Received: 27 May 2026 | Revised: 7 July 2026 | Accepted: 20 July 2026

DOI: 10.1002/alz.71746

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Long-term safety and immunogenicity of ABvac40 active immunotherapy in mild cognitive impairment and very mild Alzheimer's disease: Results from AB1601 phase 2 extension study

María Pascual-Lucas[1] | Ana María Lacosta[1] | María Montañés[1] | Jesús Canudas[1] | Jorge Loscos[1] | Inmaculada Monleón[1] | José Antonio Allué[1] | Leticia Sarasa[1] | Noelia Fandos[1] | Judith Romero[1] | Manuel Sarasa[1,†] | Mireia Torres[2] | Dermot Whyms[3] | Jose Terencio[1,2] | Gerard Piñol-Ripoll[4,5,6] | Mercè Boada[7,8]

[1]R&D, Araclon Biotech-Grifols, Zaragoza, Spain

[2]Scientific Innovation Office, Grifols, Sant Cugat del Vallès, Barcelona, Spain

[3]Biometry, GrifolsWorldwide Operations Limited, Clondalkin, Dublin, Ireland

[4]Cognition and Behaviour Study Group, Institut de Recerca Biomèdica de Lleida – Fundació Dr. Pifarré, IRBLleida, Lleida, Spain

[5]Unitat de Trastorns Cognitius, Hospital Universitari Santa Maria de Lleida, Universitat de Lleida, IRBLleida, Lleida, Spain

[6]Department of Experimental Medicine, Faculty of Medicine, Universitat de Lleida (UdL), Lleida, Spain

[7]Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya, Barcelona, Spain

[8]Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain

Correspondence
María Pascual-Lucas, Araclon Biotech-Grifols, Vía Hispanidad 21, 50009 Zaragoza, Spain.
Email: mpascual@araclon.com

Funding information
Araclon Biotech-Grifols.

Abstract

INTRODUCTION: ABvac40 is an active immunotherapy targeting Aβ40, the main component of cerebrovascular deposition in Alzheimer's disease (AD). A 24-month randomized, placebo-controlled phase 2 study (Part A) showed favorable safety and robust immunogenicity, with exploratory signals of clinical efficacy. Here, we report results from Part B, an 18-month extension evaluating long-term safety and immunological memory.

METHODS: Participants treated with ABvac40 in Part A received placebo plus a delayed booster, whereas previous placebo participants received ABvac40. Exploratory endpoints included safety, tolerability, and immunogenicity.

RESULTS: Seventy-seven participants entered Part B. Treatment-emergent adverse events (TEAEs) occurred in 75.0% of participants in placebo + booster group and 81.1% in ABvac40 group; serious TEAEs were 5.0% and 16.2%, respectively. No ARIA-E or meningoencephalomyelitis were observed, with one ARIA-H event. ABvac40 induced

[†]Deceased author

robust antibody responses following delayed booster, with detectable anti-Aβ40 antibodies in CSF.

DISCUSSION: ABvac40 showed favorable long-term safety and durable immunogenicity, supporting further clinical development.

TRIAL REGISTRATION: ClinicalTrials.gov: NCT03461276, registered March 2, 2018. EudraCT: 2016-004352-30, registered March 10, 2017.

KEYWORDS

ABvac40, active immunotherapy, Alzheimer's disease, amyloid-β40, Aβ40, cerebral amyloid angiopathy, clinical trial, long-term, phase 2, vaccine

Highlights

- ABvac40 demonstrated a favorable long-term safety and tolerability profile in early Alzheimer's disease.
- No amyloid-related imaging abnormalities-edema (ARIA-E) or encephalitis observed; a single ARIA-hemorrhage (ARIA-H) event occurred during the extension phase.
- ABvac40 elicited a durable and boostable antibody response consistent with sustained immunological memory over up to 42 months.
- Anti-Aβ40 antibodies were detectable in cerebrospinal fluid and correlated with plasma levels.
- These findings support the continued clinical development of ABvac40.

1 | BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in the elderly population. Despite decades of research, its multifactorial nature, slowly evolving course and long preclinical phase pose significant challenges for therapeutic intervention, and consequently, effective disease-modifying therapies remain limited.

Given the chronic and progressive nature of AD, therapeutic strategies capable of generating sustained biological effects with manageable treatment burden are of particular interest. Active immunotherapy offers several potential advantages in this context. By stimulating the patient's own immune system to trigger an antibody response against a specific target, vaccination may provide durable immunological activity with fewer injections, improved adherence, and a more favorable cost-effectiveness profile compared with monoclonal antibody therapies.[1] The ability to elicit immunological memory further enhances its suitability for long-term treatment scenarios in slowly progressing diseases such as AD.

An early and extensively studied pathological feature of AD is the accumulation of amyloid-β (Aβ) peptides. While Aβ42 is the principal component of parenchymal amyloid plaques, Aβ40 is the predominant species deposited in cerebral blood vessels and is strongly associated with cerebral amyloid angiopathy (CAA).[2] This condition leads to vessel wall damage, resulting in hemorrhages and impaired vascular function. In AD, CAA is highly prevalent, with approximately 80% of patients exhibiting at least mild vascular amyloid deposition.[3] Its presence has been associated with earlier dementia onset[4] and faster cognitive decline.[5] Importantly, CAA contributes to cognitive impairment independently of senile plaques and neurofibrillary tangles,[5–8] highlighting its distinct role in AD pathophysiology. Furthermore, underlying CAA has been closely linked to the occurrence of amyloid-related imaging abnormalities (ARIA),[9] an adverse event observed with passive anti-amyloid therapies.[10] Together, these observations underscore the broader relevance of CAA to AD pathophysiology, clinical presentation, and potential treatment considerations.

ABvac40 is an active immunotherapy (vaccine) that specifically targets the C-terminal end of the Aβ40 peptide. In Part A of a randomized, double-blind, placebo-controlled phase 2 clinical trial involving individuals with amnestic mild cognitive impairment (a-MCI) or very mild AD, ABvac40 demonstrated a favorable safety and tolerability profile, along with robust immunogenicity.[11] Additionally, exploratory positive trends were observed in cognitive outcomes and brain atrophy measures, supporting its therapeutic potential for AD. However, long-term data on safety and immunological memory are essential for the development of vaccine-based strategies in AD.

To this end, an 18-month extension study (Part B) was conducted. This phase of the trial aimed to (1) evaluate the long-term safety

RESEARCH IN CONTEXT

1. **Systematic review**: A literature search was conducted using PubMed and clinicaltrials.gov to identify clinical studies evaluating active immunotherapies targeting amyloid-β (Aβ) in Alzheimer's disease (AD). Active Aβ-targeting vaccination strategies remain limited, and long-term data on safety and immunogenicity are scarce. Among these, ABvac40 is the only active immunotherapy specifically designed to target Aβ40. The previously reported phase 2 Part A study demonstrated its safety, tolerability, and immunogenicity in early-stage AD, with exploratory signals of clinical efficacy.
2. **Interpretation**: This phase 2 extension study provides long-term evidence on the safety, tolerability, and immunogenicity of ABvac40. ABvac40 was well tolerated over 42 months and elicited a durable and boostable antibody response, suggesting sustained immunological memory. Anti-Aβ40 antibodies were detectable in cerebrospinal fluid, with levels correlating with plasma concentrations.
3. **Future directions**: These findings support continued clinical development of ABvac40. Further studies are warranted to optimize long-term immunization strategies and to evaluate clinical efficacy.

and immunological memory in patients who had previously received ABvac40 and were administered a delayed booster dose in Part B; and (2) to obtain additional safety and immunogenicity data of ABvac40 in patients who had initially received placebo in Part A and were vaccinated for the first time in Part B.

2 | METHODS

2.1 | Study design

This study was a multicenter, randomized, double-blind, placebo-controlled, phase 2 study (AB1601: EudraCT number 2016-004352-30; ClinicalTrials.gov identifier NCT03461276) conducted in two sequential parts. The first consisted of a confirmatory phase 2 clinical trial with two parallel treatment arms (ABvac40 and placebo, 1:1), lasting up to 24 months (Part A). This was followed by an 18-month extension study (Part B). Methods and primary results from Part A have been previously reported.[11] Here, we present results from Part B, and Part A data are included only for contextual reference.

During Part A, subjects received five monthly subcutaneous injections (months 0–4) of ABvac40 (0.2 mg of immunogenic peptide; see rationale for dose selection in supplementary methods in Supporting Information) or placebo, followed by a delayed dose at month 10, and follow-up visits up to month 24. In Part B, participants who had been randomized to the placebo group during Part A (ABvac40 arm in Part B) received five monthly subcutaneous immunizations with ABvac40 (months 0–4) followed by a booster dose after 6 months (month 10). Conversely, participants randomized to ABvac40 during Part A were administered placebo following the same schedule, except for a single ABvac40 booster injection at month 4 of Part B (Placebo + Booster arm in Part B). Treatment assignments remained blinded to both investigators and participants throughout Part A and Part B.

The extension (Part B) was implemented as a protocol amendment which was approved after some participants had already completed the 24-month period of Part A. Consequently, the timing of Part B initiation varied among participants: some entered the extension after completing their 18-month visit in Part A, whereas others began after their final 24-month visit. Part B of the AB1601 study was conducted across 19 sites in 3 countries (Spain, France and Sweden) between November 18, 2020, and March 23, 2023.

The overall study design is illustrated in Figure 1.

The study was conducted in full conformance with standards for Good Clinical Practices and the Declaration of Helsinki. The protocol was prepared in accordance with the International Council for Harmonization (ICH) guidelines, and was approved by Institutional Review Boards/Ethics Committees (IRBs/ECs) from the sites and the health authorities from all countries. All enrolled participants and their caregivers provided written informed consent.

2.2 | Participants

In Part A, eligible participants were 55–80 years of age and had a diagnosis of a-MCI, as defined by the National Institute on Aging and Alzheimer's Association (NIA-AA),[12] or very mild AD, as defined by the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[13] Participants were required to have a Mini-Mental State Examination (MMSE) score of 24–30, a Clinical Dementia Rating (CDR) global score of 0.5, and a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score of $\leq$85. Enrollment was independent of amyloid positron emission tomography (PET) status. Key exclusion criteria included: presence or history of immunodeficiency, significant kidney and/or liver disease, a major uncontrolled systemic condition, history or signs of cerebrovascular disease (including vascular dementia), presence on MRI of a relevant pattern of microvascular disease or > 1 lacunar or territorial infarcts (presence of up to 3 microhemorrhages was acceptable), treatment with anticoagulants or antiaggregant therapy, or suicidal behavior or ideation. Additional inclusion and exclusion criteria are listed in the Supporting Information. To be eligible for the extension (Part B), participants had to complete at least the 18-month visit of Part A.

2.3 | Study objectives

The primary objectives of AB1601 study were defined for Part A and focused on confirming the safety, tolerability, and

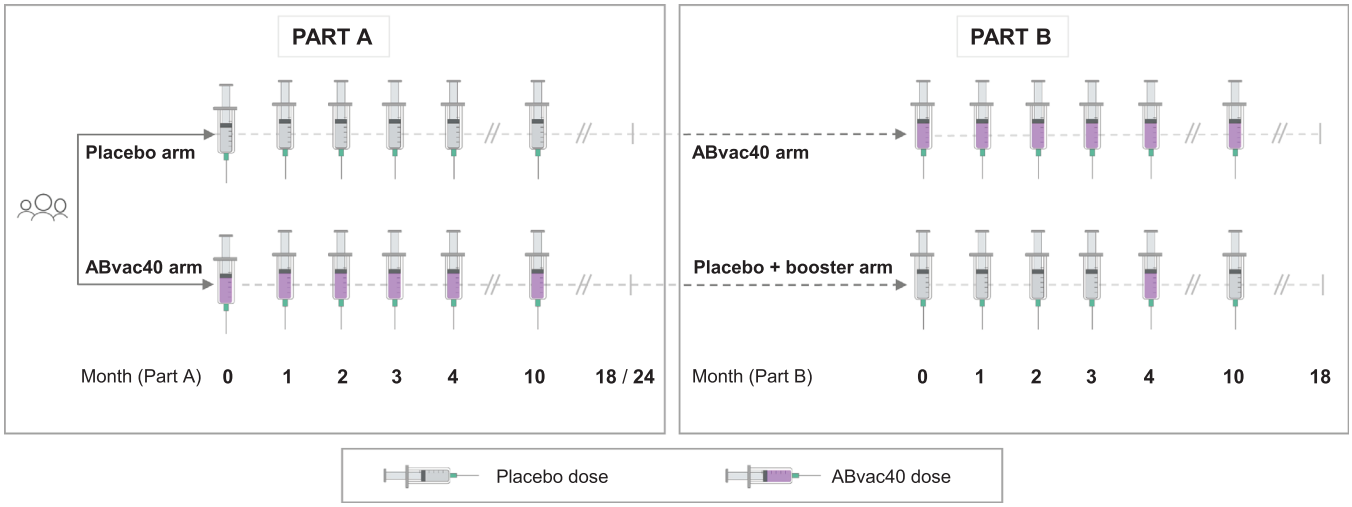

FIGURE 1 Study design of AB1601study including the confirmatory phase (Part A) and the extension phase (Part B).

immunogenicity of ABvac40 during the initial vaccination regimen. In contrast, the objectives of the extension were exploratory in nature.

The exploratory safety objective for Part B was to evaluate the safety and tolerability of ABvac40 in participants vaccinated for the first time in Part B, as well as the long-term safety and tolerability of ABvac40 in participants who had previously received ABvac40 in Part A and received a booster in Part B. The exploratory immunogenicity objectives in Part B were to assess the immune response elicited by ABvac40 in participants vaccinated for the first time in Part B and to evaluate the response to delayed booster administration in participants who had previously received ABvac40 in Part A.

2.4 | Safety assessments

Safety and tolerability were assessed at regular intervals during Part B and included monitoring of adverse events (AEs), physical and neurological examinations, laboratory assessments, and brain MRIs. MRI scans were performed at months 2.5, 6, 9, 12, and 18, with the exception of French sites, where scans were taken at months 1.5, 3.5, 6, 9, 12, and 18. An additional MRI scan was performed before Part B initiation only if the most recent MRI assessment during Part A had been obtained more than 6 months (± 15 days) before treatment initiation in Part B. All images were reviewed through a centralized radiology assessment. MRI scans were acquired using scanners with a magnetic field strength of 1.5T or 3.0T. Further details, including MRI sequences, are provided in supplementary methods in Supporting Information.

All AEs were coded using version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA) and categorized as treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), or TESAEs of special interest (TESAESIs). TESAESIs included ARIA, either ARIA-hemorrhage (ARIA-H, includes microhemorrhages and superficial siderosis), or ARIA-vasogenic edema and/or sulcal effusion (ARIA-E), as well as aseptic meningoencephalomyelitis.

2.5 | Immune response assessments

A monoclonal chimeric mouse (antigen-binding domains)/human (constant domains) antibody specific for Aβ40 (Araclon Biotech, Zaragoza, Spain) was used as an internal standard for the quantification of anti-Aβ40 antibodies. Further methodological details have been reported previously.[11] In Part B, the immune response to ABvac40 was assessed in peripheral blood and cerebrospinal fluid (CSF) samples by quantifying anti-Aβ40 antibody levels using enzyme-linked immunosorbent assays (ELISA).

Plasma samples analyzed corresponded to selected Part B time points for each treatment group: in participants receiving ABvac40 (previously randomized to placebo), samples from months 0.5, 1.5, 2.5, 3.5, 4.5, 6, 9.5, 10.5, 12, and 18 were analyzed; in participants receiving placebo + booster (previously randomized to ABvac40), samples from months 3.5, 4.5, 6, 9.5, 12, and 18 were analyzed. For participants in the placebo + booster group, the month 10.5 assessment was not included, as antibody levels were assessed at months 9.5 and 12, which were considered sufficient to characterize antibody kinetics around this period of the extension phase in the absence of an intervening immunization.

In addition, CSF samples collected via lumbar puncture at a single time point (month 12 of Part B) were analyzed to evaluate the presence of anti-Aβ40 antibodies in the central nervous system.

2.6 | Plasma biomarkers

Aβ40 and Aβ42 concentrations were quantified using a mass spectrometry-based assay (ABtest-MS, Araclon Biotech, Zaragoza, Spain) in plasma samples collected at predefined study visits. In the placebo + booster group, analyzed samples corresponded to months

3.5, 4.5, 6, 9.5, 12, and 18, whereas in the ABvac40 group, analyzed samples corresponded to months 1.5, 3.5, 4.5, 9.5, 10.5, 12, and 18. The month 10.5 assessment in the placebo + booster group and the month 6 assessment in the ABvac40 group were not included in plasma biomarker analyses, as the selected time points were considered sufficient to characterize longitudinal Aβ40 trajectories during the vaccination and follow-up period.

2.7 | Statistical analysis

Statistical analyses, tabulations, and data visualization were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism, version 5.03 (GraphPad Software, San Diego, CA, USA). Statistical analyses for Part A have been previously published.[11] All endpoints in Part B were exploratory and no formal hypothesis testing was performed.

Safety endpoints were summarized according to the treatment received for the safety population, consisting of all randomized participants who received at least one dose of study treatment. Safety results were presented as the number and percentage of participants experiencing at least one AE, categorized by treatment group, system organ class, preferred term and maximum severity, as appropriate.

Immunogenicity endpoints were analyzed descriptively according to the treatment assigned for the intent-to-treat (ITT) population, consisting of all randomized patients who received at least one dose of study treatment, regardless of the treatment received. Data were summarized using descriptive statistics, including mean or median values with 95% confidence intervals (CI) or interquartile ranges (IQR), as appropriate. Spearman's rank correlation coefficient (rho) was used to assess correlations between: (1) the time interval from the last ABvac40 dose in Part A to the booster in Part B and the fold increase in anti-Aβ40 antibody levels (in participants in the ABvac40 Part A / placebo + booster Part B treatment sequence); (2) age at ABvac40 treatment initiation and maximum plasma anti-Aβ40 antibody concentrations; and (3) plasma and CSF anti-Aβ40 antibody levels in Part B.

Two participants randomized to placebo in Part A inadvertently received one dose of ABvac40 in Part A. In accordance with the predefined analysis populations, in Part A these participants were included in the ABvac40 group for safety and in the placebo group for immunogenicity analyses. In Part B, these participants received ABvac40 according to their predefined treatment sequence (placebo in Part A and ABvac40 in Part B) and were included in the ABvac40 group for both safety and immunogenicity analyses.

3 | RESULTS

3.1 | Participants

A total of 124 patients were enrolled and treated in Part A of the study (ABvac40, $N = 62$; placebo, $N = 62$). Of the 108 participants who completed Part A, 77 entered the extension (Part B), comprising 40 in the placebo + booster group and 37 in the ABvac40 group. Among these, 38 participants (95%) in the placebo + booster group and 33 (89%) in the ABvac40 group completed the 18-month extension. Discontinuations during Part B were mainly due to participant or caregiver decisions ($n = 3$); other reasons included one due to an AE, one withdrawal of consent, and one loss to follow-up. The flow of participants throughout the study is summarized in Figure 2.

Demographic and clinical baseline characteristics from the initial phase (Part A) have been previously published,[11] whereas baseline characteristics at the start of Part B are summarized in Table 1. Mean (standard deviation, SD) age was 72.2 (5.7) years in the placebo + booster group (ABvac40 group in Part A) and 72.2 (5.4) years in the ABvac40 group (placebo group in Part A). The proportion of female participants was similar between groups (52.5% and 54.1%, respectively). Most participants were Caucasian, and APOE ε4 carrier status was slightly more frequent in the ABvac40 group. MRI findings relevant to safety, specifically cerebral microbleeds and superficial siderosis, are summarized in Table S1. MRI data obtained within 6 months prior to Part B initiation were available according to the study protocol for safety monitoring purposes, whereas standardized neuropsychological or other clinical assessments were not conducted at the start of Part B.

3.2 | Safety and tolerability

Safety findings from Part A have been previously reported.[11] A brief summary is provided here to contextualize the results of the extension. Overall, the safety profile of ABvac40 during Part A was comparable to placebo, with similar rates of TEAEs and TESAEs. Table 2 summarizes the incidence of TEAEs across study phases.

No cases of ARIA-E or aseptic meningoencephalomyelitis were reported in either part of the study (Table 2). ARIA-H occurred at comparable frequencies between treatment groups during Part A and was reported in only one participant during Part B (ABvac40 group, 2.7%); this event was asymptomatic, did not lead to treatment discontinuation and was not considered treatment-related.

In Part B, TEAEs occurred in 75.0% of participants in the placebo + booster group (i.e., those previously treated with ABvac40) and in 81.1% of those in the ABvac40 group (previously placebo; Table 2). No deaths or TEAEs leading to treatment discontinuation occurred during this extension phase.

A detailed description of the most commonly reported non-serious TEAEs is provided in Table 3. In both treatment groups, corona virus (COVID-19) and urinary tract infections were the most frequent events.

TESAEs were infrequent in Part B, reported in 5.0% of participants in the placebo + booster group and 16.2% in the ABvac40 group (Table 2); only one TESAE was considered treatment-related (lacunar infarction), occurring in the placebo + booster group. The distribution of TESAEs (excluding TESAEs of special interest) classified by system organ class (MedDRA v20.0) is presented in Table 4, while their distribution by maximum severity is summarized in Table S2.

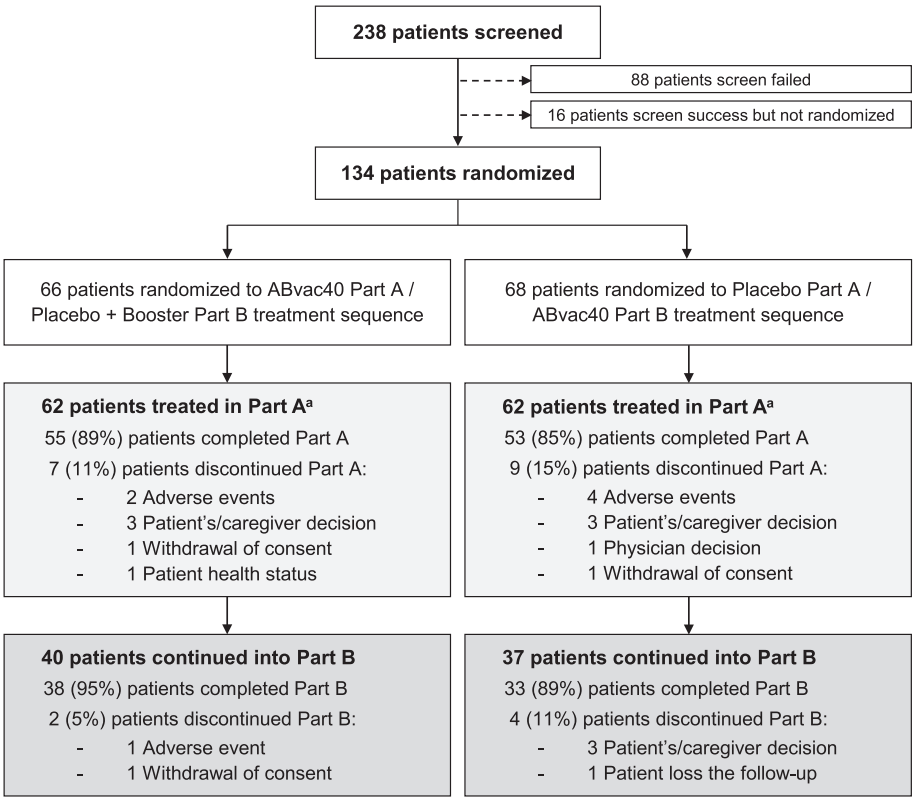

FIGURE 2 Patient disposition during Part A and the extension phase (Part B) of AB1601 study. [a] In Part A, two participants randomized to placebo inadvertently received one dose of ABvac40 and were included in the ABvac40 group for the safety analyses; therefore, safety analyses in Part A included $N = 64$ in ABvac40 and $N = 60$ in placebo.

TABLE 1 Baseline demographic characteristics of participants at the start of Part B—ITT population.

Characteristic	Placebo + booster (ABvac40 in Part A) ($N = 40$)	ABvac40 (Placebo in Part A) ($N = 37$)
Age, years (SD)	72.2 (5.7)	72.2 (5.4)
Female sex, *n* (%)	21 (52.5)	20 (54.1)
Race / Ethnicity, *n* (%)		
Caucasian	36 (90.0)	37 (100.0)
Other	1 (2.5)	0 (0.0)
Missing	3 (7.5)	0 (0.0)
Highest level of education, *n* (%)		
University degree	13 (32.5)	14 (37.9)
College graduate	2 (5.0)	3 (8.1)
High school graduate	13 (32.5)	13 (35.1)
Some school	12 (30.0)	7 (18.9)
APOE ε4 status, *n* (%)		
Non-carriers	18 (45.0)	12 (32.4)
Carriers: Heterozygous	15 (37.5)	21 (56.8)
Carriers: Homozygous	7 (17.5)	4 (10.8)

Note: Data are expressed as mean (standard deviation) for continuous variables and as counts (%) for categorical variables.
Abbreviations: *APOE*, apolipoprotein E; *N/n*, number of participants; SD, standard deviation.

TABLE 2 Summary of treatment-emergent adverse events (TEAEs)—Safety population.

	Part A		Part B	
TEAEs, *n (%)*	ABvac40 (*N* = 64)	Placebo (*N* = 60)	Placebo + Booster (*N* = 40)	ABvac40 (*N* = 37)
Any TEAE	58 (90.6)	56 (93.3)	30 (75.0)	30 (81.1)
Any treatment-related TEAE	29 (45.3)	26 (43.3)	12 (30.0)	13 (35.1)
Any TEAEs leading to treatment discontinuation	4 (6.3)	7 (11.7)	0 (0.0)	0 (0.0)
Any TEAE leading to death[a]	1 (1.6)	1 (1.7)	0 (0.0)	0 (0.0)
Any serious TEAE (TESAE)	17 (26.6)	16 (26.7)	2 (5.0)	6 (16.2)
Any treatment-related TESAE	3 (4.7)	8 (13.3)	1 (2.5)	0 (0.0)
Any TESAE leading to treatment discontinuation	2 (3.1)	4 (6.7)	0 (0.0)	0 (0.0)
Any TESAE leading to death[a]	1 (1.6)	1 (1.7)	0 (0.0)	0 (0.0)
Any TESAE of special interest (TESAESI)	8 (12.5)	9 (15.0)	0 (0.0)	1 (2.7)
Aseptic meningoencephalomyelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ARIA-E	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ARIA-H	8 (12.5)	9 (15.0)	0 (0.0)	1 (2.7)
ARIA-H leading to treatment discontinuation	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)
ARIA-H by *APOE ε4* carrier status				
Non-carrier	4/25 (16.0)	4/23 (17.4)	0/18 (0.0)	0/12 (0.0)
Heterozygous carrier	3/30 (10.0)	5/32 (15.6)	0/15 (0.0)	1/21 (4.8)
Homozygous carrier	1/9 (11.1)	0/5 (0.0)	0/7 (0.0)	0/4 (0.0)

Abbreviations: *APOE*, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema; ARIA-H, ARIA-hemorrhage; *N/n*, number of participants; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TESAESI, treatment-emergent serious adverse event of special interest.

[a]TEAE/TESAE leading to death: General physical health deterioration (ABvac40), not related to treatment; Pancreatic neoplasm (placebo), not related to treatment.

Physical and neurological examinations, as well as laboratory analyses, revealed infrequent clinically significant abnormalities across groups, as expected in this elderly population, with no recurrent or persistent abnormalities suggestive of a treatment-related effect (Table S3).

3.3 | Immunogenicity

In Part B, the evolution of circulating anti-Aβ40 antibody concentrations reflected participants' prior exposure to ABvac40. Participants who had received placebo in Part A and were vaccinated for the first time during the extension showed a response profile comparable to that previously observed in vaccinated subjects in Part A. Antibody levels increased progressively throughout the vaccination schedule, reaching a mean concentration of 36.89 µg/mL (95% CI 25.98, 47.80), at month 4.5 (after five doses). Levels declined thereafter but rose again following the booster at month 10, reaching 36.95 µg/mL (95% CI 20.58, 53.32), and then gradually decreased to 4.43 µg/mL (95% CI 2.79, 6.07) at month 18, the end of follow-up.

Participants who had received ABvac40 during Part A entered Part B with low antibody concentrations, measuring 3.47 µg/mL (95% CI 1.81, 5.12) at month 3.5, just before receiving the booster. Following booster administration at month 4, antibody levels increased sharply, peaking at 262.53 µg/mL (95% CI 169.22, 355.84) at month 4.5. This robust response was followed by a progressive decline, reaching 12.90 µg/mL (95% CI 5.34, 20.46) at month 18. Plasma immunogenicity kinetics for both groups are depicted in Figure 3A.

In the placebo + booster group (ABvac40 in Part A), the timing of the Part B booster relative to the last immunization in Part A varied due to the staggered initiation of the extension. Specifically, the interval between the last vaccine dose in Part A (month 10) and the single booster in Part B (month 4) ranged across participants (median 15.5 months; IQR 14–21 months). The influence of this variability on the magnitude of immune response elicited by the Part B booster was assessed. No significant correlation was observed between the interval length and the increase in anti-Aβ40 antibody levels following the Part B booster, relative to the post-booster response in Part A (Spearman's rho = 0.142; $p = 0.422$; Figure 3B). These findings indicate that, within this time window, the booster consistently elicited a robust and comparable immune response in all participants, demonstrating the durability of immunological memory induced by ABvac40.

To explore the potential relationship between age and vaccine-induced immune response, correlation analyses were performed between age at ABvac40 treatment initiation and the maximum anti-Aβ40 antibody concentrations observed after first vaccination with

TABLE 3 Non-serious treatment emergent adverse events (TEAEs) experienced by ≥ 5% of subjects by preferred term—Safety population.

	Part A		Part B	
Non-serious TEAEs experienced by ≥ 5% of subjects by preferred term, *n (%)*	**ABvac40 (*N* = 64)**	**Placebo (*N* = 60)**	**Placebo + Booster (*N* = 40)**	**ABvac40 (*N* = 37)**
Patients with any events	57 (89.1)	53 (88.3)	30 (75.0)	30 (81.1)
Corona virus infection	4 (6.3)	1 (1.7)	9 (22.5)	6 (16.2)
Urinary tract infection	11 (17.2)	3 (5.0)	4 (10.0)	5 (13.5)
Erythema	10 (15.6)	7 (11.7)	0 (0.0)	3 (8.1)
Fall	9 (14.1)	4 (6.7)	4 (10.0)	0 (0.0)
Headache	5 (7.8)	7 (11.7)	3 (7.5)	3 (8.1)
Injection site reaction	4 (6.3)	4 (6.7)	3 (7.5)	4 (10.8)
Peripheral swelling	1 (1.6)	1 (1.7)	1 (2.5)	4 (10.8)
Hypertension	3 (4.7)	6 (10.0)	0 (0.0)	0 (0.0)
Injection site erythema	6 (9.4)	4 (6.7)	1 (2.5)	3 (8.1)
Pruritus	2 (3.1)	1 (1.7)	0 (0.0)	3 (8.1)
Depression	1 (1.6)	3 (5.0)	0 (0.0)	3 (8.1)
Injection site swelling	5 (7.8)	1 (1.7)	1 (2.5)	2 (5.4)
Injection site pain	2 (3.1)	1 (1.7)	3 (7.5)	1 (2.7)
Injection site induration	3 (4.7)	1 (1.7)	3 (7.5)	1 (2.7)
Fatigue	3 (4.7)	4 (6.7)	2 (5.0)	2 (5.4)
Tooth infection	0 (0.0)	4 (6.7)	1 (2.5)	0 (0.0)
Cough	0 (0.0)	4 (6.7)	0 (0.0)	0 (0.0)
Anxiety	4 (6.3)	2 (3.3)	1 (2.5)	1 (2.7)
Back pain	4 (6.3)	3 (5.0)	2 (5.0)	0 (0.0)
Insomnia	1 (1.6)	2 (3.3)	1 (2.5)	2 (5.4)
Bronchitis	0 (0.0)	2 (3.3)	0 (0.0)	2 (5.4)
Constipation	1 (1.6)	0 (0.0)	0 (0.0)	2 (5.4)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)
Anemia	2 (3.1)	2 (3.3)	0 (0.0)	2 (5.4)
Atrial fibrillation	2 (3.1)	0 (0.0)	0 (0.0)	2 (5.4)
Musculoskeletal pain	2 (3.1)	2 (3.3)	2 (5.0)	2 (5.4)
Inflammation	3 (4.7)	0 (0.0)	2 (5.0)	1 (2.7)
Dizziness	3 (4.7)	2 (3.3)	2 (5.0)	0 (0.0)
Irritability	3 (4.7)	1 (1.7)	2 (5.0)	0 (0.0)
Vomiting	2 (3.1)	3 (5.0)	1 (2.5)	0 (0.0)
Iron deficiency	0 (0.0)	0 (0.0)	2 (5.0)	1 (2.7)
Hyperglycemia	0 (0.0)	1 (1.7)	2 (5.0)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	3 (5.0)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	3 (5.0)	0 (0.0)	0 (0.0)
Loss of consciousness	0 (0.0)	0 (0.0)	2 (5.0)	0 (0.0)
Periodontitis	0 (0.0)	0 (0.0)	2 (5.0)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	2 (5.0)	0 (0.0)

Abbreviations: *N/n*, number of participants, TEAEs, treatment emergent adverse events.

TABLE 4 Treatment-emergent serious adverse events (TESAEs) classified by system organ class (excluding TESAEs of special interest)—Safety population.

	Part A		Part B	
TESAEs by system organ class[a], *n (%)*	ABvac40 (*N* = 64)	Placebo (*N* = 60)	Placebo + Booster (*N* = 40)	ABvac40 (*N* = 37)
Patients with any events	11 (17.2)	9 (15.0)	2 (5.0)	5 (13.5)
Cardiac disorders	0 (0.0)	1 (1.7)	0 (0.0)	3 (8.1)
Gastrointestinal disorders	1 (1.6)	1 (1.7)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (1.7)	1 (2.5)	0 (0.0)
Injury, poisoning and procedural complications	2 (3.1)	1 (1.7)	0 (0.0)	1 (2.7)
Neoplasm benign, malignant and unspecified	1 (1.6)	3 (5.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (1.6)	2 (3.3)	1 (2.5)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	3 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (1.6)	0 (0.0)	0 (0.0)	1 (2.7)

[a]Excluding TESAEs of special interest, which included aseptic meningoencephalomyelitis, amyloid-related imaging abnormalities (ARIA)-edema, and ARIA-hemorrhagic.
Abbreviations: *N/n*, number of participants, TESAEs, treatment-emergent serious adverse events.

ABvac40, both in participants treated in Part A and in those vaccinated for the first time in Part B. No significant correlation was observed (Spearman's rho = −0.011; $p = 0.914$; Figure 3C), indicating that within the studied age range, antibody responses were not influenced by age.

Anti-Aβ40 antibodies were measured in CSF at month 12 of Part B (Figure 4A). In participants receiving ABvac40 for the first time during Part B, the median CSF concentration was 15.48 ng/mL (IQR 0.00-31.30). In participants in the placebo + booster group (previously ABvac40), median CSF antibody levels were 10.21 ng/mL (IQR 0.00-29.73) at the same nominal time point. Although CSF samples were collected simultaneously at month 12 in both groups, the timing relative to the last vaccine dose differed: in the ABvac40 group, the sample was obtained 2 months after the booster administered at month 10, whereas in the placebo + booster group, it was obtained 8 months after the single booster administered at month 4. Despite this difference, anti-Aβ40 antibodies were detectable in CSF in both groups, supporting central nervous system exposure following peripheral vaccination. CSF levels correlated with plasma concentrations (both groups combined, Spearman's rho: 0.750, $p < 0.0001$; Figure 4B).

3.4 | Plasma biomarkers

Total plasma levels of Aβ40 peptide, quantified using a mass spectrometry-based assay, paralleled the increase observed in anti-Aβ40 antibodies, with a marked booster effect at month 4.5 in the placebo + booster group (Figure 3D). The levels of plasma Aβ42 remained stable in both arms throughout the study (data not shown).

4 | DISCUSSION

In this 18-month extension of a phase 2 clinical trial, ABvac40 active immunotherapy was associated with a favorable safety and tolerability profile, together with robust immunogenicity, in patients with a-MCI or very mild AD. The results from Part B complement and extend the findings from the randomized phase (Part A), offering additional insights into long-term tolerability and vaccine-induced immunological memory.

Throughout the extension, the observed safety profile of ABvac40 was consistent with previous observations in Part A of the phase 2 study[11] and the phase 1 trial.[14] The frequencies of TEAEs and TESAEs in Part B appeared lower than those observed during Part A, although these comparisons are contextual only, given differences in study duration, exposure history, and participant populations between study phases. Within Part B, the lowest rates of TEAEs and TESAEs were observed in participants previously exposed to ABvac40 who received placebo plus a booster injection, further supporting the long-term safety and tolerability of the vaccine.

The most frequent TEAEs included COVID-19, consistent with the pandemic period during which Part B was conducted, urinary tract infections, falls, and headaches, which are common in this elderly population, as well as injection-site and other mild skin reactions typically observed with vaccines and injectable therapies. No deaths were reported during Part B.

Importantly, no cases of ARIA-E or aseptic meningoencephalomyelitis were observed during Part B, mirroring the findings from the randomized phase.[11] Only a single case of asymptomatic ARIA-H was reported in the extension, considered not treatment-related by the

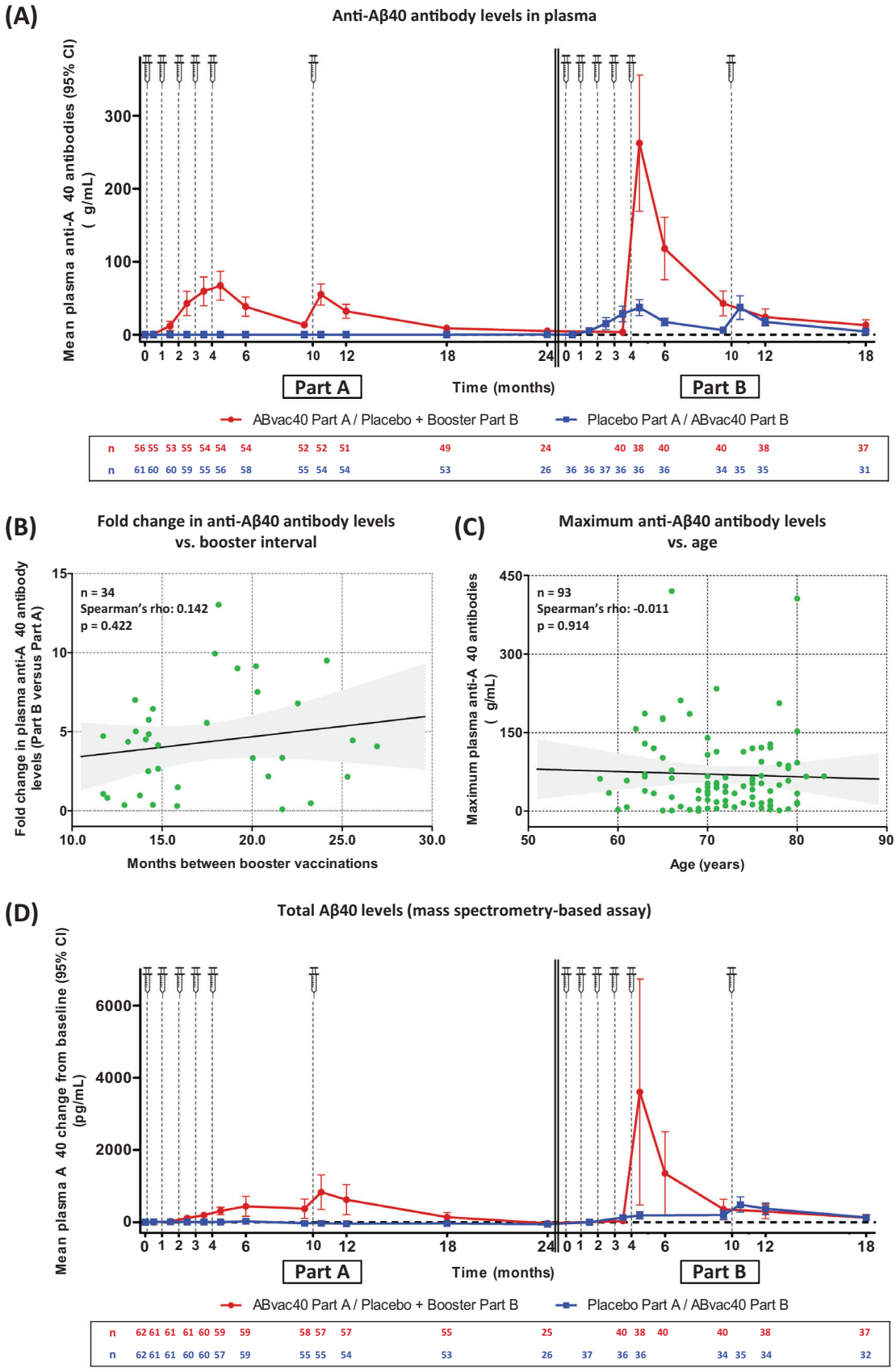

FIGURE 3 (A) Anti-Aβ40 antibody concentrations in plasma over time for both treatment sequences (ABvac40 Part A / placebo + booster Part B and placebo Part A / ABvac40 Part B), across Part A and Part B (ITT population). Values are presented as mean ± 95% CI. (B) Correlation between the time interval from the last ABvac40 dose in Part A (month 10) to the booster dose in Part B (month 4), and the fold increase in anti-Aβ40

antibody levels following the Part B booster relative to the response after the Part A booster, in participants treated with ABvac40 in Part A and placebo + booster in Part B. Spearman's rho correlation coefficient is shown. (C) Correlation between age at ABvac40 treatment initiation and maximum plasma anti-Aβ40 antibody concentrations. Data from participants in the ABvac40 groups of Part A and Part B were combined. Spearman's rho correlation coefficient is shown. (D) Plasma levels of Aβ40 peptide measured by a mass spectrometry-based assay across Part A and Part B (ITT population). Plot shows mean change from baseline and 95% CI. Aβ, amyloid-beta; CI, confidence interval; ITT, intent-to-treat; n, number of participants. Syringe symbol: time points of product administration.

investigator due to its deep location, suggestive of a hypertensive origin rather than an amyloid-related process. These data suggest that repeated exposure to ABvac40 is not associated with the occurrence of ARIA, distinguishing its vascular safety profile from that reported for several passive anti-Aβ monoclonal antibodies.[15–19] Although the biological mechanisms underlying ARIA are not fully known, differences in pharmacodynamic kinetics and target engagement may partly explain these divergent safety profiles.[9]

Long-term safety is particularly relevant in AD, a chronic and slowly progressive disorder requiring prolonged treatment. Recently approved anti-Aβ monoclonal antibodies, such as lecanemab and donanemab, require frequent MRI monitoring to manage ARIA,[20–22] which can impose a considerable burden during chronic treatment. In contrast, ABvac40 demonstrated a favorable safety profile with minimal ARIA events over up to 42 months, highlighting its potential as a safer and more manageable option for sustained treatment in AD.

From an immunogenicity perspective, the extension study demonstrated both the reproducibility of the ABvac40-induced immune response and evidence of functional immunological memory. Participants receiving ABvac40 for the first time in Part B showed an antibody response pattern that closely mirrored that observed in ABvac40-treated participants in Part A, with progressive increases during the initial dosing schedule and reactivation following the booster dose. In participants previously vaccinated in Part A, antibody levels increased robustly after the vaccine booster administered in Part B, despite a variable interval since the last immunization. The absence of an asso-

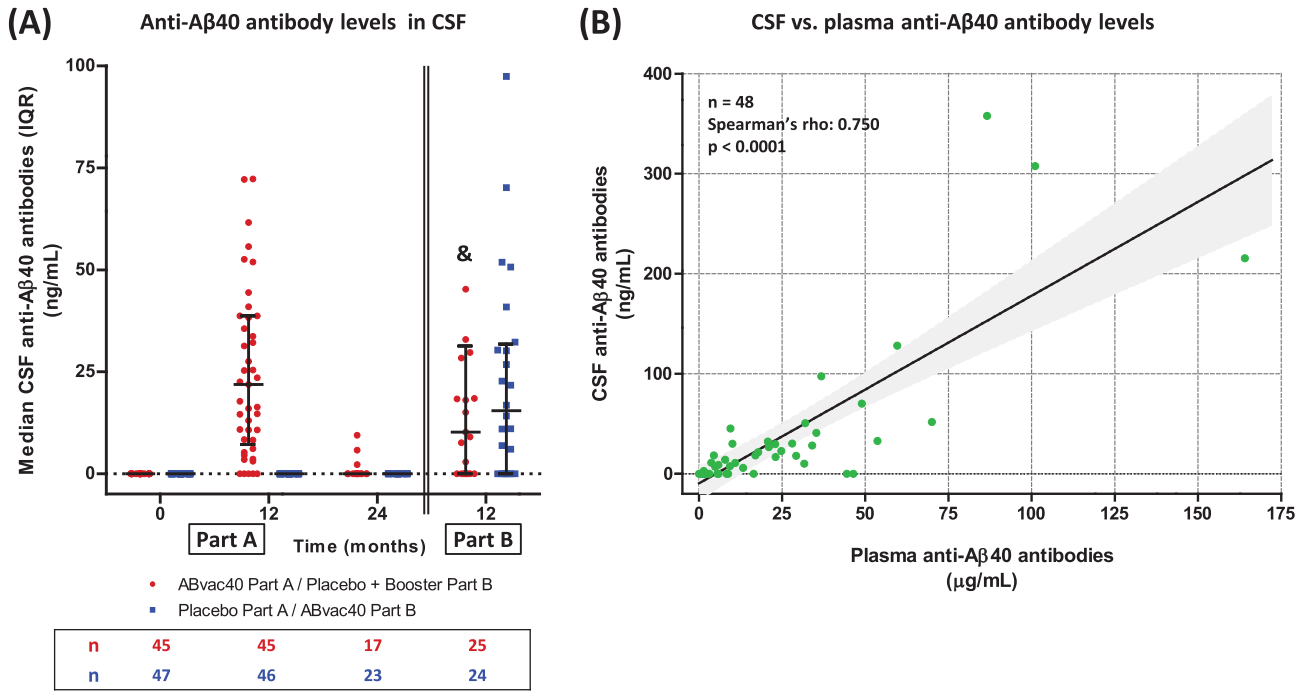

FIGURE 4 (A) Anti-Aβ40 antibody concentrations in CSF samples across Part A and Part B (ITT population). Values are presented as median and IQR. Extreme values in both treatment sequences — two in the ABvac40 group of Part A at month 12 (219.28 and 119.10 ng/mL) and four in the placebo + booster group of Part B (357.78, 307.60, 215.43, and 128.12 ng/mL) — were excluded for clarity of visualization, but were included in median and IQR calculations. (B) Correlation between plasma and CSF anti-Aβ40 antibody levels at 12 months of Part B (ITT population, both groups combined). Spearman's rho correlation coefficient is shown. Aβ, amyloid-beta; CSF, cerebrospinal fluid; IQR, interquartile range; ITT, intent-to-treat; n, number of participants. Syringe symbol: time points of product administration. & At the 12-month timepoint in Part B, CSF sampling in the placebo + booster group occurred 8 months after the single booster administered at month 4 of Part B. In comparison, in the ABvac40 group in Part B, sampling occurred 2 months after the last ABvac40 dose; in Part A, the 12-month timepoint also corresponded to 2 months post-booster.

ciation between this interval and the magnitude of the post-booster response supports the persistence of functional immune memory within the timeframe studied. Notably, antibody levels achieved after the Part B booster in participants previously vaccinated in Part A were 4-fold higher than those observed after the booster in Part A. This enhanced response may reflect immunological mechanisms such as affinity maturation and the activation of memory B-cell populations.[23,24] In addition, evidence of peripheral target engagement was observed, as total plasma Aβ40 levels increased in parallel with rising anti-Aβ40 antibody levels, replicating the pattern described in Part A.[11]

The detection of anti-Aβ40 antibodies in CSF at 12 months of Part B further supports central nervous system exposure following peripheral vaccination. As observed in Part A, antibody concentrations in CSF correlated with plasma levels, confirming a consistent relationship between systemic immune response and antibody presence in the central compartment. The persistence of detectable anti-Aβ40 antibodies in CSF 8 months after the last vaccine dose in the placebo + booster group is consistent with the sustained peripheral antibody levels and supports a mechanism of action based on long-lasting systemic immunity with continued antibody access to the central nervous system. Together with the previously reported findings of ex vivo recognition of vascular amyloid deposits by ABvac40-induced antibodies,[11] these findings support the biological relevance of the immune response induced by vaccination.

Immunosenescence represents a potential concern for active immunotherapies in elderly populations, as advancing age may attenuate vaccine-induced immune responses.[25] In the present study, however, no significant association was observed between age and peak anti-Aβ40 antibody concentrations during the initial vaccination scheme across Part A and Part B. While this does not rule out the presence of immunosenescence, it suggests that within the studied age range (58–83 years) and within the studied population, the humoral immune response to ABvac40 was not substantially influenced by age.

To date, data on long-term immunogenicity and immune memory induced by active immunotherapies for AD are limited. Previous studies of Aβ-targeting vaccines have primarily focused on relatively short-term antibody responses compared with the long natural course of the disease.[26–31] This provided limited insight into the persistence and functionality of immunological memory over extended periods, a critical aspect in the context of active immunotherapy for chronic neurodegenerative disorders. In contrast, the robust and boostable immune response observed with ABvac40 during the 24 months of the randomized phase 2 study was further complemented by the extension study, which demonstrated sustained immunological memory over an additional 18 months, resulting in a total follow-up of up to 42 months. Together, these findings highlight the capacity of ABvac40 to induce long-lasting functional immunity. Such durability has important practical implications for the management of slowly progressive diseases such as AD, as effective immune memory may reduce the need for frequent administrations and thereby minimize the treatment burden in an elderly and potentially frail population. Approved anti-Aβ monoclonal antibodies generally require repeated dosing.[20,21] In this context, vaccination with ABvac40 provides a long-acting, lower-frequency therapeutic strategy that, together with a favorable safety profile, may reduce treatment burden and improve adherence in patients with AD.

Several limitations should be acknowledged. First, as an exploratory extension incorporated to obtain additional long-term safety and immunogenicity data, Part B was not designed with formal prespecified primary and secondary endpoints. Consequently, the findings from this phase should be interpreted as exploratory and complementary to those obtained in the randomized Part A. Second, the sample size in the extension phase was relatively small, and enrollment was restricted to participants who completed Part A without major safety findings, introducing a potential selection bias toward participants with favorable tolerability profiles. However, the safety and immunogenicity findings observed in Part B were consistent with those previously reported in Part A, supporting the overall robustness of the results. Third, the extension phase did not include a true placebo control group, which precludes direct comparisons and limits the ability to draw definitive conclusions. Accordingly, this phase primarily provides descriptive data and long-term safety should be interpreted in terms of the absence of emerging safety signals. Fourth, amyloid PET positivity was not used as an inclusion criterion, which may have implications for the interpretation of safety findings. However, exploratory analyses in Part A (with 74% PET-positive at baseline[11]) did not indicate differences in ARIA-H incidence according to amyloid PET status. Although the inclusion of amyloid PET-negative participants may have influenced the overall incidence of ARIA, the similar ARIA-H rates observed in PET-positive and PET-negative participants, together with the absence of ARIA-E across PET subgroups, do not suggest an apparent relationship between baseline amyloid PET status and safety findings in this study. Finally, efficacy endpoints were not formally evaluated in the extension phase. Although neuropsychological assessments, volumetric MRI, and amyloid PET data were collected, the absence of a dedicated baseline visit at the start of Part B, together with the variable timing of entry into the extension phase (ranging from immediately after the Part A 18-month follow-up visit to several months following the 24-month visit), prevented valid longitudinal alignment of efficacy assessments across participants relative to disease stage and treatment exposure. In addition, the relatively small sample size and the absence of a placebo group further limited the feasibility of robust efficacy analyses. In this context, exploratory efficacy analyses from Part A have been previously reported and suggested potential biological effects associated with the anti-Aβ40 antibody response.[11] Further studies will be required to evaluate the clinical efficacy of ABvac40, including CAA-related endpoints.

In conclusion, this phase 2 extension study has demonstrated that ABvac40 induces a durable and boostable immune response and suggests a favorable safety and tolerability profile over long-term follow-up. These findings support the continued development of ABvac40 as an active immunotherapy for AD, particularly in the context of chronic treatment strategies requiring long-term safety and tolerability and sustained immune response. Further studies are warranted to define

the optimal immunization strategy and to evaluate the clinical efficacy of ABvac40.

ACKNOWLEDGMENTS

The authors would like to thank all study participants, as well as their families and caregivers, for their invaluable contribution to this research. The authors also thank the investigators, site staff, and the clinical trial team for their dedication, time, and commitment to the study. The authors thank Pedro Pesini and Elisabet Molina for their contributions to the study design and conduct, as well as all Araclon Biotech staff involved throughout its course. We also acknowledge the Publications team at Grifols for their editorial assistance. Finally, we acknowledge the AB1601 study group for their collaboration in the conduct of this trial. This study was funded by Araclon Biotech-Grifols.

We used AI tools to support language editing and improve clarity during manuscript preparation.

CONFLICT OF INTEREST STATEMENT

MPL, AML, MM, JC, JL, IM, JAA, LS, NF, and JR are full-time employees of Araclon Biotech-Grifols. MS was a full-time employee of Araclon Biotech–Grifols, held several patents related to AD diagnosis and treatment, and was the founder and a shareholder of Araclon Biotech–Grifols. MT, DW, and JT are full-time employees of Grifols. GPR has received consultancy fees, honoraria for lectures, and/or participated in advisory boards from the following companies: Grifols, Araclon Biotech, Lilly, Almirall, Nutricia, Schwabe Pharma, Roche, and Esteve. MB has received consultancy fees, honoraria for lectures, and/or participated in advisory boards from the following companies: Grifols, Araclon Biotech, Roche, Biogen, Lilly, Merck, Novo Nordisk, Bioiberica, Eisai, Servier, Schwabe Pharma, Nutricia, and Terumo. MB has also obtained research funding from Life Molecular Imaging, Bioiberica, Grifols, Araclon Biotech, Lilly, Roche, Janssen, Alzehon, Cortyzime, Novo Nordisk, and Schwabe Pharma. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants provided written informed consent prior to any study-related procedures.

DATA AVAILABILIY STATEMENT

Data and supporting documents, including the study protocol and statistical analysis plan, are available from the corresponding author upon reasonable request.

ORCID

María Pascual-Lucas https://orcid.org/0000-0002-4638-3153

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pascual-Lucas M, Lacosta AM, Montañés M, et al. Long-term safety and immunogenicity of ABvac40 active immunotherapy in mild cognitive impairment and very mild Alzheimer's disease: Results from AB1601 phase 2 extension study. *Alzheimer's Dement*. 2026;22:e71746. https://doi.org/10.1002/alz.71746