Clinical trial results:
A Multi-center, Randomized, Double-blind, Placebo-controlled, 24 months Study in Patients with amnestic Mild Cognitive Impairment or Very Mild Alzheimer's Disease to Investigate the Safety, Tolerability and Immune Response of Repeated Subcutaneous Injections of ABvac40

Summary

EudraCT number	2016-004352-30
Trial protocol	ES SE FR IT
Global end of trial date	23 March 2023

Results information

Result version number	v1 (current)
This version publication date	07 April 2024
First version publication date	07 April 2024

Trial information

Trial identification

Sponsor protocol code	AB1601

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03461276
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Araclon Biotech, S.L. a Grifols company
Sponsor organisation address	Vía de la Hispanidad, 21, Zaragoza, Spain, 50009
Public contact	Araclon Biotech, S.L. a Grifols company, Araclon Biotech, S.L. a Grifols company, info@araclon.com
Scientific contact	Maria Pascual Lucas, Araclon Biotech, S.L. a Grifols company, mpascual@araclon.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2023
Global end of trial reached?	Yes
Global end of trial date	23 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Safety Objective:
- To evaluate the safety and tolerability of repeated doses of ABvac40 in a population of patients with amnestic mild cognitive impairment (a-MCI) or very mild Alzheimer's Disease (vm-AD).

Primary Efficacy (Immunogenicity) Objective:
- To assess (quantify) the immune response produced during the study by repeated doses of ABvac40 in a population of a-MCI or vm-AD.

Protection of trial subjects:

Documented approvals to the study (including the protocol, all amendments and informed consents) were obtained for all participating centers/countries prior to study start from appropriate Institutional Review Board/Ethics Committee (IRBs/ECs), according to ICH good clinical practice (GCP) guidelines, local laws, regulations and organizations.
The procedures described in the clinical study protocol, pertaining to the conduct, evaluation, and documentation of the study were designed to ensure that the sponsor and investigator abide by ICH GCP guidelines. The study was also carried out in keeping with applicable local law(s) and regulation(s).
Written informed consent form (ICF) was obtained from the patients (or legal representatives, if applicable) and from a close relative/caregiver before any study specific procedure took place.
Subjects records and personal data were handled in strictest confidence and in accordance with local data protection laws and with the European General Data Protection Regulation (2016/679) (GDPR).
No medical waivers for protocol inclusion/exclusion criteria were allowed by the sponsor, and that in case the need for a change to the protocol was identified, it was submitted as a protocol amendment to the competent regulatory authority and/or IRBs/ECs as applicable per regulations.
Direct advertising was used in this study in order to solicit subject participation. Direct advertising included, but were not necessarily limited to: newspaper, radio, television, bulletin boards, posters that were intended for candidate subjects. Any advertisement was submitted for review and approval to the IRBs/ECs charged with this responsibility to ensure that the information contained in the advertisement was not misleading and that the procedure for recruiting subjects gave adequate protection for the rights and welfare of the subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 107
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 2

Worldwide total number of subjects	124
EEA total number of subjects	124

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	104
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 23 centers in Spain (n=18), France (n=3), Italy (n=1) and Sweden (n=1) recruited subjects in this study.
The subjects' recruitment was competitive until the required number of subjects was completed.

Pre-assignment

Screening details:

238 subjects were screened and assessed for eligibility. 88 subjects were screening failures and an additional 16 subjects dropped out the study before randomized. 134 subjects were randomized. Finally, 10 randomized subjects did not receive the allocated IMP. Accordingly, 124 subjects received any IMP dose, constituting the SAF analysis set.

Period 1

Period 1 title	Part A (18-24 months duration)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Only the independent representative of the Sponsor and the independent statistician worked without blinding in order to label study medication and to prepare all the data safety monitoring board (DSMB) documentation, respectively.
Blinding was only to be broken for safety concerns requiring immediate medical treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo arm Part A

Arm description:

Subjects who received Placebo during Part A

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Six administrations: the first five administered once every 4 weeks (28±3 days) and the sixth at week 42 (Visit 18), 26 weeks after the fifth. Each administration consisted of 1 mL injection of ABvac40 vehicle without its active ingredient.

Arm title	ABvac40 arm Part A

Arm description:

Subjects who received ABvac40 during Part A

Arm type	Experimental
Investigational medicinal product name	ABvac40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Six administrations: the first five administered once every 4 weeks (28±3 days) and the sixth at week 42 (Visit 18), 26 weeks after the fifth. Each administration consisted of 1 mL injection of ABvac40 (containing 0.2 mg of Aβx-40).

Number of subjects in period 1	Placebo arm Part A	ABvac40 arm Part A
Started	62	62
Completed	53	55
Not completed	9	7
Adverse event, serious fatal	1	1
Physician decision	1	-
Consent withdrawn by subject	1	1
Adverse event, non-fatal	3	1
Patient heath status	-	1
Patient/caregiver's decision	3	3

Period 2

Period 2 title	Part B (18 months duration)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

For the Part B of the study, both the sites' principal investigators and the patients remained blinded. Blinding was only to be broken for safety concerns requiring immediate medical treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo arm Part A/ABvac40 arm Part B

Arm description:

Subjects randomized to Placebo during Part A received ABvac40 during Part B

Arm type	Experimental
Investigational medicinal product name	ABvac40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Six administrations: the first five administered once every 4 weeks (28±3 days) and the sixth at week 42 (Visit 18B), 26 weeks after the fifth immunization. Each administration consisted of 1 mL injection of ABvac40 (containing 0.2 mg of Aβx-40).

Arm title	ABvac40 arm Part A/Placebo+Booster arm Part B

Arm description:

Subjects randomized to ABvac40 during Part A received Placebo+ABvac40 booster during Part B

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Five administrations: the first four administered once every 4 weeks (28±3 days) and the fifth at week 42 (Visit 18B), 30 weeks after the forth. Each administration consisted of 1 mL injection of ABvac40 vehicle without its active ingredient.

Investigational medicinal product name	ABvac40
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One administration (booster) at week 16 (Visit 13B). The administration consisted of 1 mL injection of ABvac40 (containing 0.2 mg of Aβx-40).

Number of subjects in period 2[1]	Placebo arm Part A/ABvac40 arm Part B	ABvac40 arm Part A/Placebo+Booster arm Part B
Started	37	40
Completed	33	38
Not completed	4	2
Patient lost follow-up	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1
Patient/caregiver's decision	3	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 108 subjects completed Part A, 53 in the Placebo arm and 55 in the ABvac40 arm. Out of these, 16 subjects in the Placebo arm and 15 in the ABvac40 arm did not continue to Part B. Accordingly, a total of 77 subjects continued into Part B, 37 in treatment sequence Placebo arm Part A/ABvac40 arm Part B and 40 in treatment sequence ABvac40 arm Part A/Placebo+Booster arm Part B.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo arm Part A
Reporting group description:	
Subjects who received Placebo during Part A	
Reporting group title	ABvac40 arm Part A
Reporting group description:	
Subjects who received ABvac40 during Part A	

Reporting group values	Placebo arm Part A	ABvac40 arm Part A	Total
Number of subjects	62	62	124
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	70.1	70.6	
standard deviation	± 5.49	± 5.95	-
Gender categorical			
Units: Subjects			
Female	36	38	74
Male	26	24	50
Study disease			
Units: Subjects			
amnestic Mild Cognitive Impairment (a-MCI)	42	38	80
Very Mild Alzheimer’s Disease (VM-AD)	20	24	44
a-PET status			
amyloid-positron emission tomography (a-PET) status			
Units: Subjects			
Positive	45	47	92
Negative	17	15	32
ApoE status			
Apolipoprotein E (ApoE) status			
Units: Subjects			
Noncarriers: E2/E2 and E2/E3, E3/E3	24	24	48
Carriers (Heterozygous: E2/E4, E3/E4)	33	29	62

Carriers (Homozygous: E4/E4)	5	9	14

Time from Disease Diagnosis to Informed Consent			
Units: month			
arithmetic mean	14.48	14.68	
standard deviation	± 15.81	± 13.71	-

Subject analysis sets

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety (SAF) analysis set consisted of all randomized subjects who received any amount of IMP. All safety analyses used the SAF analysis set. Subjects were analyzed according to the treatment received, regardless of the treatment assigned.

Note: Subjects S04-002 and S14-006 were randomized to the Placebo arm in Part A and inadvertently received ABvac40 on Visit 10 and Visit 7 respectively. They received ABvac40 in Part B. These 2 subjects were summarized for the SAF analysis set in ABvac40 arm for Part A and Part B.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-treat (ITT) analysis set consisted of all subjects randomized who received any IMP.
Analysis of all secondary efficacy endpoints was carried out using the ITT analysis set. Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-treat (mITT) analysis set comprised all subjects in the ITT analysis set who had a Baseline- and at least 1 post-Baseline anti-Aβ40 antibody assessment (optical density [OD] in ELISA without pre-adsorption).
Analysis of the primary efficacy endpoint was carried out using the mITT analysis set. Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.

Subject analysis set title	PP (Part A)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per protocol (PP) analysis set (Part A) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1, V4, V7, V10, V13 and V18 in Part A), attended the safety visit after Booster (V20 in Part A) and had no major protocol deviations that could have affected the efficacy analyses.
Analysis of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers in Part A was repeated using the Part A PP analysis set. Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.
Note: Summaries of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers over the entire duration of the study (Parts A and B combined) were repeated using subjects who were in Part A PP analysis set and the Part B PP analysis set.

Subject analysis set title	PPc (Part A)
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol cognition (PPc) analysis set (Part A) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1, V4, V7, V10, V13 and V18 in Part A), attended the safety visit after Booster (V20 in Part A), had no major protocol deviations that could have affected the efficacy analyses or major protocol deviations that were classified as "Use of disallowed concomitant medication", relating to use of anti-AD medication.
Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life in Part A was repeated using the Part A PPc analysis set.

Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.
Note: Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life over the entire duration of the study (Parts A and B combined), were repeated using subjects who were in Part A PPc analysis set and the Part B PPc analysis set.

Subject analysis set title	PP (Part B)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per protocol (PP) analysis set (Part B) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), attended the safety visit after Booster (V20B in Part B) and had no major protocol deviations that could have affected the summary of efficacy.
Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received
Note: Summaries of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers over the entire duration of the study (Parts A and B combined) were repeated using subjects who were in Part A PP analysis set and the Part B PP analysis set.

Subject analysis set title	PPc (Part B)
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol cognition (PPc) analysis set (Part B) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), attended the safety visit after Booster (V20B in Part B), had no major protocol deviations that could have affected the efficacy analyses or major protocol deviations that were classified as "Use of disallowed concomitant medication", relating to use of anti-AD medication.
Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.
Note: Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life over the entire duration of the study (Parts A and B combined), were repeated using subjects who were in Part A PPc analysis set and the Part B PPc analysis set

Reporting group values	SAF	ITT	mITT
Number of subjects	124	124	122
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean		70.4	
standard deviation	±	± 5.71	±
Gender categorical Units: Subjects			
Female		74	
Male		50	

Study disease Units: Subjects			
amnestic Mild Cognitive Impairment (a-MCI)		80	
Very Mild Alzheimer’s Disease (VM-AD)		44	
a-PET status			
amyloid-positron emission tomography (a-PET) status			
Units: Subjects			
Positive		92	
Negative		32	
ApoE status			
Apolipoprotein E (ApoE) status			
Units: Subjects			
Noncarriers: E2/E2 and E2/E3, E3/E3		48	
Carriers (Heterozygous: E2/E4, E3/E4)		62	
Carriers (Homozygous: E4/E4)		14	
Time from Disease Diagnosis to Informed Consent Units: month			
arithmetic mean		14.58	
standard deviation	±	± 14.74	±

Reporting group values	PP (Part A)	PPc (Part A)	PP (Part B)
Number of subjects	100	97	65
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female			
Male			
Study disease Units: Subjects			
amnestic Mild Cognitive Impairment (a-MCI)			
Very Mild Alzheimer’s Disease (VM-AD)			

a-PET status			
amyloid-positron emission tomography (a-PET) status			
Units: Subjects			
Positive			
Negative			
ApoE status			
Apolipoprotein E (ApoE) status			
Units: Subjects			
Noncarriers: E2/E2 and E2/E3, E3/E3			
Carriers (Heterozygous: E2/E4, E3/E4)			
Carriers (Homozygous: E4/E4)			
Time from Disease Diagnosis to Informed Consent			
Units: month			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	PPc (Part B)		
Number of subjects	63		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			
Study disease			
Units: Subjects			
amnestic Mild Cognitive Impairment (a-MCI)			
Very Mild Alzheimer’s Disease (VM-AD)			
a-PET status			
amyloid-positron emission tomography (a-PET) status			
Units: Subjects			
Positive			
Negative			
ApoE status			

Apolipoprotein E (ApoE) status			
Units: Subjects			
Noncarriers: E2/E2 and E2/E3, E3/E3 Carriers (Heterozygous: E2/E4, E3/E4) Carriers (Homozygous: E4/E4)			
Time from Disease Diagnosis to Informed Consent Units: month arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Placebo arm Part A
Reporting group description:	
Subjects who received Placebo during Part A	
Reporting group title	ABvac40 arm Part A
Reporting group description:	
Subjects who received ABvac40 during Part A	
Reporting group title	Placebo arm Part A/ABvac40 arm Part B
Reporting group description:	
Subjects randomized to Placebo during Part A received ABvac40 during Part B	
Reporting group title	ABvac40 arm Part A/Placebo+Booster arm Part B
Reporting group description:	
Subjects randomized to ABvac40 during Part A received Placebo+ABvac40 booster during Part B	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety (SAF) analysis set consisted of all randomized subjects who received any amount of IMP. All safety analyses used the SAF analysis set. Subjects were analyzed according to the treatment received, regardless of the treatment assigned.

Note: Subjects S04-002 and S14-006 were randomized to the Placebo arm in Part A and inadvertently received ABvac40 on Visit 10 and Visit 7 respectively. They received ABvac40 in Part B. These 2 subjects were summarized for the SAF analysis set in ABvac40 arm for Part A and Part B.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-treat (ITT) analysis set consisted of all subjects randomized who received any IMP.
Analysis of all secondary efficacy endpoints was carried out using the ITT analysis set. Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-to-treat (mITT) analysis set comprised all subjects in the ITT analysis set who had a Baseline- and at least 1 post-Baseline anti-Aβ40 antibody assessment (optical density [OD] in ELISA without pre-adsorption).
Analysis of the primary efficacy endpoint was carried out using the mITT analysis set. Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.

Subject analysis set title	PP (Part A)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per protocol (PP) analysis set (Part A) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1, V4, V7, V10, V13 and V18 in Part A), attended the safety visit after Booster (V20 in Part A) and had no major protocol deviations that could have affected the efficacy analyses.
Analysis of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers in Part A was repeated using the Part A PP analysis set. Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.
Note: Summaries of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers over the entire duration of the study (Parts A and B combined) were repeated using subjects who were in Part A PP analysis set and the Part B PP analysis set.

Subject analysis set title	PPc (Part A)
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol cognition (PPc) analysis set (Part A) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1, V4, V7, V10, V13 and V18 in Part A), attended the safety visit after Booster (V20 in Part A), had no major protocol deviations that could have affected the efficacy analyses or major protocol deviations that were classified as "Use of disallowed concomitant medication", relating to use of anti-AD medication.
Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life in Part A was repeated using the Part A PPc analysis set.
Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.
Note: Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life over the entire duration of the study (Parts A and B combined), were repeated using subjects who were in Part A PPc analysis set and the Part B PPc analysis set.

Subject analysis set title	PP (Part B)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per protocol (PP) analysis set (Part B) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), attended the safety visit after Booster (V20B in Part B) and had no major protocol deviations that could have affected the summary of efficacy.
Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received
Note: Summaries of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers over the entire duration of the study (Parts A and B combined) were repeated using subjects who were in Part A PP analysis set and the Part B PP analysis set.

Subject analysis set title	PPc (Part B)
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol cognition (PPc) analysis set (Part B) comprised all subjects in the ITT analysis set who received all doses of the IMP (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), attended the safety visit after Booster (V20B in Part B), had no major protocol deviations that could have affected the efficacy analyses or major protocol deviations that were classified as "Use of disallowed concomitant medication", relating to use of anti-AD medication.
Subjects were analyzed according to their randomized treatment assignment, regardless of the treatment received.
Note: Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life over the entire duration of the study (Parts A and B combined), were repeated using subjects who were in Part A PPc analysis set and the Part B PPc analysis set

Primary: MΔ of anti-Aβ40 antibody signal (OD in ELISA)

End point title	MΔ of anti-Aβ40 antibody signal (OD in ELISA)

End point description:

Average maximal increment (MΔ) of plasma anti-Aβ40 antibody signal (optical density [OD] in ELISA) in each subject with regard to Baseline visit.
For the primary efficacy analysis, the trial was considered successfully confirmatory regarding efficacy (immunogenicity) of ABvac40 since the average MΔ of anti-Aβ40 antibody signal in the ABvac40 arm was significantly greater that the average MΔ in anti-Aβ40 antibody signal in the Placebo arm.

End point type	Primary

End point timeframe:

Maximal increment (MΔ) from Baseline across all Part A post-Baseline visits

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[1]	61[2]		
Units: no unit of measure since results are OD				
arithmetic mean (standard deviation)	0.12 (± 0.21)	3.27 (± 0.75)		

Notes:

[1] - mITT analysis set

[2] - mITT analysis set

Statistical analyses

Statistical analysis title	t-test

Statistical analysis description:

1-sided t-test to compare the ABvac40 and placebo groups

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	t-test, 1-sided

Notes:

[3] - The trial was considered successfully confirmatory regarding efficacy (immunogenicity) of ABvac40 if the average MΔ of anti-Aβ40 antibody signal (OD in ELISA) in the ABvac40 group was significantly greater than the average MΔ of anti-Aβ40 antibody signal in the Placebo group. i.e.
– Null hypothesis: average MΔ anti-Aβ40 (ABvac40) ≤ average MΔ anti-Aβ40 (placebo).
– Alternative hypothesis: average MΔ anti-Aβ40 (ABvac40) > average MΔ anti-Aβ40 (placebo)

[4] - A 1-sided t-test with a significance level of 0.025 was employed

Statistical analysis title	Mann-Whitney U test
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Additional test

[6] - 1-sided

Statistical analysis title	ANCOVA model

Statistical analysis description:

The average MΔ of anti-Aβ40 antibody signal between the two treatment groups was compared using an ANCOVA model, using the MΔ anti-Aβ40 antibody signal as the dependent variable, baseline anti-Aβ40 antibody signal (OD in ELISA) as covariate and treatment group and amyloid positivity as fixed effects.

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least squares mean differences
Point estimate	3.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.96
upper limit	3.34
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	t-test (sensitivity hypothesis)

Statistical analysis description:

1-sided t-test to compare the ABvac40 and placebo groups

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	t-test, 1-sided

Notes:

[7] - The primary analysis (t-test) was repeated, using the mITT Analysis Set to test the hypothesis:
- Null hypothesis: average MΔ anti-Aβ40 (ABvac40) - average MΔ anti-Aβ40 (placebo) ≤ 1.778
- Alternative hypothesis: average MΔ anti-Aβ40 (ABvac40) - average MΔ anti-Aβ40 (placebo) > 1.778
The alternative hypothesis was confirmed.

[8] - A 1-sided t-test with a significance level of 0.025 was employed

Statistical analysis title	MMRM

Statistical analysis description:

The change in anti-Aβ40 antibody signal from baseline to each post-baseline efficacy visit was analyzed using a Mixed-Model Repeated Measures (MMRM), using the mITT Analysis Set.
Dependent variable: change from baseline in anti-Aβ40 antibody signal. Fixed effects: treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity. Covariates: baseline anti-Aβ40 antibody signal and baseline age; Repeated measure: measures within-patient at each visit.
(See chart)

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [9]
Method	Mixed models analysis

Notes:

[9] - The MMRM showed positive differences in LS mean change from Baseline of plasma anti Aβ40 antibody signal between the ABvac40 and Placebo arms at all Part A post Baseline visits (p<0.05)

Secondary: Subject discontinuations due to TEAEs

End point title	Subject discontinuations due to TEAEs

End point description:

Number of withdrawn subjects due to treatment-emergent adverse events (TEAEs) during the whole study.
There were 7 TEAEs leading to study withdrawal in 7 subjects (2 [2.0%] subjects in the ABvac40 (Part A)/ABvac40 (Part B) group, 4 [6.5%] subjects in the Placebo (Part A) group, and 1 [2.5%] in the Placebo (Part B)/Booster (Part B) group).

End point type	Secondary

End point timeframe:

Whole study duration (Part A+Part B; up to 42 months)

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: subjects	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormalities in physical examination

End point title	Number of subjects with clinically significant abnormalities in physical examination

End point description:

Clinically significant (CS) abnormalities in physical examination during the study.
There were a total of 14 CS abnormalities in 11 subjects:
3 subjects presented a total of 5 CS abnormalities in treatment sequence ABvac40 arm Part A/Placebo+Booster arm Part B
8 subjects presented a total of 9 CS abnormalities in treatment sequence Placebo arm Part A/ABvac40 arm Part B
No consistently recurrent or persistent CS abnormalities were observed in the physical examination, suggesting no IMP impact.

End point type	Secondary

End point timeframe:

Whole study duration (Part A+Part B; up to 42 months)

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: subjects	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormalities in neurological examination

End point title	Number of subjects with clinically significant abnormalities in neurological examination

End point description:

Clinically significant (CS) abnormalities in neurological examination during the study.
There were a total of 110 CS abnormalities in 13 subjects:
6 subjects presented a total of 67 CS abnormalities in treatment sequence ABvac40 arm Part

A/Placebo+Booster arm Part B
7 subjects presented a total of 43 CS abnormalities in treatment sequence Placebo arm Part A/ABvac40 arm Part B

The most frequently reported CS abnormalities were related to cortical functions, which may be anticipated in this study population. No other consistently recurrent or persistent CS abnormalities were observed in the neurological examination, suggesting no IMP impact.

End point type	Secondary

End point timeframe:

Whole study duration (Part A+Part B; up to 42 months)

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: subjects	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormalities in analytical hematology

End point title	Number of subjects with clinically significant abnormalities in analytical hematology

End point description:

Clinically significant (CS) abnormalities in hematology parameters during the study.
There were a total of 60 CS abnormalities in 12 subjects:
7 subjects presented a total of 24 CS abnormalities in treatment sequence ABvac40 arm Part A/Placebo+Booster arm Part B
5 subjects presented a total of 36 CS abnormalities in treatment sequence Placebo arm Part A/ABvac40 arm Part B
No consistently recurrent or persistent clinically significant abnormalities were observed in the hematology parameters, suggesting no IMP impact.

End point type	Secondary

End point timeframe:

Whole study duration (Part A+Part B; up to 42 months)

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormalities in analytical biochemistry

End point title	Number of subjects with clinically significant abnormalities in analytical biochemistry

End point description:

Clinically significant (CS) abnormalities in biochemistry parameters during the study.
There were a total of 91 CS abnormalities in 24 subjects:
9 subjects presented a total of 24 CS abnormalities in treatment sequence ABvac40 arm Part A/Placebo+Booster arm Part B
15 subjects presented a total of 67 CS abnormalities in treatment sequence Placebo arm Part A/ABvac40 arm Part B
No consistently recurrent or persistent clinically significant abnormalities were observed in the biochemistry parameters, suggesting no IMP impact.

End point type	Secondary

End point timeframe:

Whole study duration (Part A+Part B; up to 42 months)

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: subjects	24			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormalities in coagulation

End point title	Number of subjects with clinically significant abnormalities in coagulation

End point description:

Clinically significant (CS) abnormalities in coagulation parameters during the study.
There were a total of 16 CS abnormalities in 8 subjects:
3 subjects presented a total of 7 CS abnormalities in treatment sequence ABvac40 arm Part A/Placebo+Booster arm Part B
5 subjects presented a total of 9 CS abnormalities in treatment sequence Placebo arm Part A/ABvac40 arm Part B
No consistently recurrent or persistent clinically significant abnormalities were observed in the coagulation parameters, suggesting no IMP impact.

End point type	Secondary

End point timeframe:

Whole study duration (Part A+Part B; up to 42 months)

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: subjects	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Level of anti-Aβ40 antibodies in CSF

End point title	Level of anti-Aβ40 antibodies in CSF

End point description:

The change in levels of anti-Aβ40 antibodies in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were differences ($p<0.05$) between groups at Week 50A and Week 104A.

The MMRM included the recorded outcome value as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: ng/mL				
least squares mean (standard error)				
Week 50A	0.1654 (± 3.86502)	30.1826 (± 3.90756)		
Week 104A	0.2014 (± 0.36753)	1.2437 (± 0.41902)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	ABvac40 arm Part A v Placebo arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.047
Method	Mixed models analysis

Secondary: Level of anti-Aβ40 antibodies in plasma

End point title	Level of anti-Aβ40 antibodies in plasma

End point description:

The change in levels of anti-Aβ40 antibodies in plasma from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were differences ($p<0.05$) between groups at each Part A visit (except at Week 2A, Week 77A and Week 104A).

The MMRM included the recorded outcome value as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline age as covariates; and measures within-patient at each visit as a repeated measure. A compound symmetric variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: µg/mL				
least squares mean (standard error)				
Week 2A	1.5580 (± 4.22100)	1.5112 (± 4.40221)		
Week 6A	1.5580 (± 4.22100)	13.7052 (± 4.44801)		
Week 10A	1.6172 (± 4.24276)	44.3187 (± 4.41509)		
Week 14A	1.5479 (± 4.24276)	62.1946 (± 4.43781)		
Week 18A	1.5789 (± 4.30746)	69.8861 (± 4.43781)		
Week 24A	1.5926 (± 4.26432)	39.9483 (± 4.44151)		
Week 40A	1.6027 (± 4.33264)	14.6139 (± 4.48526)		
Week 44A	1.5463 (± 4.35267)	57.5771 (± 4.48568)		

Week 50A	1.5993 (± 4.35363)	33.5366 (± 4.51418)		
Week 77A	1.5232 (± 4.37735)	10.8197 (± 4.57100)		
Week 104A	1.7400 (± 5.57743)	10.8365 (± 5.82224)		

Statistical analyses

Statistical analysis title	MMRM - Week 2A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9936
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 6A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0391
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 10A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 14A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 18A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 40A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0299
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 44A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1267
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2477
Method	Mixed models analysis

Secondary: Level of antibody-secreting cells

End point title	Level of antibody-secreting cells

End point description:

The change in levels of antibody-secreting cells from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were differences ($p<0.05$) between groups at each Part A visit (except at Week 2A and Week 104A).

The MMRM included the recorded outcome value as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: clinical subgroup – mild cognitive impairment or very mild Alzheimer Disease.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: SFU/0.5x10^6 PBMCs				
least squares mean (standard error)				
Week 2A	-0.4365 (± 0.37501)	0.1868 (± 0.34352)		
Week 6A	-0.0906 (± 0.72718)	2.3144 (± 0.67867)		
Week 10A	0.3092 (± 0.79081)	4.0397 (± 0.73611)		
Week 14A	-0.1484 (± 1.44968)	7.5119 (± 1.36804)		
Week 18A	0.2873 (± 1.02944)	6.8827 (± 0.93624)		
Week 24A	0.4827 (± 0.74628)	3.6323 (± 0.68609)		
Week 40A	-0.5201 (± 0.41447)	1.2117 (± 0.37194)		
Week 44A	-1.1915 (± 2.45820)	10.3597 (± 2.23485)		
Week 50A	-0.3489 (± 1.07737)	4.5496 (± 1.00962)		
Week 77A	-0.3969 (± 0.52153)	1.8382 (± 0.47244)		
Week 104A	0.1732 (± 0.40914)	0.3638 (± 0.40349)		

Statistical analyses

Statistical analysis title	MMRM - Week 2A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2151
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 6A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0169
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 10A

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0008
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 14A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 18A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0023
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 40A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0021
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 44A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0012
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0018
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.738
Method	Mixed models analysis

Secondary: Level of Aβ40 peptides in plasma – ABtest-IA

End point title	Level of Aβ40 peptides in plasma – ABtest-IA

End point description:

The change in levels of anti-Aβ40 peptides in plasma (ABtest-IA) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were differences ($p<0.05$) between groups at each Part A visit (except at Week 2A, Week 6A and Week 10A).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at

each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factors were significantly associated with the response measure ($p < 0.15$) and were included in the model: baseline use of Alzheimer Disease symptomatic medication and clinical subgroup – mild cognitive impairment or very mild Alzheimer Disease.

End point type	Secondary
End point timeframe:	
Part A	

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 2A	2.5948 (± 2.22120)	3.4620 (± 2.16724)		
Week 6A	3.2541 (± 2.66184)	8.3468 (± 2.60510)		
Week 10A	4.2669 (± 3.43764)	-3.3200 (± 3.38626)		
Week 14A	4.7946 (± 4.75127)	-10.5837 (± 4.71154)		
Week 18A	7.7216 (± 4.68637)	-13.4213 (± 4.61987)		
Week 24A	6.3608 (± 4.06529)	-30.6595 (± 4.00199)		
Week 40A	4.7336 (± 4.73069)	-43.2898 (± 4.62000)		
Week 44A	7.4722 (± 5.45150)	-36.7343 (± 5.32882)		
Week 50A	6.5136 (± 5.56714)	-36.9475 (± 5.43416)		
Week 77A	9.9852 (± 5.15517)	-31.8000 (± 5.04184)		
Week 104A	7.9352 (± 7.65221)	-16.5218 (± 7.67117)		

Statistical analyses

Statistical analysis title	MMRM - Week 2A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7623
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 6A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1506
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 10A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1071
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 14A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0212
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 18A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 40A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 44A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0251
Method	Mixed models analysis

Secondary: Level of Aβ42 peptides in plasma – ABtest-IA

End point title	Level of Aβ42 peptides in plasma – ABtest-IA

End point description:

The change in levels of anti-Aβ42 peptides in plasma (ABtest-IA) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were differences ($p<0.05$) between groups only at Week 40A and Week 44A.

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 2A	0.6745 (± 0.47690)	0.3868 (± 0.47126)		
Week 6A	1.2776 (± 0.77358)	1.6248 (± 0.76131)		
Week 10A	1.2091 (± 0.88576)	2.1331 (± 0.87167)		
Week 14A	1.6433 (± 0.73975)	1.0209 (± 0.72987)		
Week 18A	1.9821 (± 0.55465)	1.2815 (± 0.54507)		
Week 24A	2.8599 (± 0.72452)	1.6125 (± 0.71101)		
Week 40A	2.0361 (± 0.84268)	-1.2781 (± 0.81992)		
Week 44A	1.7850 (± 1.00896)	-0.9785 (± 0.98520)		
Week 50A	2.6958 (± 1.24460)	0.5563 (± 1.21767)		
Week 77A	2.9304 (± 1.15392)	0.9045 (± 1.13274)		
Week 104A	0.8402 (± 1.36427)	0.5027 (± 1.34946)		

Statistical analyses

Statistical analysis title	MMRM - Week 2A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6515
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 6A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7447
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 10A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4518
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 14A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5416
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 18A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3504
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2109
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 40A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0049
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 44A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0498
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2181
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2087
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8599
Method	Mixed models analysis

Secondary: Level of Aβ40 peptides in plasma – ABtest-MS

End point title	Level of Aβ40 peptides in plasma – ABtest-MS

End point description:

The change in levels of anti-Aβ40 peptides in plasma (ABtest-MS) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were differences ($p<0.05$) between groups at each Part A visit between Week 14A and Week 50A.

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. A compound symmetric variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 2A	15.0554 (± 86.19364)	7.2235 (± 87.23687)		
Week 6A	12.9981 (± 86.19364)	26.8351 (± 87.24290)		
Week 10A	10.8314 (± 86.57079)	123.0016 (± 87.42725)		
Week 14A	10.1449 (± 86.57079)	277.9974 (± 87.75818)		
Week 18A	10.1987 (± 87.66045)	397.6406 (± 88.10607)		
Week 24A	31.0861 (± 86.93514)	453.1893 (± 88.16061)		

Week 40A	-26.9761 (± 88.54373)	377.7762 (± 88.44661)		
Week 44A	-28.4349 (± 88.50690)	846.1633 (± 88.82717)		
Week 50A	-34.2153 (± 88.91637)	628.9483 (± 88.88059)		
Week 77A	-30.9656 (± 89.32946)	155.5480 (± 89.69327)		
Week 104A	-37.3585 (± 110.48329)	85.9804 (± 113.05734)		

Statistical analyses

Statistical analysis title	MMRM - Week 2A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9469
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 6A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9063
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 10A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3418
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 14A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0236
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 18A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0012
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 40A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0008
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 44A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1255
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4232
Method	Mixed models analysis

Secondary: Level of Aβ42 peptides in plasma – ABtest-MS

End point title	Level of Aβ42 peptides in plasma – ABtest-MS

End point description:

The change in levels of anti-Aβ42 peptides in plasma (ABtest-MS) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factors were significantly associated with the response measure ($p < 0.15$) and were included in the model: ApoE carrier status and clinical subgroup – mild cognitive impairment or very mild Alzheimer Disease.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 2A	-0.1364 (± 1.23360)	0.0301 (± 1.23242)		
Week 6A	-0.1492 (± 1.32406)	1.8092 (± 1.32222)		
Week 10A	-1.0248 (± 1.33166)	0.8740 (± 1.32527)		
Week 14A	0.1680 (± 1.15553)	0.4841 (± 1.15690)		
Week 18A	0.6469 (± 1.51683)	-0.9551 (± 1.49962)		
Week 24A	-0.0526 (± 1.38574)	-1.6059 (± 1.38522)		
Week 40A	2.9633 (± 1.71207)	3.3472 (± 1.68092)		
Week 44A	1.6060 (± 1.52120)	1.9498 (± 1.49737)		
Week 50A	0.2069 (± 1.49045)	2.7196 (± 1.46044)		
Week 77A	1.4766 (± 1.61328)	4.7243 (± 1.58567)		
Week 104A	4.7604 (± 2.18825)	2.6870 (± 2.19551)		

Statistical analyses

Statistical analysis title	MMRM - Week 2A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9211
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 6A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2817
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 10A

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2984
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 14A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8402
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 18A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4428
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4156
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 40A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8706
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 44A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8691
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2188
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1448
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5004
Method	Mixed models analysis

Secondary: Cortical fibrillary amyloid deposition assessed by a-PET scans

End point title	Cortical fibrillary amyloid deposition assessed by a-PET scans

End point description:

The change in amyloid-PET (a-PET) standard centiloid global cortical area (reference Pons) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences between groups at either Week 50A (P=0.1058) or Week 104A.

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at

each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Centiloids				
least squares mean (standard error)				
Week 50A	1.411 (± 1.1203)	3.561 (± 1.0918)		
Week 104A	4.461 (± 1.3841)	1.241 (± 1.5403)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1058
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0922
Method	Mixed models analysis

Secondary: Percentage of change in brain volume

End point title	Percentage of change in brain volume

End point description:

The percent change in brain volume from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable;

treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: percent				
least squares mean (standard error)				
Week 24A	-1.39 (± 0.157)	-1.40 (± 0.165)		
Week 50A	-2.05 (± 0.175)	-1.75 (± 0.187)		
Week 104A	-4.16 (± 0.470)	-3.11 (± 0.412)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9313
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2243
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0952
Method	Mixed models analysis

Secondary: Percentage of change in hippocampal volume

End point title	Percentage of change in hippocampal volume

End point description:

The percent change in right and left hippocampal volume from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model (only for left hippocampus): clinical subgroup – mild cognitive impairment or very mild Alzheimer Disease.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: percent				
least squares mean (standard error)				
Week 24A - left	-1.60 (± 0.454)	-2.14 (± 0.450)		
Week 50A - left	-4.13 (± 0.588)	-4.24 (± 0.571)		
Week 104A - left	-7.13 (± 1.060)	-8.15 (± 0.965)		
Week 24A - right	-1.37 (± 0.442)	-1.44 (± 0.439)		
Week 50A - right	-3.34 (± 0.513)	-3.23 (± 0.506)		
Week 104A - right	-6.37 (± 1.001)	-6.49 (± 0.901)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A - left
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3599
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A - left
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8913
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A - left
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4736
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A - right
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9095
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A - right
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8744
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A - right
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9307
Method	Mixed models analysis

Secondary: Percentage of change in ventricular volume

End point title	Percentage of change in ventricular volume

End point description:

The percent change in ventricular volume from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.
The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: percent				
least squares mean (standard error)				
Week 24A	5.30 (± 0.584)	5.94 (± 0.573)		
Week 50A	10.63 (± 0.809)	10.21 (± 0.819)		
Week 104A	22.51 (± 1.887)	21.26 (± 1.848)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3982
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7035
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6334
Method	Mixed models analysis

Secondary: Level of Aβ42 Peptides in CSF

End point title	Level of Aβ42 Peptides in CSF

End point description:

The change in levels of Aβ42 peptides in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 50A	29.0 (± 19.40)	-2.0 (± 19.79)		
Week 104A	-15.3 (± 22.51)	4.0 (± 25.82)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2193
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5543
Method	Mixed models analysis

Secondary: Level of Aβ40 peptides in CSF

End point title	Level of Aβ40 peptides in CSF

End point description:

The change in levels of Aβ40 peptides in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 50A	-62.3 (± 173.57)	-141.8 (± 180.07)		
Week 104A	-652.4 (± 227.08)	-192.5 (± 260.67)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7324
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1719
Method	Mixed models analysis

Secondary: Aβ42/Aβ40 ratio in CSF

End point title	Aβ42/Aβ40 ratio in CSF

End point description:

The change in Aβ42/Aβ40 ratio in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: n/a				
least squares mean (standard error)				
Week 50A	0.0005 (± 0.00135)	0.0009 (± 0.00129)		
Week 104A	0.0016 (± 0.00183)	0.0020 (± 0.00205)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7977
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8828
Method	Mixed models analysis

Secondary: Level of total Tau in CSF

End point title	Level of total Tau in CSF

End point description:

The change in levels of total Tau in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary

End point timeframe:
Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 50A	23.4 (± 12.20)	27.6 (± 12.39)		
Week 104A	25.9 (± 14.20)	14.7 (± 16.38)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7954
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5895
Method	Mixed models analysis

Secondary: Level of p-Tau 181 in CSF

End point title	Level of p-Tau 181 in CSF

End point description:

The change in levels of p-Tau 181 in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 50A	2.43 (± 1.684)	3.15 (± 1.697)		
Week 104A	1.55 (± 2.387)	0.82 (± 2.634)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.743
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.832
Method	Mixed models analysis

Secondary: Level of neurofilament light in CSF

End point title	Level of neurofilament light in CSF

End point description:

The change in levels of neurofilament light in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 50A	59.36 (± 76.513)	181.20 (± 78.606)		
Week 104A	317.11 (± 190.948)	276.14 (± 216.781)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2283
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.886
Method	Mixed models analysis

Secondary: Level of neurogranin in CSF

End point title	Level of neurogranin in CSF

End point description:

The change in levels of neurogranin in cerebrospinal fluid (CSF) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, and treatment-by-visit interaction as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: pg/mL				
least squares mean (standard error)				
Week 50A	-4.69 (± 8.023)	-5.93 (± 8.328)		
Week 104A	-34.97 (± 13.533)	-31.13 (± 15.571)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.909
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8498
Method	Mixed models analysis

Secondary: Mini Mental State Examination Score

End point title	Mini Mental State Examination Score

End point description:

The change in Mini Mental State Examination (MMSE) score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at

each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: baseline use of Alzheimer Disease symptomatic medication.

End point type	Secondary
End point timeframe:	
Part A	

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 24A	-2.15 (± 0.422)	-2.24 (± 0.420)		
Week 50A	-3.64 (± 0.465)	-2.65 (± 0.460)		
Week 77A	-4.58 (± 0.628)	-4.15 (± 0.621)		
Week 104A	-5.98 (± 0.816)	-4.97 (± 0.816)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	ABvac40 arm Part A v Placebo arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8711
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1098
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6179
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3715
Method	Mixed models analysis

Secondary: Clinical Dementia Rating-Sum of Boxes score

End point title	Clinical Dementia Rating-Sum of Boxes score

End point description:

The change in clinical dementia rating-sum of boxes (CDR-SB) score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: ApoE carrier status.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 24A	0.75 (± 0.152)	0.73 (± 0.156)		
Week 50A	1.41 (± 0.222)	1.36 (± 0.221)		
Week 77A	2.12 (± 0.328)	2.05 (± 0.325)		
Week 104A	3.21 (± 0.463)	2.90 (± 0.462)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8949
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8712
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8748
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6402
Method	Mixed models analysis

Secondary: Repeatable Battery for the Assessment of Neuropsychological Status score

End point title	Repeatable Battery for the Assessment of Neuropsychological Status score

End point description:

The change in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 24A	-1.30 (± 1.009)	-2.10 (± 1.022)		
Week 50A	-5.45 (± 1.076)	-5.56 (± 1.077)		
Week 77A	-4.71 (± 1.273)	-2.66 (± 1.255)		
Week 104A	-3.17 (± 1.798)	-1.33 (± 1.793)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.552
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9371
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2354
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4608
Method	Mixed models analysis

Secondary: Alzheimer's Disease Cooperative Study - Activities of Daily Living, Mild Cognitive Impairment score

End point title	Alzheimer's Disease Cooperative Study - Activities of Daily Living, Mild Cognitive Impairment score

End point description:

The change in Alzheimer’s Disease Cooperative Study – Activities of Daily Living, Mild Cognitive Impairment (ADCS-ADL MCI) total score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 24A	-0.99 (± 0.834)	-2.08 (± 0.844)		
Week 50A	-4.15 (± 1.124)	-3.78 (± 1.112)		
Week 77A	-6.33 (± 1.399)	-6.54 (± 1.380)		
Week 104A	-9.87 (± 2.002)	-10.02 (± 1.982)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3246
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8047
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.916
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9582
Method	Mixed models analysis

Secondary: Trail Making Test scores

End point title	Trail Making Test scores

End point description:

The change in Trail Making Test (TMT) scores (Trail A and Trail B) from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits for either TMT score, except at Week 77A for Trail A (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: ApoE carrier status (only for Trail A).

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: seconds				
least squares mean (standard error)				
Week 24A - Trail A	0.54 (± 2.960)	-0.59 (± 2.939)		
Week 50A - Trail A	11.34 (± 4.186)	3.59 (± 4.023)		
Week 77A - Trail A	17.42 (± 4.669)	2.79 (± 4.425)		
Week 104A - Trail A	20.09 (± 7.253)	9.24 (± 6.967)		
Week 24A - Trail B	5.43 (± 8.102)	-8.47 (± 8.464)		
Week 50A - Trail B	18.83 (± 8.503)	18.43 (± 9.122)		
Week 77A - Trail B	17.13 (± 8.680)	2.38 (± 9.762)		
Week 104A - Trail B	20.81 (± 10.715)	-4.64 (± 11.206)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A - Trail A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.777
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A - Trail A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1727
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A - Trail A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0218
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A - Trail A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2789
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 24A - Trail B
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2261
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A - Trail B
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9743
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 77A - Trail B
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2556
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A - Trail B
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1008
Method	Mixed models analysis

Secondary: Investigator Global Evaluation score

End point title	Investigator Global Evaluation score

End point description:

The change in Investigator Global Evaluation (IGE) score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included IGE after baseline as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: ApoE carrier status.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 24A	4.02 (± 0.075)	4.07 (± 0.077)		
Week 50A	4.26 (± 0.101)	4.21 (± 0.101)		
Week 104A	4.55 (± 0.180)	4.45 (± 0.184)		

Statistical analyses

Statistical analysis title	MMRM - Week 24A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6189
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6937
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6981
Method	Mixed models analysis

Secondary: Columbia Suicide Severity Rating Scale	
End point title	Columbia Suicide Severity Rating Scale
End point description: Summary statistics of subjects with suicidal ideation or suicidal behavior since last visit.	
End point type	Secondary
End point timeframe: Part A	

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[10]	58[11]		
Units: subjects				
Week 24A - suicidal ideation	1	1		
Week 24A - suicidal behavior	0	0		
Week 50A - suicidal ideation	1	2		
Week 50A - suicidal behavior	0	0		
Week 77A - suicidal ideation	1	4		
Week 77A - suicidal behavior	0	0		
Week 104A - suicidal ideation	0	0		
Week 104A - suicidal behavior	0	0		

Notes:

[10] - At Week 24A, n=57; at Week 50A, n=56; at Week 77A, n=54; at Week 104A, n=26

[11] - At Week 24A, n=58; at Week 50A, n=58; at Week 77A, n=56; at Week 104A, n=25

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol 5 Dimensions 5 Levels Overall Severity Index Score

End point title	EuroQol 5 Dimensions 5 Levels Overall Severity Index Score

End point description:

The change in Euroqol 5 Dimensions 5 levels (EQ-5D-5L) - overall severity index score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 50A	-0.99 (± 1.204)	-2.71 (± 1.196)		
Week 104A	-3.06 (± 1.740)	-0.92 (± 1.725)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2863
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3703
Method	Mixed models analysis

Secondary: EuroQol 5 Dimensions 5 Levels - Visual Analogue Scale Score

End point title	EuroQol 5 Dimensions 5 Levels - Visual Analogue Scale Score

End point description:

The change in Euroqol 5 Dimensions 5 levels (EQ-5D-5L) - visual analogue scale (VAS) score from baseline to each applicable post-baseline efficacy visit (Part A) was analyzed using a Mixed-Model Repeated Measures (MMRM), and the ITT analysis set. There were no differences of note between groups at applicable Part A visits (referring to MMRM p-values).

The MMRM included change from baseline in the efficacy parameter as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline efficacy parameter and baseline age as covariates; and measures within-patient at each visit as a repeated measure. An unstructured variance-covariance matrix was used. The following factor was significantly associated with the response measure ($p < 0.15$) and was included in the model: ApoE carrier status and clinical subgroup – mild cognitive impairment or very mild Alzheimer Disease.

End point type	Secondary

End point timeframe:

Part A

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: score on a scale				
least squares mean (standard error)				
Week 50A	-5.20 (± 2.335)	-5.07 (± 2.289)		
Week 104A	-5.55 (± 3.109)	-1.84 (± 3.111)		

Statistical analyses

Statistical analysis title	MMRM - Week 50A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9663
Method	Mixed models analysis

Statistical analysis title	MMRM - Week 104A
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3843
Method	Mixed models analysis

Other pre-specified: MΔ of anti-Aβ40 antibody signal (OD in ELISA) - Sensitivity	
End point title	MΔ of anti-Aβ40 antibody signal (OD in ELISA) - Sensitivity

End point description:

Average maximal increment (MΔ) of plasma anti-Aβ40 antibody signal (optical density [OD] in ELISA) in each subject with regard to Baseline visit.
Sensitivity analyses in the PP (Part A) analysis set.
Results were aligned with primary analysis in the mITT analysis set.

End point type	Other pre-specified

End point timeframe:

Maximal increment (MΔ) from Baseline across all Part A post-Baseline visits

End point values	Placebo arm Part A	ABvac40 arm Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[12]	54[13]		
Units: no unit of measure since results are OD				
arithmetic mean (standard deviation)	0.10 (± 0.13)	3.29 (± 0.67)		

Notes:

[12] - PP analysis set.

[13] - PP analysis set.

Statistical analyses

Statistical analysis title	t-test

Statistical analysis description:

1-sided t-test to compare the ABvac40 and placebo groups

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001 [15]
Method	t-test, 1-sided

Notes:

[14] - The trial was considered successfully confirmatory regarding efficacy (immunogenicity) of ABvac40 if the average MΔ of anti-Aβ40 antibody signal (OD in ELISA) in the ABvac40 group was significantly greater than the average MΔ of anti-Aβ40 antibody signal in the Placebo group. i.e.
– Null hypothesis: average MΔ anti-Aβ40 (ABvac40) ≤ average MΔ anti-Aβ40 (placebo).
– Alternative hypothesis: average MΔ anti-Aβ40 (ABvac40) > average MΔ anti-Aβ40 (placebo)

[15] - A 1-sided t-test with a significance level of 0.025 was employed

Statistical analysis title	Mann-Whitney U test
Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.0001 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Additional test

[17] - 1-sided

Statistical analysis title	ANCOVA model

Statistical analysis description:

The average MΔ of anti-Aβ40 antibody signal between the two treatment groups was compared using an ANCOVA model, using the MΔ anti-Aβ40 antibody signal as the dependent variable, baseline anti-Aβ40 antibody signal (OD in ELISA) as covariate and treatment group and amyloid positivity as fixed effects.

Comparison groups	Placebo arm Part A v ABvac40 arm Part A
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least squares mean differences
Point estimate	3.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.02
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	0.09

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Whole study duration (Part A+Part B; up to 42 months)	
Adverse event reporting additional description:	
Only treatment-emergent adverse events are reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	ABvac40 (Part A) ABvac40 (Part B)
Reporting group description:	
All subjects in the ABvac40 arm Part A/Placebo+Booster arm Part B treatment sequence who took ABvac40 in Part A, and all subjects in the Placebo arm Part A/ABvac40 arm Part B treatment sequence who took ABvac40 in Part B were included in summary group 'ABvac40 (part A) ABvac40 (part B)'	
Reporting group title	Placebo (Part A)
Reporting group description:	
All subjects who took Placebo in Part A of the study were included in summary group 'Placebo (Part A)'	
Reporting group title	Placebo (Part B) Booster (Part B)
Reporting group description:	
All subjects in the ABvac40 arm Part A/Placebo+Booster arm Part B treatment sequence who took either Placebo or ABvac40 booster in Part B of the study were included in summary group 'Placebo (Part B) Booster (Part B)'	

Serious adverse events	ABvac40 (Part A) ABvac40 (Part B)	Placebo (Part A)	Placebo (Part B) Booster (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 99 (23.23%)	16 / 62 (25.81%)	2 / 40 (5.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal cavity cancer			

subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic neoplasm			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 99 (2.02%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Venous thrombosis limb			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 99 (1.01%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyloid related imaging abnormalities	Additional description: All ARIA events were classified as ARIA-H per study protocol and conservatively interpreted.		
subjects affected / exposed	9 / 99 (9.09%)	9 / 62 (14.52%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	4 / 10	10 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lacunar infarction			
subjects affected / exposed	0 / 99 (0.00%)	0 / 62 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 99 (3.03%)	0 / 62 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			

subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 62 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ABvac40 (Part A) ABvac40 (Part B)	Placebo (Part A)	Placebo (Part B) Booster (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 99 (85.86%)	54 / 62 (87.10%)	30 / 40 (75.00%)
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 99 (0.00%)	0 / 62 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 99 (9.09%)	4 / 62 (6.45%)	4 / 40 (10.00%)
occurrences (all)	9	4	4
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 99 (3.03%)	6 / 62 (9.68%)	0 / 40 (0.00%)
occurrences (all)	3	6	0
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 99 (8.08%)	7 / 62 (11.29%)	3 / 40 (7.50%)
occurrences (all)	8	7	3
Dizziness			

subjects affected / exposed	3 / 99 (3.03%)	2 / 62 (3.23%)	2 / 40 (5.00%)
occurrences (all)	3	2	2
Loss of consciousness			
subjects affected / exposed	0 / 99 (0.00%)	0 / 62 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	9 / 99 (9.09%)	4 / 62 (6.45%)	1 / 40 (2.50%)
occurrences (all)	9	4	1
Injection site reaction			
subjects affected / exposed	8 / 99 (8.08%)	4 / 62 (6.45%)	3 / 40 (7.50%)
occurrences (all)	8	4	3
Injection site swelling			
subjects affected / exposed	7 / 99 (7.07%)	1 / 62 (1.61%)	1 / 40 (2.50%)
occurrences (all)	7	1	1
Fatigue			
subjects affected / exposed	5 / 99 (5.05%)	4 / 62 (6.45%)	2 / 40 (5.00%)
occurrences (all)	5	4	2
Peripheral swelling			
subjects affected / exposed	5 / 99 (5.05%)	1 / 62 (1.61%)	1 / 40 (2.50%)
occurrences (all)	5	1	1
Inflammation			
subjects affected / exposed	4 / 99 (4.04%)	0 / 62 (0.00%)	2 / 40 (5.00%)
occurrences (all)	4	0	2
Injection site induration			
subjects affected / exposed	4 / 99 (4.04%)	1 / 62 (1.61%)	3 / 40 (7.50%)
occurrences (all)	4	1	3
Injection site pain			
subjects affected / exposed	3 / 99 (3.03%)	1 / 62 (1.61%)	3 / 40 (7.50%)
occurrences (all)	3	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 99 (0.00%)	4 / 62 (6.45%)	0 / 40 (0.00%)
occurrences (all)	0	4	0
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	13 / 99 (13.13%)	7 / 62 (11.29%)	0 / 40 (0.00%)
occurrences (all)	13	7	0
Pruritus			
subjects affected / exposed	5 / 99 (5.05%)	1 / 62 (1.61%)	0 / 40 (0.00%)
occurrences (all)	5	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 99 (5.05%)	2 / 62 (3.23%)	1 / 40 (2.50%)
occurrences (all)	5	2	1
Irritability			
subjects affected / exposed	3 / 99 (3.03%)	1 / 62 (1.61%)	2 / 40 (5.00%)
occurrences (all)	3	1	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 99 (4.04%)	3 / 62 (4.84%)	2 / 40 (5.00%)
occurrences (all)	4	3	2
Musculoskeletal pain			
subjects affected / exposed	4 / 99 (4.04%)	2 / 62 (3.23%)	2 / 40 (5.00%)
occurrences (all)	4	2	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	16 / 99 (16.16%)	3 / 62 (4.84%)	4 / 40 (10.00%)
occurrences (all)	16	3	4
Coronavirus infection			
subjects affected / exposed	10 / 99 (10.10%)	1 / 62 (1.61%)	9 / 40 (22.50%)
occurrences (all)	10	1	9
Periodontitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 62 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Tooth infection			
subjects affected / exposed	0 / 99 (0.00%)	4 / 62 (6.45%)	1 / 40 (2.50%)
occurrences (all)	0	4	1
Metabolism and nutrition disorders			
Iron deficiency			

subjects affected / exposed	1 / 99 (1.01%)	0 / 62 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Hyperglycaemia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 62 (1.61%)	2 / 40 (5.00%)
occurrences (all)	0	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2017	After an exhaustive review by the sponsor and the principal investigator, the protocol was amended to avoid any misinterpretation. Additionally, some modifications were issued due to the French and Swedish competent authorities' review. This protocol amendment was issued on 04 Aug 2017, prior to the start of the study in any site but after the approval of the study in Spain. The following main changes were performed: – Expansion of the screening period from 28 to 60 days. – Amendment of the number of sites. – Inclusion of the new potential reasons for withdrawal of subjects from this study. – Clarification of the urine analysis (urine test strips) and assessment of AD biomarkers. – Inclusion of neurofilament light as an additional disease biomarker. – Amendment of the IMP packaging text. – Clarification of the allowed concomitant medications and special safety procedures.
23 July 2018	After approximately 1 year of recruitment, it was observed that there was a low prevalence of a-PET-negative subjects among the eligible population. Accordingly, the recruitment stratification on a-PET was eliminated. This protocol amendment was issued on 23 Jul 2018 (Spain), 16 Aug 2018 (France and Sweden) and 28 Sep 2018 (Italy). The following main changes were performed: – Redefinition of secondary objectives 2 and 3. – A DSMB and an additional interim analysis were added. – The exclusion criterion 20 was modified and a new exclusion criterion 27 was added. – Clarification of the previous, concomitant, prohibited and restricted medicines. – Clarification of the statistical methods. – Modification of procedures and study visit windows in the schedule of assessments. – Amendment of the number of sites. – Simplification of the AEs causality evaluation. – Other minor changes.

22 May 2020	The main reason for the amendment was the addition of an 18-month, open label, cross-over extension of the study (Part B), aiming to assess the effects of a delayed start with ABvac40 and of a second ABvac40 booster. This amendment was triggered after the pre-planned first interim analysis conducted in July 2019, after the first 36 subjects had completed their 24 week visit (the results showed that ABvac40 has a favorable profile concerning futility criteria, safety and immunogenicity data). Additionally, the requirement of subjects being COVID-19 free to receive the IMP was added. This protocol amendment was issued on 22 May 2020 (Spain), 19 Jun 2020 (France) and 22 Jun 2020 (Italy and Sweden). The following main changes were performed: – Introduction of an 18-month, open label, cross-over extension of the study (Part B). – Requirement of subjects being COVID-19 free to receive the IMP. – Amendment of the planned study duration. – Deletion of the stratification based on a PET positivity. – Cancellation of the third interim analysis planned (after the 50-week visit).* – Adjustment of the number of participant sites. – Clarification of exclusion criterion number 26. The definition of childbearing potential woman was added. – Amendment in the study administrative structure; the members of the DSMB and medical expert were included. – Clarification of the study hypothesis. The original study hypothesis was broken down into 2 parts, including a confirmatory and satisfactory analysis. – Amendment of the reporting and follow up of Amyloid Imaging Related Abnormalities (ARIA) findings. – Clarification of the reporting of the previous concomitant medication for any disease and for Alzheimer’s disease. – Clarification in the wording of the main efficacy variable. – Clarification of the DSMB activities and procedures. – Clarification of the subject replacement

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported