Summary answer
Although crenezumab is not effective for mild to moderate AD in general, high-dose crenezumab may be effective for mild AD.

Classification of evidence
Class II.

What is known and what this paper adds
Crenezumab is a β-amyloid (Aβ)-targeting monoclonal antibody designed to avoid certain adverse effects that have been reported for similar Aβ-targeting monoclonal antibodies. This study provides tentative evidence that crenezumab may be effective for some patients with AD.

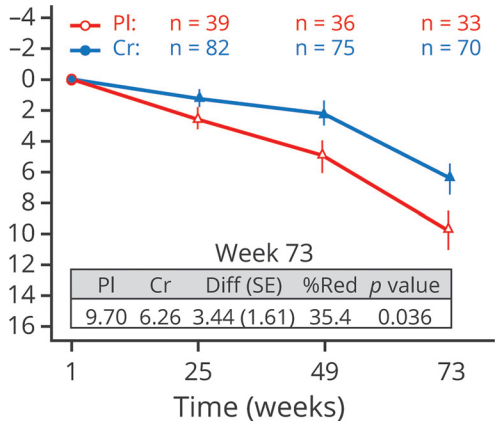
Participants and setting
This study examined 431 patients with mild to moderate probable AD at 72 sites in North America and Europe from April 25, 2011, to February 18, 2014. The patients were 50–80 years old and had Mini-Mental State Examination (MMSE) scores of 18–26 points.

Design, size, and duration
This double-blind, parallel-group phase II trial was conducted in 2 overlapping parts. In part 1, patients were randomly assigned to receive either 300 mg of subcutaneous crenezumab or placebo every 2 weeks; whereas in part 2, they received either 15 mg/kg of IV crenezumab every 4 weeks, or placebo. Dynamic hierarchic randomization was used to assign patients to crenezumab and placebo groups, and randomization into the 2 parts was independent and sequential. There were 184 part 1 patients (122 patients treated with crenezumab and 62 patients treated with placebo) and 247 part 2 patients (165 patients treated with crenezumab and 82 patients treated with placebo).

Primary outcomes
The primary efficacy outcomes were changes from baseline on the 12-item AD Assessment Scale-Cognitive Subscale (ADAS-Cog) scores and Clinical Dementia Rating-Sum of Boxes scores at week 73.

Main results and the role of chance
Part 2 patients with very mild AD (i.e., MMSE scores of 22–26) treated with crenezumab exhibited smaller from-baseline increases in ADAS-Cog scores than did part 2 patients treated with placebo ($p = 0.036$). No other drug-vs-placebo differences were noted.

Figure Mean from-baseline changes in ADAS-Cog scores in week 73 in participants who received IV crenezumab or placebo treatment



Harms
The patients treated with crenezumab and patients treated with placebo had similar adverse event rates.

Bias, confounding, and other reasons for caution
The primary endpoints were not met, and the findings for patients with very mild AD require confirmation in follow-up studies.

Generalizability to other populations
The large international patient group favors the generalizability of the results.

Study funding/potential competing interests
This study was funded by Genentech, a member of the Roche Group. Several authors are current or former employees of Genentech or Roche Diagnostics and own stock or stock options in Roche. Some authors report receiving research support, honoraria, and consulting fees from various healthcare companies including Genentech and Roche. Go to Neurology.org/N for full disclosures.

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