EU Clinical Trials Register

Clinical trial results:
"ADAMANT"
A 24-months randomised, placebo-controlled, parallel group, double blinded, multi centre, phase 2 study to assess safety and efficacy of AADvac1 applied to patients with mild Alzheimer's disease

Summary

EudraCT number	2015-000630-30
Trial protocol	AT CZ SE DE SK SI
Global end of trial date	25 June 2019

Results information

Result version number	v1 (current)
This version publication date	11 July 2020
First version publication date	11 July 2020

Trial information

Trial identification

Sponsor protocol code	AC-AD-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02579252
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AXON NEUROSCIENCE SE
Sponsor organisation address	4, Arch. Makariou & Kalogreon, NICOLAIDES SEA VIEW CITY 5th floor, office 506, Larnaka, Cyprus, 6016
Public contact	Medical department, AXON Neuroscience CRM Services SE, 00421 220921620, adamant@axon-neuroscience.eu
Scientific contact	Medical department, AXON Neuroscience CRM Services SE, 00421 220921620, adamant@axon-neuroscience.eu

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	19 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2019
Global end of trial reached?	Yes
Global end of trial date	25 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and tolerability of long-term AADvac1 treatment of patients with mild Alzheimer's disease.

Protection of trial subjects:

All the measurements of safety, tolerability, and efficacy used in this study are widely used and generally recognised as reliable, accurate, and relevant. The safety assessments were implemented appropriately based on the investigated condition and study population. The investigators assessed subjects safety on an ongoing basis. If the subject's safety or life was to be jeopardized, they were withdrawn from the study. This study was monitored regularly by a clinical monitor according to ICH GCP Guidelines and the respective standard operating procedures. The study safety data were regularly evaluated by an independent Data Safety Monitoring Board.

Background therapy:

As per standard treatment of care of patients with mild Alzheimer's disease, all patients enrolled in the study were required to be on treatment with a stable dose of acetylcholine esterase inhibitors for at least 3 months prior to screening (V01) and throughout the whole course of the study. If a study subject was on an add-on treatment with memantine, they must have been at a stable dose regimen for at least 3 months prior to screening (V01) and for the entire duration of the clinical study.

Evidence for comparator: -

Actual start date of recruitment	16 June 2016
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	Poland: 55
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Slovakia: 52
Country: Number of subjects enrolled	Slovenia: 10
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Germany: 22
Worldwide total number of subjects	196
EEA total number of subjects	196

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)	39
From 65 to 84 years	157
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment was performed at 42 investigational sites in 8 European countries from 16 Jun 2016 until 30 May 2017. The investigational sites were hospital units or out-patient clinics specialized in neurology or psychiatry with extensive experience in treating patients with Alzheimer's disease (AD).

Pre-assignment

Screening details:

During the screening period, investigators continuously assessed patients' eligibility, each time when receiving results from any examination or laboratory or imaging assessments. Eligibility was finally confirmed by the Sponsor, based on the investigator's written justification of the diagnosis of AD, and eCRF, Laboratory and MRI data.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

AADvac1 and placebo vials were identical in weight, viscosity and appearance. The allocation concealment was ensured by central randomised allocation of treatment codes performed by the IWRS, where only the unblinded biostatisticians at the Contract Research Organization and dedicated personnel at the IWRS provider had access to treatment codes. The treatment allocation was not to be revealed prior to the planned study unblinding after database lock, except in medical emergencies.

Arms

Are arms mutually exclusive?	Yes
Arm title	AADvac1

Arm description:

AADvac1

Arm type	Experimental
Investigational medicinal product name	AADvac1
Investigational medicinal product code	AADvac1
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The active pharmaceutical ingredient is Axon Peptide 108 (coupled to KLH). One dose contains 40 µg Axon Peptide 108 formulated with aluminium hydroxide (0.5 mg Al3+/0.30 mL dose) in a phosphate buffer (in single-use vials). Six vaccinations of AADvac1 were administered as subcutaneous injections at intervals of 4 weeks, to complete the 6-dose primary vaccination series (Visit V02 to V07). Booster vaccinations with AADvac1 were administered at intervals of approximately 3 months (14 weeks) thereafter, at visits V08a (Week 34), V10 (Week 48), V11a (Week 62), V13 (Week 76) and V14a (Week 90).

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One dose of placebo contains aluminium hydroxide (0.5 mg Al3+/0.30 mL dose) in a phosphate buffer (in single-use vials). Six vaccinations of placebo were administered as subcutaneous injections at intervals of 4 weeks, to complete the 6-dose primary vaccination series (Visit V02 to V07). Booster vaccinations with placebo were administered at intervals of approximately 3 months (14 weeks) thereafter, at visits V08a (Week 34), V10 (Week 48), V11a (Week 62), V13 (Week 76) and V14a (Week 90).

Number of subjects in period 1	AADvac1	Placebo
Started	117	79
Completed	100	63
Not completed	17	16
Adverse event, serious fatal	2	-
Consent withdrawn by subject	9	10
Physician decision	2	1
Adverse event, non-fatal	4	2
Unable to perform MRI examination	-	1
Lost to follow-up	-	1
Caregiver refused to accompany the patient	-	1

Baseline characteristics

Reporting groups

Reporting group title	AADvac1
Reporting group description:	
AADvac1	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	AADvac1	Placebo	Total
Number of subjects	117	79	196
Age categorical			
Units: Subjects			
Adults (18-64 years)	29	10	39
From 65-84 years	88	69	157
Age continuous			
Units: years			
arithmetic mean	70.6	72.7	
standard deviation	± 8.37	± 6.83	-
Gender categorical			
Units: Subjects			
Female	62	47	109
Male	55	32	87

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety set includes all subjects who have received at least one dose of study treatment and who have at least one post-Baseline value for safety. The Safety set was the primary data set of interest for the analysis of all safety variables. A conservative approach was used for the Safety set, any subjects that received AADvac1 at least once in the study was analysed in the AADvac1 group, and any subjects that received Placebo only was displayed in the Placebo group.

Subject analysis set title	Full Analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis set (FAS) was used for analyses of efficacy and included all randomised subjects who have received at least one dose of study treatment and who have at least one post-baseline value for efficacy. This population was the primary population of interest for the analysis of all efficacy variables. All subjects in the FAS was analysed according to the treatment they were randomised to receive and not according to what they actually received, in the event there is a discrepancy.

Reporting group values	Safety set	Full Analysis set	
Number of subjects	196	193	
Age categorical			
Units: Subjects			
Adults (18-64 years)	39	39	
From 65-84 years	157	154	

Age continuous Units: years			
arithmetic mean	71.4	71.4	
standard deviation	± 7.84	± 7.83	
Gender categorical Units: Subjects			
Female	109	106	
Male	87	87	

End points

End points reporting groups

Reporting group title	AADvac1
Reporting group description:	
AADvac1	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	

The Safety set includes all subjects who have received at least one dose of study treatment and who have at least one post-Baseline value for safety. The Safety set was the primary data set of interest for the analysis of all safety variables. A conservative approach was used for the Safety set, any subjects that received AADvac1 at least once in the study was analysed in the AADvac1 group, and any subjects that received Placebo only was displayed in the Placebo group.

Subject analysis set title	Full Analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	

The Full Analysis set (FAS) was used for analyses of efficacy and included all randomised subjects who have received at least one dose of study treatment and who have at least one post-baseline value for efficacy. This population was the primary population of interest for the analysis of all efficacy variables. All subjects in the FAS was analysed according to the treatment they were randomised to receive and not according to what they actually received, in the event there is a discrepancy.

Primary: Drug-related Treatment Emergent Adverse Events

End point title	Drug-related Treatment Emergent Adverse Events[1]
End point description:	

The protocol-defined safety endpoint was mapped to the incidence of Drag-related Treatment-Emergent Adverse Events as primary endpoint for the purpose of results posting.

End point type	Primary
End point timeframe:	
24 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The adverse events have been assessed by summarizing the counts for treatment group. No formal comparison for purpose of primary analysis was performed.

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	79		
Units: Rate				
number (not applicable)	29	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Dementia Rating - Sum of Boxes (CDR-SB) - FAS

End point title	Clinical Dementia Rating - Sum of Boxes (CDR-SB) - FAS

End point description:

CDR assesses a subject's cognitive and functional performance in six areas. For the purpose of the CDR-SB, the scores of the six individual boxes are added to obtain a total score of 0–18. Mean change in CDR-SB score from baseline to Week 104 is assessed comparing AADvac1 and placebo treatment groups.

End point type	Secondary

End point timeframe:

24 months

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	61		
Units: Score				
least squares mean (standard error)	3.35 (± 0.314)	3.23 (± 3.939)		

Statistical analyses

Statistical analysis title	MMRM analysis of Change from Baseline

Statistical analysis description:

Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score Mixed Model Repeated Measures (MMRM) Analysis of Change from Baseline after two years of treatment

Comparison groups	AADvac1 v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.806
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.504

Notes:

[2] - A mixed model with repeated measures (MMRM) analysis was used to analyse change from baseline to V16 (Week 104) for CDR-SB. The MMRM model included fixed effect terms for treatment group, visit, pooled country, sex, age, years of education, ApoE4 status, baseline MRI hippocampal volume and baseline CDR-SB. The Least Squares (LS) mean treatment difference (AADvac1 – Placebo) at Week 104 (Visit V16) was presented along with the 95% CI and the two-sided p-value for treatment effect.

Secondary: ADCS-MCI-ADL-24 - FAS

End point title	ADCS-MCI-ADL-24 - FAS

End point description:

The assessment of the subject's everyday functioning was performed via the Alzheimer's Disease Co-

operative Study – Activities of Daily Living Score (Mild Cognitive Impairment Version) ADCS-MCI-ADL, a structured informant interview with the subject's caregiver. The assessment included a total of 24 items. The scores from items were summed to provide a total score, with lower values corresponding to a more severe impairment.

End point type	Secondary
End point timeframe:	
24 months	

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	61		
Units: Score				
least squares mean (standard error)	-11.7 (± 1.14)	-10.2 (± 1.42)		

Statistical analyses

Statistical analysis title	MMRM analysis of Change from Baseline
Statistical analysis description:	

Alzheimer's Disease Co-operative Study — Activities of Daily Living (Mild Cognitive Impairment Version) (ADCS-MCI-ADL) Mixed Model Repeated Measures (MMRM) Analysis of Change from Baseline at Visit 16 (Week 104)

Comparison groups	AADvac1 v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.431
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	1.83

Notes:

[3] - A mixed model with repeated measures (MMRM) analysis was used to analyse change from baseline to V16 (Week 104) for ADCS-MCI-ADL-24. The MMRM model included fixed effect terms for treatment group, visit, pooled country, sex, age, years of education, ApoE4 status, baseline MRI hippocampal volume, baseline CDR-SB and ADL. The Least Squares (LS) mean treatment difference (AADvac1 – Placebo) at Week 104 (Visit V16) was presented along with the 95% CI and the two-sided p-value for treatment effect.

Secondary: Custom Cognitive Battery Composite z-score - FAS

End point title	Custom Cognitive Battery Composite z-score - FAS
End point description:	

A battery of 8 cognitive tests was used to assess subjects' cognition, these comprised of measures of memory, executive function, attention and processing speed. The tests were administered as both computerised tests and 'paper and pencil' cognitive tests. The primary task scores from the individual

tests were used to calculate a composite z-score for each subject for analysis at specific visit. The composite z-score was defined as the arithmetic mean of the individual z-scores obtained for each individual test from subjects within the relevant Analysis set. No weighting of tests was performed.

End point type	Secondary
End point timeframe:	
24-months	

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	56		
Units: z-score				
least squares mean (standard error)	-0.3537 (± 0.05533)	-0.3017 (± 0.06975)		

Statistical analyses

Statistical analysis title	MMRM analysis of Change from Baseline
Statistical analysis description:	
Custom Cognitive Battery (CCB) Composite z-Score Mixed Model Repeated Measures (MMRM) Analysis of Change from Baseline at Visit 16 (Week 104)	
Comparison groups	AADvac1 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.561
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.0519
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2282
upper limit	0.1244
Variability estimate	Standard error of the mean
Dispersion value	0.08919

Notes:

[4] - A mixed model with repeated measures (MMRM) analysis was used to analyse change from baseline to V16 (Week 104) for CCB composite z-score. The MMRM model included fixed effect terms for treatment group, visit, pooled country, sex, age, years of education, ApoE4 status, baseline MRI hippocampal volume and baseline CDR-SB. The Least Squares (LS) mean treatment difference (AADvac1 – Placebo) at Week 104 (Visit V16) was presented along with the 95% CI and the two-sided p-value for treatment effect.

Secondary: Antibody Responders Rates - FAS

End point title	Antibody Responders Rates - FAS[5]
End point description:	

Number of AADvac1-treated subjects who developed an IgG antibody response against the "Axon Peptide 108" component of AADvac1. A subject was defined as having an IgG antibody response if the subject had detectable Anti Axon Peptide 108 IgG antibodies (positive titres) at any post-Baseline visit i.e. > 100.

End point type	Secondary

End point timeframe:

24 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The antibody response was assess by presenting the values over time. No statistical tests were performed.

End point values	AADvac1			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: Number of subjects	114			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean IgG antibody titres against Axon peptide 108 Week 24 - FAS

End point title	Mean IgG antibody titres against Axon peptide 108 Week 24 - FAS[6]

End point description:

Geometric mean titre of AADvac1-induced IgG antibodies against Axon Peptide 108 after 6 initial vaccinations in 1-month intervals at Visit 8 (Week 24).

End point type	Secondary

End point timeframe:

24 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The antibody response was assess by presenting the values over time. No statistical tests were performed.

End point values	AADvac1			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Antibody titres				
geometric mean (confidence interval 95%)	17349.8 (12809.1 to 23500.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean IgG antibody titres against Axon peptide 108 Week 104 - FAS

End point title	Mean IgG antibody titres against Axon peptide 108 Week 104 - FAS[7]

End point description:

Geometric mean titre of AADvac1-induced IgG antibodies against Axon Peptide 108 after 6 initial vaccinations in 1-month intervals and 5 additional boosters in 3-month intervals at Visit 16 (Week 104).

End point type	Secondary

End point timeframe:

104 weeks

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The antibody response was assess by presenting the values over time. No statistical tests were performed.

End point values	AADvac1			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Titres				
geometric mean (confidence interval 95%)	10351.3 (7287.7 to 14702.9)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: p-Tau 181 in cerebrospinal fluid - FAS

End point title	p-Tau 181 in cerebrospinal fluid - FAS

End point description:

Increased phosphorylated-tau 181 (p-Tau 181) in cerebrospinal fluid (CSF) indicates the presence of tau pathology in the brain. CSF sampling was included as an optional part of the study and was collected in subjects that provided informed consent for this part of the study.

End point type	Other pre-specified

End point timeframe:

24 months

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	7		
Units: ng/L				
least squares mean (standard error)	-10.8 (± 3.52)	1.3 (± 6.13)		

Statistical analyses

Statistical analysis title	MMRM analysis of Change from Baseline

Statistical analysis description:

p-Tau 181 Mixed Model Repeated Measures (MMRM) Analysis of Change from Baseline at Visit 16 (Week 104)

Comparison groups	AADvac1 v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.076
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.6
upper limit	1.4
Variability estimate	Standard error of the mean
Dispersion value	6.55

Notes:

[8] - A mixed model with repeated measures (MMRM) analysis was used to analyse change from baseline to V16 (Week 104). The MMRM model included fixed effect terms for treatment group, visit, pooled country, sex, age, years of education, ApoE4 status, baseline MRI hippocampal volume and baseline CDR-SB. The Least Squares (LS) mean treatment difference (AADvac1 – Placebo) at Week 104 (Visit V16) was presented along with the 95% CI and the two-sided p-value for treatment effect.

Other pre-specified: Total Tau in cerebrospinal fluid - FAS

End point title	Total Tau in cerebrospinal fluid - FAS

End point description:

Increased total Tau in cerebrospinal fluid (CSF) indicates the ongoing neurodegenerative processes (intensity of neuronal damage) in the brain. CSF sampling was included as an optional part of the study and was collected in subjects that provided informed consent for this part of the study.

End point type	Other pre-specified

End point timeframe:

24 months

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	7		
Units: ng/L				
least squares mean (standard error)	-56.0 (± 42.30)	82.5 (± 69.72)		

Statistical analyses

Statistical analysis title	MMRM analysis of Change from Baseline
Comparison groups	Placebo v AADvac1

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.078
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-138.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-293.7
upper limit	16.7
Variability estimate	Standard error of the mean
Dispersion value	75.1

Notes:

[9] - A mixed model with repeated measures (MMRM) analysis was used to analyse change from baseline to V16 (Week 104). The MMRM model included fixed effect terms for treatment group, visit, pooled country, sex, age, years of education, ApoE4 status, baseline MRI hippocampal volume and baseline CDR-SB. The Least Squares (LS) mean treatment difference (AADvac1 – Placebo) at Week 104 (Visit V16) was presented along with the 95% CI and the two-sided p-value for treatment effect.

Other pre-specified: Neurofilament light chain protein (NfL) in plasma - FAS

End point title	Neurofilament light chain protein (NfL) in plasma - FAS

End point description:

Neurofilament light chain protein (NfL) is a sensitive marker of neuroaxonal damage and its increased levels in plasma are thought to reflect ongoing neurodegeneration in patient with Alzheimer's disease.

End point type	Other pre-specified

End point timeframe:

24 months

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	62		
Units: pg/mL				
least squares mean (standard error)	2.094 (± 0.6881)	5.067 (± 0.8120)		

Statistical analyses

Statistical analysis title	ANCOVA analysis of Change from Baseline

Statistical analysis description:

ANCOVA Analysis of Change from Baseline in Neurofilament light chain protein (NfL) Assay at Week 104

Comparison groups	AADvac1 v Placebo

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.972
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.849
upper limit	-1.096

Notes:

[10] - The ANCOVA modelled the change from Baseline to Week 104 result including terms for treatment group, pooled country, sex, age, years of education, ApoE4 status, Baseline MRI hippocampal volume, and Baseline CDR SB. The LS mean treatment difference (AADvac1 – Placebo) was presented along with the 95 % CI and the two-sided p value for treatment effect.

Other pre-specified: DTI Fracional anisotrophy of fornix - FAS

End point title	DTI Fracional anisotrophy of fornix - FAS

End point description:

Fractional anisotropy as the main parameter of white matter integrity measured by Diffusion Tensor Imaging (DTI), a MRI imaging method. The increase in Fractional anisotropy implies a greater degree of white matter organisation and integrity. Region Fornix includes pathway which originates from the hippocampus and connects regions affected severely in the disease.

End point type	Other pre-specified

End point timeframe:

24 months

End point values	AADvac1	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: degree				
least squares mean (standard error)	0.035 (± 0.0181)	-0.046 (± 0.0250)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA Analysis of Change from Baseline in Fractional anisotrophy of Fornix of Corpus callosum at Visit 16 (Week 104)

Comparison groups	Placebo v AADvac1

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.048
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.162

Notes:

[11] - The ANCOVA modelled the change from Baseline to Week 104 result including terms for treatment group, pooled country, sex, age, years of education, ApoE4 status, Baseline MRI hippocampal volume, and Baseline CDR SB. The LS mean treatment difference (AADvac1 – Placebo) was presented along with the 95 % CI and the two-sided p value for treatment effect.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Adverse event reporting additional description:

The protocol-defined safety endpoint was mapped to the incidence of drug-related AEs as primary endpoint for the purpose of results posting.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	AADvac1

Reporting group description:

AADvac1

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	AADvac1	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 117 (17.09%)	19 / 79 (24.05%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 117 (0.85%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleomorphic adenoma			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Metastases to bone

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Vascular disorders

Aortic aneurysm

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Arteriosclerosis

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Surgical and medical procedures

Hospitalisation

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Reproductive system and breast disorders

Testicular swelling

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders

Aspiration

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Respiratory failure

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pulmonary embolism		
subjects affected / exposed	1 / 117 (0.85%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epiglottic cyst		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Asthma		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Psychiatric disorders		
Neuropsychiatric symptoms		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Injury, poisoning and procedural complications		
Alcohol poisoning		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Femur fracture		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Contusion		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Sternal fracture		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral neck fracture		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lumbar vertebral fracture		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac disorders		
Cardiac arrest		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Coronary artery disease		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery stenosis		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial ischaemia		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorders		
Motor dysfunction		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Cognitive disorder		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhagic stroke		
subjects affected / exposed	1 / 117 (0.85%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral sensorimotor neuropathy		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transient ischaemic attack		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vertebrobasilar insufficiency		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Blood and lymphatic system disorders		
Splenic infarction		
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ear and labyrinth disorders		
Vertigo positional		
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Eye disorders		
Keratitis		

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Gastrointestinal disorders

Incarcerated inguinal hernia

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Faecaloma

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Vomiting

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Constipation

subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Diarrhoea

subjects affected / exposed	0 / 117 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Gastric polyps

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Large intestine polyp

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Rectal polyp

subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic encephalopathy			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory tract infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AADvac1	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 117 (84.62%)	64 / 79 (81.01%)	
Investigations			
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	11 / 117 (9.40%)	4 / 79 (5.06%)	
occurrences (all)	12	4	
Blood folate decreased			
subjects affected / exposed	7 / 117 (5.98%)	7 / 79 (8.86%)	
occurrences (all)	7	7	
Fibrin D dimer increased			

subjects affected / exposed	7 / 117 (5.98%)	10 / 79 (12.66%)
occurrences (all)	8	12
C-reactive protein increased		
subjects affected / exposed	6 / 117 (5.13%)	1 / 79 (1.27%)
occurrences (all)	6	1
Injury, poisoning and procedural complications		
Contusion		
subjects affected / exposed	7 / 117 (5.98%)	3 / 79 (3.80%)
occurrences (all)	9	3
Fall		
subjects affected / exposed	6 / 117 (5.13%)	2 / 79 (2.53%)
occurrences (all)	7	2
Vascular disorders		
Hypertension		
subjects affected / exposed	11 / 117 (9.40%)	6 / 79 (7.59%)
occurrences (all)	15	8
Nervous system disorders		
Headache		
subjects affected / exposed	22 / 117 (18.80%)	13 / 79 (16.46%)
occurrences (all)	55	23
Dizziness		
subjects affected / exposed	12 / 117 (10.26%)	9 / 79 (11.39%)
occurrences (all)	17	10
General disorders and administration site conditions		
Fatigue		
subjects affected / exposed	13 / 117 (11.11%)	6 / 79 (7.59%)
occurrences (all)	25	13
Injection site erythema		
subjects affected / exposed	38 / 117 (32.48%)	14 / 79 (17.72%)
occurrences (all)	129	37
Injection site nodule		
subjects affected / exposed	28 / 117 (23.93%)	5 / 79 (6.33%)
occurrences (all)	90	9
Injection site swelling		
subjects affected / exposed	25 / 117 (21.37%)	6 / 79 (7.59%)
occurrences (all)	69	14

Injection site pain			
subjects affected / exposed	18 / 117 (15.38%)	10 / 79 (12.66%)	
occurrences (all)	36	21	
Injection site pruritus			
subjects affected / exposed	9 / 117 (7.69%)	1 / 79 (1.27%)	
occurrences (all)	23	3	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	9 / 117 (7.69%)	2 / 79 (2.53%)	
occurrences (all)	14	5	
Diarrhoea			
subjects affected / exposed	8 / 117 (6.84%)	10 / 79 (12.66%)	
occurrences (all)	10	14	
Nausea			
subjects affected / exposed	7 / 117 (5.98%)	5 / 79 (6.33%)	
occurrences (all)	18	9	
Psychiatric disorders			
Depression			
subjects affected / exposed	7 / 117 (5.98%)	3 / 79 (3.80%)	
occurrences (all)	7	3	
Confusional state			
subjects affected / exposed	6 / 117 (5.13%)	0 / 79 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 117 (5.98%)	3 / 79 (3.80%)	
occurrences (all)	7	5	
Back pain			
subjects affected / exposed	7 / 117 (5.98%)	5 / 79 (6.33%)	
occurrences (all)	8	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 117 (16.24%)	12 / 79 (15.19%)	
occurrences (all)	34	15	
Urinary tract infection			

subjects affected / exposed	14 / 117 (11.97%)	12 / 79 (15.19%)
occurrences (all)	21	22
Upper respiratory tract infection		
subjects affected / exposed	9 / 117 (7.69%)	7 / 79 (8.86%)
occurrences (all)	14	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2016	AC-AD-003_Clinical study protocol_v3.0_29Apr2016 included the following changes: • Exclusion criteria were revised. • The options for re-screening were adjusted. • Text for the packaging and labelling of the IMP was revised to be consistent with the IMPD. • Storage and accountability of the IMP were revised. • Minor corrections and clarifications in Prior and concomitant therapy sections were made. • The description of medical history was revised. • The wording for subject information and informed consent was corrected in line with GCP and local legislations.
10 November 2016	AC-AD-003_Clinical study protocol_v4.0_19Sep2016 included the following changes: • Inclusion criterion 4 was expanded to allow biomarker evidence of the AD pathophysiological process to be satisfied either by medial temporal lobe atrophy seen in MRI, or by a positive AD biomarker signature in the CSF. • Exclusion criteria were revised. • Safety procedures were clarified. • Additional safety procedures related to eventual meningoencephalitis were included: a meningoencephalitis emergency treatment plan was included in the protocol. • Minor corrections were implemented and various changes were made to improve wording, consistency and clarity throughout the document. • Sponsor details were updated.
05 January 2017	AC-AD-003_Clinical study protocol_v5.0_19Dec2016 included the following changes: • The vaccination regimen was changed to administer 5 booster vaccinations at intervals of approximately 3 months, instead of the planned 2 booster vaccinations at intervals of 6 months. • Vaccine administration instructions were adjusted. • Clarification was provided for the order of assessments at Screening and subsequent visits. • Minor corrections were implemented and various changes were made to improve wording, consistency and clarity throughout the document.
17 August 2017	AC-AD-003_Clinical study protocol_v6.0_21Jun2017 included the following changes: • The storage, handling, and administration section was updated and Instructions for administration of the vaccine were updated. • Packaging and Labelling of Investigational Medicinal Product was updated. • The secondary endpoints regarding immunogenicity were revised to include a definition of a responder. • Exploratory endpoints were expanded. • The visit windows for some visits were expanded. • Additional preclinical study data was included. • The possibility to arrange unscheduled visits for purposes other than safety assessment was included.

09 March 2018	AC-AD-003_CT PROTOCOL_7.0_FINAL_2018-01-24 included the following changes: • Visit windows were broaden for some procedures. • Minor revisions were made to the text for endpoints and exclusion criteria and end of study definition to improve clarity. • Various formal changes were made to improve wording, consistency and clarity throughout the document.
14 August 2018	AC-AD-003_CT PROTOCOL_8.0_FINAL_2018-06-18 included the following changes: • The list of visits where CSF sampling may be performed was expanded. • Visit window for some procedures was clarified. • Various formal changes were made to improve wording, consistency and clarity throughout the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported