# 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<br>Units: Subjects | | | |
| Adults (18-64 years) | 29 | 10 | 39 |
| From 65-84 years | 88 | 69 | 157 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 70.6 | 72.7 | |
| standard deviation | ± 8.37 | ± 6.83 | - |
| Gender categorical<br>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<br>Units: Subjects | | | |
| Adults (18-64 years) | 39 | 39 | |
| From 65-84 years | 157 | 154 | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 71.4 | 71.4 | |
| standard deviation | ± 7.84 | ± 7.83 | |
| Gender categorical<br>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:<br>• Exclusion criteria were revised.<br>• The options for re-screening were adjusted.<br>• Text for the packaging and labelling of the IMP was revised to be consistent with the IMPD.<br>• Storage and accountability of the IMP were revised.<br>• Minor corrections and clarifications in Prior and concomitant therapy sections were made.<br>• The description of medical history was revised.<br>• 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:<br>• 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.<br>• Exclusion criteria were revised.<br>• Safety procedures were clarified.<br>• Additional safety procedures related to eventual meningoencephalitis were included: a meningoencephalitis emergency treatment plan was included in the protocol.<br>• Minor corrections were implemented and various changes were made to improve wording, consistency and clarity throughout the document.<br>• Sponsor details were updated. |
| 05 January 2017 | AC-AD-003_Clinical study protocol_v5.0_19Dec2016 included the following changes:<br>• 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.<br>• Vaccine administration instructions were adjusted.<br>• Clarification was provided for the order of assessments at Screening and subsequent visits.<br>• 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:<br>• The storage, handling, and administration section was updated and Instructions for administration of the vaccine were updated.<br>• Packaging and Labelling of Investigational Medicinal Product was updated.<br>• The secondary endpoints regarding immunogenicity were revised to include a definition of a responder.<br>• Exploratory endpoints were expanded.<br>• The visit windows for some visits were expanded.<br>• Additional preclinical study data was included.<br>• 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:<br>• Visit windows were broaden for some procedures.<br>• Minor revisions were made to the text for endpoints and exclusion criteria and end of study definition to improve clarity.<br>• 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:<br>• The list of visits where CSF sampling may be performed was expanded.<br>• Visit window for some procedures was clarified.<br>• 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