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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.