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Alzheimer's & Dementia

Featured Article

Multiple-dose ponezumab for mild-to-moderate Alzheimer's disease: Safety and efficacy

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Abstract

Introduction: Multiple intravenous doses of ponezumab, an anti-amyloid antibody, were evaluated in subjects with mild-to-moderate Alzheimer's disease (AD).

Methods: In part A, 77 subjects were randomized to ponezumab 0.1, 0.5, or 1 mg/kg (75 treated) and 26 to placebo (24 treated). In part B, 63 subjects were randomized and treated with ponezumab 3 or 8.5 mg/kg and 32 with placebo. Subjects received 10 infusions over 18 months and were followed for 6 months thereafter.

Results: Ponezumab was generally safe and well tolerated. Most common adverse events were fall (16.7% ponezumab, 21.4% placebo), headache (13.8%, 21.4%), and cerebral microhemorrhage (13.8%, 19.6%). Plasma ponezumab increased dose-dependently with limited accumulation. Cerebrospinal fluid penetration was low. Plasma $A\beta_{1-x}$ and $A\beta_{1-40}$ showed robust increases, but cerebrospinal fluid biomarkers showed no dose response. Ponezumab had no effects on cognitive/functional outcomes or brain volume.

Conclusions: Multiple-dose ponezumab was generally safe, but not efficacious, in mild-to-moderate AD.

Keywords: Alzheimer's disease; Amyloid β; Biomarkers; Cerebrospinal fluid; Immunotherapy; Monoclonal antibody; Pharmacokinetics; Pharmacodynamics; Phase-II study; Ponezumab

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1. Introduction

The accumulation of amyloid β (Aβ) is thought to be integral to the pathogenesis of Alzheimer's disease (AD), contributing to the formation of neuritic plaques [1]. The mean level of soluble Aβ in the brain parenchyma is increased 3-fold in patients with AD compared with age-matched controls and correlates highly with measures of tau reactivity in tangles and plaques, as well as neurofibrillary tangle density [2]. Reducing amyloid deposits in brain may be warranted in some subpopulations of mild-to-moderate AD. However, amyloid is thought to begin accumulating long before the clinical symptoms of AD appear; therefore, removal of Aβ from brains of patients who have already progressed to dementia may have limited value.

The brains of patients with AD also typically display cerebral amyloid angiopathy (CAA), a pathological condition caused by the progressive deposition of $A\beta_{1–40}$ surrounding cerebral blood vessel walls [3]. Although comorbidity of AD and CAA is almost universal, there are clear distinctions between them, such as the Aβ species being deposited ($A\beta_{1–42}$ in AD vs. $A\beta_{1–40}$ in CAA), the location of the Aβ deposits (brain parenchyma vs. brain vasculature), and the presence of cerebral microhemorrhages that are the signature of CAA [3].

Current therapeutic options for AD provide limited clinical benefit. Recent advances in the development of therapies targeting Aβ include the anti-Aβ antibodies bapineuzumab, solanezumab, and aducanumab [4–7]. Although the approach initially appeared promising, bapineuzumab did not improve clinical outcomes [4]. Similarly, solanezumab failed to significantly improve cognitive or functional ability in patients with mild-to-moderate AD [5], although secondary analyses suggested that it may be associated with less worsening of cognition than placebo in individuals with mild AD [6]. Data from the extension arm of the solanezumab studies using a delayed-start design indicated a potential modifying effect on underlying disease progression [7]. A phase-Ib study is currently under way to evaluate aducanumab (BIIB037) in patients with prodromal or mild AD (PRIME, NCT01677572) [8]. The double-blind portion showed a statistically significant reduction of brain amyloid as assessed by the florbetapir PET scan. Clinical progression also appeared to be slowed, although amyloid-related imaging abnormalities (ARIAs; magnetic resonance imaging [MRI] signal changes thought to represent vasogenic edema and cerebral microhemorrhage) were commonly observed adverse events (AEs), raising some safety concerns [9]. Two phase-III studies of aducanumab are ongoing in subjects with early AD (EMERGE, NCT02484547; ENGAGE, NCT02477800) [10,11].

Ponezumab is a humanized $IgG_2\Delta a$ anti-Aβ monoclonal antibody that targets specific amino acids (30–40 of $A\beta_{40}$) in the C-terminus of the Aβ sequence. It binds only to soluble Aβ and has a low propensity to induce immune responses [12]. Ponezumab's primary mechanism of action is believed to be sequestration of Aβ in the blood and shifting the brain-blood equilibrium toward the periphery, thereby depleting central Aβ stores (the peripheral sink hypothesis). Studies of ponezumab in preclinical murine models of amyloid overexpression have reported depletion of insoluble brain Aβ deposits and reversal of cognitive defects [13].

Single intravenous doses of ponezumab 0.1–10 mg/kg were shown to be safe and well tolerated in Western and Japanese subjects with mild-to-moderate AD [14–16]. This phase-II, double-blind, randomized, placebo-controlled study was conducted to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), efficacy (secondary objective), and immunogenicity of multiple intravenous doses of ponezumab in subjects with mild-to-moderate AD.

2. Methods

2.1. Subjects

Eligible subjects were males and females of nonchildbearing potential, who were aged ≥50 years with a diagnosis of mild-to-moderate AD based on a Mini–Mental State Examination (MMSE) score of 16 to 26 inclusive, and probable AD consistent with criteria from the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association, and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Subjects were also required to have a Rosen-Modified Hachinski Ischemic Score ≤4 at enrollment.

Subjects were required to be in general good health, without known presenilin mutations or a history of familial (early onset) AD and on a stable dose of background cholinesterase inhibitor and/or memantine at least 60 days before dosing. Background therapy was not mandatory for world regions where it was not the standard of care or where intolerant.

The main exclusion criteria are summarized in the Online Supplement. Specific exclusionary brain MRI findings included the following: cortical infarct of any size; >2 microhemorrhages; strategically located subcortical gray-matter infarct (e.g., hippocampus, thalamus, caudate head); and multiple (two or more) white-matter lacunes.

Informed consent was obtained from all subjects, and the study was approved by the institutional review boards and/or independent ethics committees at each investigational center. The study was conducted in compliance with the Declaration of Helsinki and with all the International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements were also followed.

2.2. Study design

The study was conducted between December 2008 and August 2011 at 30 centers worldwide. The study was composed of two parts, with a total of five ponezumab and two placebo dose arms; in part A, subjects were randomized to receive ponezumab 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, or placebo, and in part B, three additional cohorts were randomized to receive ponezumab 3 mg/kg, 8.5 mg/kg, or placebo.

Treatment was administered as ten 2-hour infusions every 60 days over 18 months. The treatment phase was followed by a 6-month safety follow-up, for a total study duration of 24 months (Fig. 1).

2.3. Study objectives

The primary objectives of the study were to characterize the safety, tolerability, and PK of multiple doses of ponezumab. Secondary objectives included the following: assessment of cognitive efficacy; changes in biomarkers (Aβ species in cerebrospinal fluid [CSF] and plasma, as well as CSF tau and phospho-tau [p-tau] levels); and immunogenicity after repeat dosing.

2.4. Assessments

2.4.1. Safety

Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), body weight, 12-lead electrocardiograms (ECGs), AEs, safety laboratory tests, physical examinations, neurological examinations, brain MRIs, continuous cardiac monitoring by telemetry during infusion (for abnormal rhythms), and immunogenicity.

AEs were assessed predose and postdose on all dosing days (months 0, 2, 4, 6, 8, 10, 12, 14, 16, and 18); by telephone at months 1, 9, 11, 15, 17, 21, and 23; and during follow-up visits at months 3, 5, 7, 13, 19, 22, and 24. For all the observed and patient-reported AEs, investigators documented the type and intensity (mild, moderate, or severe), and their opinion of relationship to study treatment. AEs included (but were not limited to) adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, clinically significant changes in physical or neurological examination findings, and clinically significant test findings (ECG, laboratory, etc.).

Safety data were reviewed at regular intervals throughout the study by an external, independent data safety monitoring board. In addition to the scheduled data reviews, four interim analyses were planned for part A and four for part B.

Core safety assessments were supplemented by six mandatory brain MRIs (with no more than 6 months between each MRI) and optional lumbar punctures at baseline, month 3, and month 19. Safety laboratory evaluations and ECGs were conducted at screening; predose on each dosing day; and at months 3, 7, 13, 19, and 24.

Monitoring for intracranial pathology, including cerebral microhemorrhages, superficial siderosis, and vasogenic edema was performed by two external radiologists (central reader) experienced in reading T2* gradient-echo (GRE) images (C.R.J. and K.K.). Microhemorrhages were defined as homogenous hypointense lesions up to 10 mm in diameter in the gray or white matter on T2* GRE images. Superficial siderosis was defined as curvilinear hypointensities overlying the cortical surface, distinct from vascular flow voids [17]. All the scans were read immediately locally for safety but also transmitted to a central reader for neuroimaging analysis and additional safety review.

In addition to the T2* GRE images, sequences in the MRI protocol included 3D MP-RAGE/SPGR sagittal, fluid-attenuated inversion recovery axial, diffusion-weighted imaging axial, and T1 axial pregadolinium (gadolinium contrast optional). Brain volumetrics (hippocampal, ventricular, and whole brain) were measured by MRI at baseline and at months 3, 7, 13, 19, and 24.

2.4.2. Efficacy

Cognitive efficacy was assessed using the 70-point Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and Disability Assessment for Dementia (DAD) scale at baseline and at months 3, 7, 13, 19, and 24. Exploratory measures of efficacy included the MMSE, the Cognitive State (CogState) computerized battery, the Neuropsychological Test Battery (NTB), and the Neuropsychiatric Inventory (NPI-12), which were conducted at the same visits as the ADAS-Cog and DAD. In this study, the NTB included the controlled oral word association test, the category fluency test, and the trail-making test. The Clinical Dementia Rating (CDR) Scale global score and CDR Sum of Boxes (CDR-SB) were recorded at baseline and month 19. Quality of life was assessed with the EuroQoL-5D (EQ-5D) instrument at baseline and months 13, 19, and 24.

2.4.3. Pharmacokinetics and pharmacodynamics

Plasma, urine, and optional CSF samples were collected to define ponezumab PK profile and its PD effects on Aβ species, total tau, and p-tau. Plasma and urine samples were collected predose and postdose on each dosing day (months 0, 2, 4, 6, 8, 10, 12, 14, 16, and 18) and at months 3, 5, 7, 13, 19, 22, and 24. Optional CSF samples for PK and PD analyses were collected at baseline and at months 3 and 19.

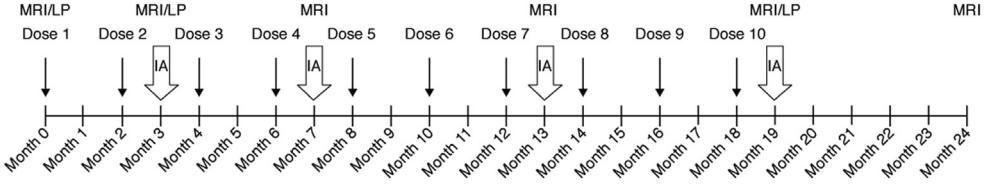


Fig. 1. Study schematic. Abbreviations: IA, interim analysis; LP, lumbar puncture; MRI, magnetic resonance imaging.

Plasma, urine, and CSF samples were analyzed for ponezumab concentrations using validated, sensitive, and specific enzyme-linked immunosorbent assay methods. The lower limits of quantification were 78.1 ng/mL for plasma, 60 ng/mL for urine, and 12 ng/mL for CSF.

Plasma samples were analyzed for $A\beta_{1-x}$, $A\beta_{1-40}$, and $A\beta_{1-42}$. Urine samples were analyzed for $A\beta_{1-x}$ only. The CSF samples were analyzed for all Aβ species, total tau, and p-tau using validated assays (Supplementary Table 1).

2.4.4. Immunogenicity assessments

Blood samples were collected for assessment of immunogenicity (antidrug antibodies [ADAs]) before ponezumab infusion on each dosing day, as well as at months 3, 5, 7, 13, 19, 22, and 24. Serum was analyzed following a tiered approach using screening, confirmation, and titer/quantitation assays, as applicable. A validated semiquantitative enzyme-linked immunosorbent assay method was used. Assay precision was <8% coefficient of variation (CV) for the positive control and <10.2% CV for the negative control (used to calculate cut point).

2.4.5. Pharmacogenomics

A blood sample was obtained at baseline for apolipoprotein E (*APOE*) genotyping. Subjects who were classified as *APOE* ε4 positive had a genotype that included at least one copy of the *APOE* ε4 allele.

2.5. Statistical analysis

All analyses were performed for each study part separately. A mixed model repeat measures approach was applied to compare the mean change from baseline for ADAS-Cog total score, DAD total score, MMSE total score, CogState individual tasks and composite score, NTB individual tests and composite score, NPI total score, EQ-5D visual analogue scale, and brain volumes between each active dose and placebo for each visit for the full analysis set (FAS; all subjects who were randomized and received at least one infusion of study medication). The primary assessment was the change from baseline at the month 19 visit (approximately 30 days following the last study drug infusion). The fixed effects in the model were time (as categorical), treatment, treatment-by-time interaction, baseline value, and country. An unstructured variance-covariance matrix was assumed for the within-subject errors. Analysis of covariance was used to compare the mean change from baseline for CDR-SB between each active dose and placebo at month 19 using the FAS. The effects in the model were treatment, baseline CDR-SB, and country.

Two-sided hypothesis tests comparing each active treatment with placebo were conducted for each end point at the nominal $\alpha = 0.10$ level without adjustment for multiple treatment contrasts or multiple end points. Least squares means, with standard errors, for the change from baseline and treatment differences from placebo were estimated along with 90% confidence intervals.

3. Results

3.1. Subject disposition

A total of 198 subjects were randomized and 194 received at least one infusion of blinded study medication; these subjects comprised the FAS (99 in study part A and 95 in study part B). They received a median of 10 infusions (range: 1–10 infusions), with a similar number in each treatment group. Of the 194 treated subjects, 146 completed the study and 48 discontinued the study.

Demographic and baseline characteristics were comparable across treatment groups (Table 1). There were 105 females and 89 males, and the proportions were generally similar across treatment groups. Most subjects were white ($n = 138$), and ages ranged from 51 to 90 years. At screening, 121 subjects (62.4%) had mild dementia (MMSE 21–26) and 73 subjects (37.6%) had moderate dementia (MMSE 16–20). *APOE* ε4 carrier status was positive for 129 subjects (66.5%), negative (non-*APOE* ε4 carrier status) for 63 subjects (32.5%), and unknown for two subjects (1%). These proportions were also similar across treatment groups.

3.2. Safety

All subjects who received at least one infusion of study medication were included in the safety analysis set ($n = 194$). Ponezumab was generally safe and well tolerated. A total of 183 subjects had at least one treatment-emergent AE, including 86 who had an AE that was considered by the investigator to be treatment related. The most common all-causality AEs were fall (16.7% ponezumab, 21.4% placebo), headache (13.8% ponezumab, 21.4% placebo), and cerebral microhemorrhage (13.8% ponezumab, 19.6% placebo) (Table 2). The most frequently reported treatment-related AEs were incident cerebral microhemorrhage (ARIA with microhemorrhage) (8.7% ponezumab, 16.1% placebo), headache (5.1% and 7.1%, respectively), and fatigue (5.1% and 3.6%, respectively) (Table 2). No treatment-related brain macrohemorrhage or meningoencephalitis was noted. In the MRI analysis, the incidence of microhemorrhages was 16.4% in the pooled ponezumab group and 21.4% in the pooled placebo group over the 24-month observation period. Note that not all microhemorrhages identified by MRI were reported by the investigator as AEs, and the incidences are based only on subjects with a postbaseline MRI. Thus, the incidence of microhemorrhages may differ between the AE reports and the MRI analyses. Incident brain abnormalities noted on MRI included cerebral edema (one subject receiving ponezumab 0.5 mg/kg), cerebral/meningeal enhancement (one subject receiving ponezumab 0.5 mg/kg), subdural hematoma (one subject receiving ponezumab 0.5 mg/kg), cortical infarcts (one subject receiving ponezumab 0.1 mg/kg, two receiving 1 mg/kg, and one receiving 8.5 mg/kg), subcortical gray-matter infarcts (one subject receiving ponezumab 3 mg/kg and one receiving 8.5 mg/kg), white-matter infarcts (one subject receiving ponezumab 0.5 mg/kg and

Table 1
Subjects' baseline and demographic characteristics

	Ponezumab				Ponezumab		
	0.1 mg/kg	0.5 mg/kg	1.0 mg/kg	Placebo A	3.0 mg/kg	8.5 mg/kg	Placebo B
Demographic characteristic	$n = 25$	$n = 25$	$n = 25$	$n = 24$	$n = 32$	$n = 31$	$n = 32$
Gender, *n*							
Male	13	10	14	11	12	14	15
Female	12	15	11	13	20	17	17
Mean (SD) age, years	70.8 (8.2)	71.9 (9.4)	72.2 (8.4)	70.0 (7.8)	70.5 (8.9)	71.8 (7.3)	70.4 (10.3)
Race, *n*							
White	16	17	19	17	23	21	25
Black	0	0	0	1	2	0	0
Asian	9	8	6	6	7	9	7
Other	0	0	0	0	0	1	0
Mean (SD) years of education	12.4 (3.5)	12.2 (4.7)	11.7 (4.2)	12.1 (3.3)	12.4 (3.6)	12.2 (4.2)	13.7 (4.0)
Mean (SD) screening MMSE	21.5 (2.9)	21.4 (3.6)	20.8 (3.0)	21.0 (3.4)	22.5 (2.5)	20.9 (3.1)	21.9 (3.4)
Mean (SD) baseline ADAS-Cog	20.0 (7.9)	20.4 (8.2)	20.8 (6.1)	20.0 (7.0)	19.4 (7.0)	24.5 (10.1)	18.4 (7.5)

Abbreviations: SD, standard deviation; MMSE, Mini–Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale.

two receiving placebo), and white-matter hyperintensities (three subjects receiving ponezumab 0.5 mg/kg, two receiving 1 mg/kg, four receiving 3 mg/kg, and four receiving placebo).

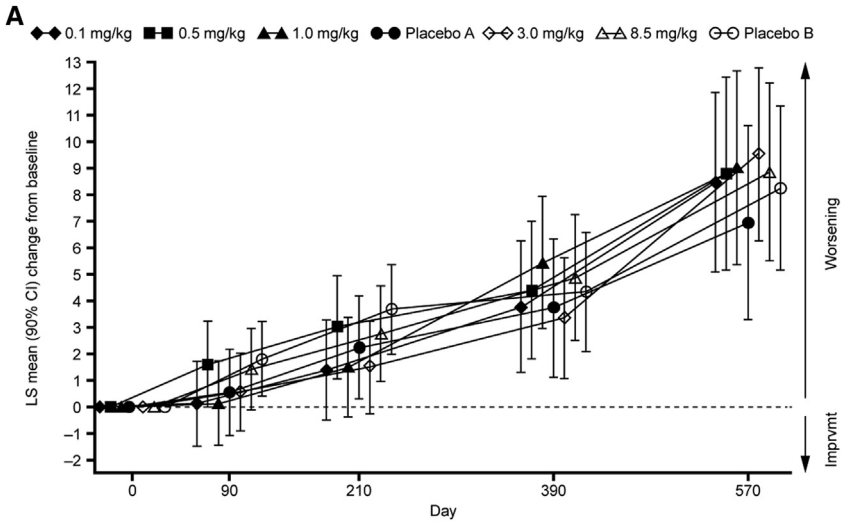
Abnormalities in laboratory parameters, vital signs, and ECG findings showed no clinically meaningful differences among treatment groups, and immunogenicity testing revealed no ADAs in any serum sample.

A total of 58/1296 (4.5%) AEs were severe, of which three were considered treatment-related by the investigator. These were meningeal thickening and bilateral subdural hygromas (resolved 6 months after onset) in one subject

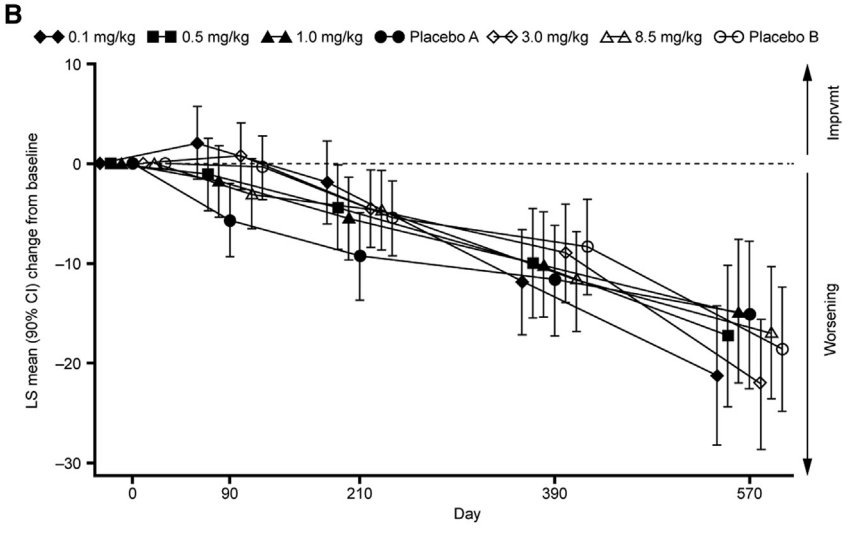
Table 2
Incidence of treatment-emergent, all-causality adverse events occurring in ≥10% of any treatment group

	Ponezumab				Ponezumab		
MedDRA (v14.0) preferred term	0.1 mg/kg	0.5 mg/kg	1.0 mg/kg	Placebo A	3.0 mg/kg	8.5 mg/kg	Placebo B
n (%)	$n = 25$	$n = 25$	$n = 25$	$n = 24$	$n = 32$	$n = 31$	$n = 32$
Cerebral microhemorrhage*	4 (16.0)	6 (24.0)	1 (4.0)	6 (25.0)	2 (6.3)	6 (19.4)	5 (15.6)
Confusional state	0	0	2 (8.0)	1 (4.2)	3 (9.4)	6 (19.4)	2 (6.3)
Fall	2 (8.0)	3 (12.0)	4 (16.0)	3 (12.5)	9 (28.1)	5 (16.1)	9 (28.1)
Headache	4 (16.0)	3 (12.0)	1 (4.0)	4 (16.7)	6 (18.8)	5 (16.1)	8 (25.0)
Fatigue	4 (16.0)	3 (12.0)	5 (20.0)	1 (4.2)	4 (12.5)	4 (12.9)	3 (9.4)
Agitation	1 (4.0)	4 (16.0)	3 (12.0)	3 (12.5)	2 (6.3)	4 (12.9)	2 (6.3)
Decreased appetite	0	1 (4.0)	2 (8.0)	0	1 (3.1)	4 (12.9)	1 (3.1)
Nasopharyngitis	4 (16.0)	0	2 (8.0)	1 (4.2)	5 (15.6)	3 (9.7)	4 (12.5)
Nausea	3 (12.0)	4 (16.0)	1 (4.0)	1 (4.2)	4 (12.5)	3 (9.7)	1 (3.1)
Constipation	3 (12.0)	2 (8.0)	2 (8.0)	0	3 (9.4)	3 (9.7)	1 (3.1)
Anxiety	3 (12.0)	5 (20.0)	1 (4.0)	3 (12.5)	3 (9.4)	3 (9.7)	2 (6.3)
Weight decreased	2 (8.0)	3 (12.0)	4 (16.0)	1 (4.2)	2 (6.3)	3 (9.7)	1 (3.1)
Contusion	1 (4.0)	4 (16.0)	1 (4.0)	2 (8.3)	6 (18.8)	2 (6.5)	5 (15.6)
Urinary tract infection	4 (16.0)	3 (12.0)	2 (8.0)	3 (12.5)	4 (12.5)	2 (6.5)	2 (6.3)
Insomnia	0	1 (4.0)	1 (4.0)	3 (12.5)	4 (12.5)	2 (6.5)	0
Back pain	2 (8.0)	2 (8.0)	4 (16.0)	1 (4.2)	3 (9.4)	2 (6.5)	4 (12.5)
Upper respiratory tract infection	5 (20.0)	4 (16.0)	5 (20.0)	7 (29.2)	1 (3.1)	2 (6.5)	1 (3.1)
Irritability	1 (4.0)	2 (8.0)	0	3 (12.5)	0	2 (6.5)	0
Depression	2 (8.0)	0	4 (16.0)	0	0	2 (6.5)	3 (9.4)
Hypertension	4 (16.0)	3 (12.0)	0	1 (4.2)	4 (12.5)	1 (3.2)	2 (6.3)
Dizziness	2 (8.0)	2 (8.0)	1 (4.0)	3 (12.5)	3 (9.4)	1 (3.2)	3 (9.4)
Cough	2 (8.0)	2 (8.0)	8 (32.0)	4 (16.7)	3 (9.4)	1 (3.2)	1 (3.1)
Diarrhea	3 (12.0)	3 (12.0)	5 (20.0)	1 (4.2)	2 (6.3)	1 (3.2)	5 (15.6)
Pneumonia	0	1 (4.0)	3 (12.0)	1 (4.2)	1 (3.1)	1 (3.2)	2 (6.3)
Aggression	3 (12.0)	2 (8.0)	1 (4.0)	1 (4.2)	1 (3.1)	1 (3.2)	0

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.
*Not all microhemorrhages identified by magnetic resonance imaging were reported by the investigator as adverse events.



	MMRM inferential analysis of ADAS-cog total score change from baseline to Day 570				
	Ponezumab dose				
	0.1 mg/kg (n=22)	0.5 mg/kg (n=18)	1.0 mg/kg (n=16)	3.0 mg/kg (n=21)	8.5 mg/kg (n=21)
Difference from placebo (90% CI)	1.38 (-3.68, 6.45)	2.02 (-3.20, 7.23)	2.27 (-2.94, 7.48)	1.73 (-2.71, 6.17)	0.85 (-3.65, 5.35)
p-value	0.6504	0.5213	0.4698	0.5183	0.7529



	MMRM inferential analysis of DAD total score change from baseline to Day 570				
	Ponezumab dose				
	0.1 mg/kg (n=21)	0.5 mg/kg (n=21)	1.0 mg/kg (n=18)	3.0 mg/kg (n=24)	8.5 mg/kg (n=22)
Difference from placebo (90% CI)	-4.07 (-13.38, 5.24)	-0.18 (-9.59, 9.22)	0.84 (-8.57, 10.25)	-4.09 (-13.77, 5.58)	0.32 (-9.48, 10.13)
p-value	0.4688	0.9743	0.8824	0.4831	0.9562

Fig. 2. (A) Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) total score LS mean (90% CI) change from baseline; (B) Disability Assessment for Dementia (DAD) total score LS mean (90% CI) change from baseline. Abbreviations: CI, confidence interval; LS, least squares.

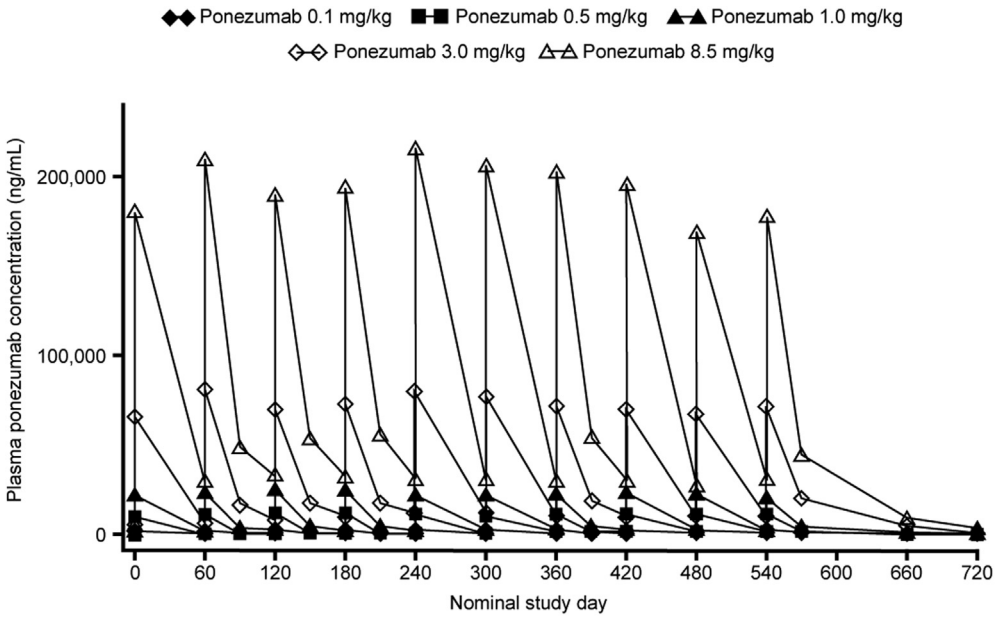


Fig. 3. Mean plasma ponezumab concentration-time profiles after a 2-hour intravenous infusion every 2 months.

randomized to ponezumab 0.1 mg/kg and headache in one subject randomized to placebo.

Serious AEs (SAEs) occurred in 45 subjects and were more common in the ponezumab groups than in the placebo groups. In part A, all-causality SAEs occurred in seven (28%) subjects receiving ponezumab 0.1 mg/kg, eight (32%) subjects receiving ponezumab 0.5 mg/kg, seven (28%) subjects receiving ponezumab 1 mg/kg, and three (12.5%) subjects receiving placebo. In part B, all-causality SAEs occurred in seven (21.9%) subjects receiving ponezumab 3 mg/kg, 10 (32.3%) subjects receiving ponezumab 8.5 mg/kg, and three (9.4%) subjects receiving placebo. Three SAEs were considered treatment related by the investigator: meningeal thickening/subdural hygromas in one subject (as mentioned previously); asymptomatic vasogenic cerebral edema (ARIA with edema) and superficial siderosis in one subject randomized to ponezumab 0.5 mg/kg, which were identified 175 days after the last dose of ponezumab and resolved approximately 2 months after onset; and prostate cancer in one subject randomized to placebo, which was still present at the last follow-up.

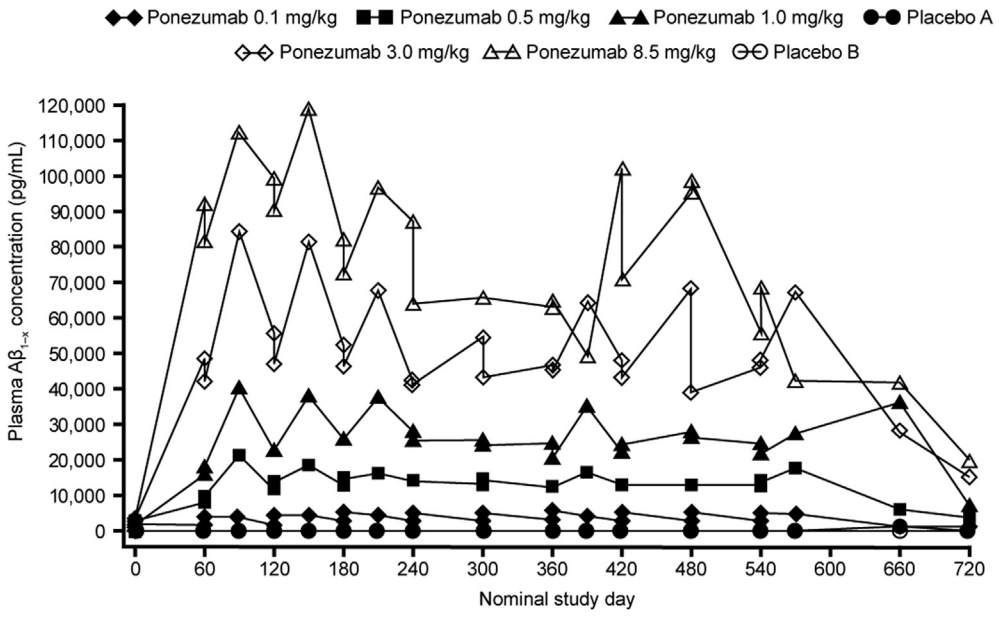


Fig. 4. Mean plasma $A\beta_{1-x}$ concentration-time profiles after a 2-hour intravenous infusion of ponezumab every 2 months. Abbreviation: Aβ, amyloid β.

A total of 20 subjects discontinued treatment or withdrew from the study because of AEs; of these, four discontinued because of treatment-related AEs: exertional dyspnea (one subject receiving 3 mg/kg), cerebral microhemorrhage (one subject receiving 0.1 mg/kg), and rash (one subject receiving 0.1 mg/kg and one receiving 8.5 mg/kg). Treatment was temporarily discontinued in 13 subjects due to an AE (one receiving 0.1 mg/kg, two receiving 0.5 mg/kg, one receiving 1 mg/kg, three receiving 3 mg/kg, one receiving 8.5 mg/kg, and five receiving placebo). In two of these patients, the AE was considered treatment related (thalamic infarction in one subject receiving 3 mg/kg and cerebral microhemorrhage in one subject receiving placebo). There were no dose reductions due to AEs.

There were three deaths: two during active treatment and one during post-treatment follow-up. They were attributable to a traffic accident (ponezumab 0.5 mg/kg), intracranial hemorrhage (placebo), and acute coronary syndrome (placebo). None were considered treatment related.

3.3. Efficacy

The FAS was the primary analysis set for the efficacy analyses. Cognition and functional ability declined over time in the ponezumab and placebo groups. Overall, the ponezumab groups did not differ from placebo in the change from baseline at month 19 in mean ADAS-Cog total score (Fig. 2A) or mean DAD total score (Fig. 2B). These changes appeared similar regardless of baseline AD severity and *APOE* ε4 status.

Generally, there were no differences between ponezumab and placebo in the change from baseline at month 19 in CogState individual items and composite score, global CDR score, CDR-SB score, MMSE total score, NPI total score, NTB score, and EQ-5D score.

In the MRI analyses, ponezumab generally did not differ significantly from placebo in the change from baseline at month 19 in mean whole-brain volume, hippocampal volume, or ventricular volume.

3.4. Pharmacokinetics

All subjects who received at least one infusion of study medication were included in the PK analyses (n = 194). After multiple dosing, plasma ponezumab concentrations increased in a dose-dependent manner and exhibited limited accumulation (Fig. 3). Mean increases were approximately 1- to 1.3-fold based on the ratio of the concentration at the end of the infusion (C_{endinf}) at month 18 to that at month 0, and 1.5- to 1.8-fold based on the ratio of trough concentration (C_{trough}) at month 18 to that at month 2.

CSF ponezumab concentrations at months 3 and 19 are shown in Supplementary Table 2. The mean CSF concentrations were <1% of mean plasma total concentrations.

Ponezumab was quantifiable in the urine of one subject at month 24 after the 0.1 mg/kg dose (14.9 ng/mL), one subject at month 10 after the 1 mg/kg dose (126 ng/mL), two subjects at month 24 after the 3 mg/kg dose (mean = 26 ng/mL), and one subject at month 19 after the 8.5 mg/kg dose (7.38 ng/mL).

3.5. Biomarkers

Robust increases in plasma $A\beta_{1-x}$ (Fig. 4) and $A\beta_{1-40}$ mean concentrations were observed, but plasma $A\beta_{1-42}$ levels were sporadic and below the lower limits of quantification (20 pg/mL) for most subjects. The appearance of $A\beta_{1-x}$ in the urine was negligible.

There was no clear dose response for any CSF biomarker ($A\beta_{1-x}$, $A\beta_{1-40}$, $A\beta_{1-42}$, tau, or p-tau) at months 3 or 19. Similar time courses were observed for these biomarkers in both the placebo and ponezumab groups. Furthermore, the percent change from baseline was highly variable for each biomarker in each dose group, with most CVs greater than 100%.

4. Discussion

Ponezumab was generally safe and well tolerated at multiple doses up to 8.5 mg/kg administered over 18 months. No ADAs were detected. Ponezumab demonstrated dose-dependent increases in plasma concentrations, limited plasma accumulation, low CSF penetration, and negligible appearance in the urine after multiple doses.

Robust increases from baseline were observed for plasma $A\beta_{1-x}$ and $A\beta_{1-40}$, consistent with ponezumab's likely mechanism of action. However, the time course of CSF biomarkers did not differ substantially for placebo versus ponezumab, nor were any dose responses observed.

There were no differences between ponezumab and placebo in cognitive or functional outcomes. However, because efficacy was assessed as a secondary objective, the results are descriptive in nature rather than inferential, and any conclusions derived from the analysis of these secondary efficacy end points are limited because of the limited sample size.

The results of this study are broadly consistent with those of the phase-III bapineuzumab and solanezumab studies in similar patient populations, which failed to meet their primary end points [4,5]. However, secondary analyses of some of these studies indicate that defined subpopulations of patients with AD may experience benefit from treatment [6,7] and further investigation is warranted.

5. Conclusions

Multiple doses of ponezumab over 18 months were generally safe and well tolerated, with no evidence of treatment-related macrohemorrhage or meningoencephalitis and a reduced rate of microhemorrhages compared with placebo. However, treatment did not alter CSF biomarkers, brain volumetrics, or clinical outcomes compared with placebo. For these reasons, development of ponezumab for mild-to-moderate AD has been discontinued.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2017.04.003.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the scientific literature on amyloid-targeted therapies in patients with mild-to-moderate Alzheimer's disease, using traditional sources (e.g., PubMed) and congress presentations. Preclinical and early clinical evidence suggested that anti–amyloid beta (Aβ) therapies could offer cognitive and functional benefits with a manageable safety profile.
2. Interpretation: This study of the anti-Aβ antibody, ponezumab, adds to the body of knowledge on the drug class. Multiple-dose regimens were generally safe and well tolerated. Treatment increased plasma Aβ, but CSF biomarkers showed no dose response and there were no cognitive or functional effects. These findings are generally consistent with those of other investigational anti-Aβ antibodies.
3. Future directions: These results should prompt further research into the pathogenic role of Aβ and timing of amyloid-reducing therapeutic interventions.

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