Clinical trial results:
A Phase I/II Double-Blind, Randomized, Placebo-Controlled, Adaptive Design Study of the Safety, Tolerability, Immunogenicity, and Efficacy of ACI-24 in Patients with Mild to Moderate Alzheimer's Disease

Summary

EudraCT number	2008-006257-40
Trial protocol	FI SE DK
Global end of trial date	16 October 2018

Results information

Result version number	v1 (current)
This version publication date	28 October 2019
First version publication date	28 October 2019

Trial information

Trial identification

Sponsor protocol code	ACI-24-0701

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AC Immune SA
Sponsor organisation address	EPFL Innovation Park - Building B, Lausanne, Switzerland, 1015
Public contact	Clinical Project Manager, AC Immune SA, +41 213459121, clinicaltrials@acimmune.com
Scientific contact	Clinical Project Manager, AC Immune SA, +41 213459121, clinicaltrials@acimmune.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2018
Global end of trial reached?	Yes
Global end of trial date	16 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall study objective was to assess the safety, immunogenicity, and efficacy of repeated doses of ACI-24 at 4 different dose levels administered to patients with mild to moderate Alzheimer's disease (AD).
The study was a 2-step seamless adaptive design study. Four doses were tested for safety and biological efficacy (Step 1). The most effective dose, assuming adequate safety, was intended to be expanded in Step 2 to obtain proof of concept in terms of cognitive efficacy. Step 2 was not performed.

Protection of trial subjects:

Only patients able to give informed consent were enrolled and patients had to be cared by a reliable spouse or other live-in caregiver who gave written consent to assist with clinical assessments and reports safety issues.
An interval of at least 1 week between first dose administration in the first 4 patients in each cohort enhanced safety.
Furthermore, the dose-cohorts were studied in a sequential manner, each cohort had to complete 4 immunizations and safety data including data 2 weeks after the fourth injection (ie, at visit 8 [Week 14]) were reviewed by the Data Safety Monitoring Board (DSMB) before enrolment into the next cohort commenced.

Note regarding long term Follow-up duration: The safety Follow-up period was reduced from 2 to 1 year for patients of Cohort 4 who received an additional boosting dose (dose 8) since no safety concerns were observed in Cohorts 1-3.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 21
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Finland: 15
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	16
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 5 sites in 3 countries (Denmark, Finland, and Sweden).
Cohort 1 FPFV - LPLV: 18Jan2010 - 05Sep2013
Cohort 2 FPFV - LPLV: 19May2011 - 03Nov2014
Cohort 3 FPFV - LPLV: 02May2012 - 14Nov2016
Cohort 4 FPFV - LPLV: 19May2014 - 16Oct2018
(FPFV = First patient first visit, LPLV = Last patient last visit)

Pre-assignment

Screening details:

Informed consent was obtained before a patient started any study-related procedures. 65 patients were screened and 48 patients were randomized to active treatment or placebo.

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, Carer, Assessor

Blinding implementation details:

The study was blinded to patients and site personnel, except to unblinded clinical personnel administrating/preparing the IMP, to pharmacists and to the unblinded CRAs. In emergency circumstances where the investigator was to identify an urgent clinical need to know whether the patient was receiving active medication or placebo, the IVRS was to allow the immediate unblinding of the patient by the investigator directly. Immediate unblinding was not required during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

9 patients were planned to receive 7 doses of ACI-24 at 10µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks

Arm type	Experimental
Investigational medicinal product name	ACI-24
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

7 doses of ACI-24 at 10µg at weeks 0, 4, 8, 12, 24, 36, and 48.

Arm title	Cohort 2

Arm description:

9 patients were planned to receive 7 doses of ACI-24 at 100µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks

Arm type	Experimental
Investigational medicinal product name	ACI-24
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

7 doses of ACI-24 at 100µg at weeks 0, 4, 8, 12, 24, 36, and 48.

Arm title	Cohort 3

Arm description:

9 patients of Cohort 3 were planned to receive 7 doses of ACI-24 at 300µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks
Data of these Cohort 3 patients including the Treatment and Follow-up period is reported under Cohort 3.

A boosting dose (dose 8) of ACI-24 at 300 µg was offered to Cohort 3 patients after the 100 weeks Follow-up period:
- 3 patients received this boosting dose 2.5 to 3.25 years after the last injection received at week 48.
Follow-up period after boosting dose: 24 weeks.
Data of these Cohort 3 patients for the boosting procedure is reported under Cohort 3 Booster where applicable.

Arm type	Experimental
Investigational medicinal product name	ACI-24
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

7 doses of ACI-24 at 300µg at weeks 0, 4, 8, 12, 24, 36, and 48 and one boosting dose (dose 8) of ACI-24 at 300 µg 2.5 to 3.25 years after the last injection received at week 48 (if applicable).

Arm title	Cohort 4

Arm description:

9 patients of Cohort 4 were planned to receive 7 doses of ACI-24 at 1000µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period (7 doses): 52 weeks
Follow-up period (7 doses): 100 weeks
A boosting dose (dose 8) of ACI-24 at 1000µg at week 74 was offered to these patients:
- 3 patients did not receive this boosting dose (2 patients did not give consent and treatment was discontinued in another patient after dose 6) and had Follow-up visits from week 64 to 152. These 3 patients plus the 9 patients until week 52 are reported under Cohort 4 (before/without Booster) where applicable.
- 6 patients received this boosting dose and followed a different visit schedule from week 52.
Treatment period (8 doses): 76 weeks
Follow-up period (8 doses): 50 weeks
Data of these patients from week 52 until study end is reported under Cohort 4 Booster where applicable.
- Compiled data of Cohort 4 (before/without Booster) and Cohort 4 Booster is reported together under reporting group Cohort 4

Arm type	Experimental
Investigational medicinal product name	ACI-24
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

7 doses of ACI-24 at 1000µg at weeks 0, 4, 8, 12, 24, 36, and 48 and one boosting dose (dose 8) of ACI-24 at 1000µg at week 74 (if applicable).
In Cohort 4, 2 concomitant injections were administered due to the higher volume of IMP needed.

Arm title	Placebo

Arm description:

The placebo patients of the 4 dose-cohorts (3 placebo patients per dose-cohort) are pooled to represent one group (a total of 12 placebo patients). Placebo patients followed the same visit/administration schedule as the corresponding actively treated patients in the same dose-cohort:
Cohort 1, 2, 3, and 4: 3 patients per dose-cohort were planned to receive 7 doses of placebo at weeks 0, 4, 8, 12, 24, 36, and 48.
A boosting dose (dose 8) of placebo was offered to patients in Cohorts 3 and 4:
- In Cohort 3, 1 patient received this boosting dose of placebo 3 years after the last injection of week 48. Data of this patient from the boosting procedure is reported under Placebo in Cohort 3 Booster where applicable.
- In Cohort 4, 1 patient received this boosting dose (dose 8) of placebo at week 74. Data of this patient from the boosting procedure is reported under Placebo in Cohort 4 Booster where applicable.

Arm type	Placebo
Investigational medicinal product name	Phosphate buffered saline (PBS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The volume of PBS administered to placebo patients was equivalent to the volume of ACI-24 administered to actively treated patients in each dose-cohort. In Cohort 4, 2 concomitant injections were administered due to the higher volume of IMP needed. Placebo patients followed the same visit/administration schedule as the corresponding actively treated patients in the same dose-cohort.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	9	9	9
Completed	8	8	6
Not completed	1	1	3
Other	1	-	1
Death	-	1	-
Adverse event	-	-	-
Consent withdrawn	-	-	2

Number of subjects in period 1	Cohort 4	Placebo
Started	9	12
Completed	8	9
Not completed	1	3
Other	-	1
Death	-	1
Adverse event	1	-
Consent withdrawn	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

9 patients were planned to receive 7 doses of ACI-24 at 10µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks

Reporting group title	Cohort 2

Reporting group description:

9 patients were planned to receive 7 doses of ACI-24 at 100µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks

Reporting group title	Cohort 3

Reporting group description:

9 patients of Cohort 3 were planned to receive 7 doses of ACI-24 at 300µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks
Data of these Cohort 3 patients including the Treatment and Follow-up period is reported under Cohort 3.

A boosting dose (dose 8) of ACI-24 at 300 µg was offered to Cohort 3 patients after the 100 weeks Follow-up period:
- 3 patients received this boosting dose 2.5 to 3.25 years after the last injection received at week 48.
Follow-up period after boosting dose: 24 weeks.
Data of these Cohort 3 patients for the boosting procedure is reported under Cohort 3 Booster where applicable.

Reporting group title	Cohort 4

Reporting group description:

9 patients of Cohort 4 were planned to receive 7 doses of ACI-24 at 1000µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period (7 doses): 52 weeks
Follow-up period (7 doses): 100 weeks
A boosting dose (dose 8) of ACI-24 at 1000µg at week 74 was offered to these patients:
- 3 patients did not receive this boosting dose (2 patients did not give consent and treatment was discontinued in another patient after dose 6) and had Follow-up visits from week 64 to 152. These 3 patients plus the 9 patients until week 52 are reported under Cohort 4 (before/without Booster) where applicable.
- 6 patients received this boosting dose and followed a different visit schedule from week 52.
Treatment period (8 doses): 76 weeks
Follow-up period (8 doses): 50 weeks
Data of these patients from week 52 until study end is reported under Cohort 4 Booster where applicable.
- Compiled data of Cohort 4 (before/without Booster) and Cohort 4 Booster is reported together under reporting group Cohort 4

Reporting group title	Placebo

Reporting group description:

The placebo patients of the 4 dose-cohorts (3 placebo patients per dose-cohort) are pooled to represent one group (a total of 12 placebo patients). Placebo patients followed the same visit/administration schedule as the corresponding actively treated patients in the same dose-cohort:
Cohort 1, 2, 3, and 4: 3 patients per dose-cohort were planned to receive 7 doses of placebo at weeks 0, 4, 8, 12, 24, 36, and 48.
A boosting dose (dose 8) of placebo was offered to patients in Cohorts 3 and 4:
- In Cohort 3, 1 patient received this boosting dose of placebo 3 years after the last injection of week 48. Data of this patient from the boosting procedure is reported under Placebo in Cohort 3 Booster where applicable.
- In Cohort 4, 1 patient received this boosting dose (dose 8) of placebo at week 74. Data of this patient from the boosting procedure is reported under Placebo in Cohort 4 Booster where applicable.

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	9	9	9
Age categorical Units: Subjects			
Adults (18-64 years)	3	5	1
From 65-84 years	6	4	8
Age continuous Units: years			
arithmetic mean	69.4	65.2	71.1
standard deviation	± 8.7	± 8.3	± 4.9
Gender categorical Units: Subjects			
Female	5	4	6
Male	4	5	3
Race Units: Subjects			
Hispanic or Latino	1	0	0
White	8	9	9

Reporting group values	Cohort 4	Placebo	Total
Number of subjects	9	12	48
Age categorical Units: Subjects			
Adults (18-64 years)	5	2	16
From 65-84 years	4	10	32
Age continuous Units: years			
arithmetic mean	62.2	69.1	
standard deviation	± 8.5	± 4.8	-
Gender categorical Units: Subjects			
Female	3	5	23
Male	6	7	25
Race Units: Subjects			
Hispanic or Latino	0	0	1
White	9	12	47

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

9 patients were planned to receive 7 doses of ACI-24 at 10µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks

Reporting group title	Cohort 2

Reporting group description:

9 patients were planned to receive 7 doses of ACI-24 at 100µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks

Reporting group title	Cohort 3

Reporting group description:

9 patients of Cohort 3 were planned to receive 7 doses of ACI-24 at 300µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period: 52 weeks
Follow-up period: 100 weeks
Data of these Cohort 3 patients including the Treatment and Follow-up period is reported under Cohort 3.

A boosting dose (dose 8) of ACI-24 at 300 µg was offered to Cohort 3 patients after the 100 weeks Follow-up period:
- 3 patients received this boosting dose 2.5 to 3.25 years after the last injection received at week 48. Follow-up period after boosting dose: 24 weeks.
Data of these Cohort 3 patients for the boosting procedure is reported under Cohort 3 Booster where applicable.

Reporting group title	Cohort 4

Reporting group description:

9 patients of Cohort 4 were planned to receive 7 doses of ACI-24 at 1000µg at weeks 0, 4, 8, 12, 24, 36, and 48.
Treatment period (7 doses): 52 weeks
Follow-up period (7 doses): 100 weeks
A boosting dose (dose 8) of ACI-24 at 1000µg at week 74 was offered to these patients:
- 3 patients did not receive this boosting dose (2 patients did not give consent and treatment was discontinued in another patient after dose 6) and had Follow-up visits from week 64 to 152. These 3 patients plus the 9 patients until week 52 are reported under Cohort 4 (before/without Booster) where applicable.
- 6 patients received this boosting dose and followed a different visit schedule from week 52.
Treatment period (8 doses): 76 weeks
Follow-up period (8 doses): 50 weeks
Data of these patients from week 52 until study end is reported under Cohort 4 Booster where applicable.
- Compiled data of Cohort 4 (before/without Booster) and Cohort 4 Booster is reported together under reporting group Cohort 4

Reporting group title	Placebo

Reporting group description:

The placebo patients of the 4 dose-cohorts (3 placebo patients per dose-cohort) are pooled to represent one group (a total of 12 placebo patients). Placebo patients followed the same visit/administration schedule as the corresponding actively treated patients in the same dose-cohort:
Cohort 1, 2, 3, and 4: 3 patients per dose-cohort were planned to receive 7 doses of placebo at weeks 0, 4, 8, 12, 24, 36, and 48.
A boosting dose (dose 8) of placebo was offered to patients in Cohorts 3 and 4:
- In Cohort 3, 1 patient received this boosting dose of placebo 3 years after the last injection of week 48. Data of this patient from the boosting procedure is reported under Placebo in Cohort 3 Booster where applicable.
- In Cohort 4, 1 patient received this boosting dose (dose 8) of placebo at week 74. Data of this patient from the boosting procedure is reported under Placebo in Cohort 4 Booster where applicable.

Subject analysis set title	Cohort 3 Booster (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Cohort 3 Booster (Safety Analysis Set) (3 patients who received a boosting dose (dose 8) of ACI-24 at 300µg 2.5 to 3.25 years after the last injection of week 48). Safety events that occurred after booster injection are reported.

Subject analysis set title	Placebo in Cohort 3 Booster (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Placebo in Cohort 3 Booster (Safety Analysis Set) (1 patient who received a boosting dose (dose 8) of placebo 3 years after the last injection of week 48). Safety events that occurred after booster injection are reported.

Subject analysis set title	Cohort 4 Booster (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Cohort 4 Booster (Safety Analysis Set) (6 patients who received a boosting dose (dose 8) of ACI-24 at 1000 µg at week 74).
These patients followed a different visit schedule from week 52 than Cohort 4 patients who did not receive a boosting dose.
Treatment period (8 doses): 76 weeks
Follow-up period (8 doses): 50 weeks
Data of these patients from week 52 until study end is reported.

Subject analysis set title	Placebo in Cohort 4 Booster (Safety Analysis Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

Placebo in Cohort 4 Booster (Safety Analysis Set) (1 patient who received a boosting dose (dose 8) of placebo at week 74. One patient of the other 2 patients did not consent for a boosting dose and the other patient died during the study).
This patient followed a different visit schedule from week 52 than Cohort 4 patients who did not receive a boosting dose.
Treatment period (8 doses): 76 weeks
Follow-up period (8 doses): 50 weeks
Data of this patient from week 52 until study end is reported.

Subject analysis set title	Cohort 4 Booster (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Cohort 4 Booster (Safety Analysis Set) (6 patients who received a boosting dose (dose 8) of ACI-24 at 1000 µg at week 74).
These patients followed a different visit schedule from week 52 than Cohort 4 patients who did not receive a boosting dose.
Treatment period (8 doses): 76 weeks
Follow-up period (8 doses): 50 weeks
Data of these patients from week 52 until study end is reported.

Subject analysis set title	Cohort 4 (before/without Booster) (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

This reporting group comprises data of 9 patients of Cohort 4 until week 52 (9 patients who were planned to receive 7 doses of ACI-24 at 1000µg at weeks 0, 4, 8, 12, 24, 36, and 48) as well as data of 3 patients of Cohort 4 who did not receive a boosting dose who had additional Follow-up visit from week 64 to 152 (Follow-up period: 100 weeks). Of these 3 patients, 2 patients did not give consent for a boosting dose and treatment was discontinued in another patient after dose 6.

Data of the other 6 patients (out of 9 patients) of Cohort 4 who received a boosting dose (dose 8) is not included in this reporting group. These patients followed a different visit schedule from week 52 and are reported under Cohort 4 Booster.

Subject analysis set title	Placebo in Cohort 4 Booster (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo in Cohort 4 Booster (Safety Analysis Set) (1 patient who received a boosting dose (dose 8) of placebo at week 74. Of the other 2 patients, 1 patient did not consent for a boosting dose and the other patient died during the study).
This patient followed a different visit schedule from week 52 than Cohort 4 patients who did not receive a boosting dose.
Treatment period (8 doses): 76 weeks

Follow-up period (8 doses): 50 weeks
Data of this patient from week 52 until study end is reported.

Primary: Overview of Adverse Events (Safety Analysis Set)

End point title	Overview of Adverse Events (Safety Analysis Set)[1]

End point description:

No hypothesis testing performed. Observations are given for the safety population (all randomized patients who received at least one dose of ACI-24 or placebo and who have at least one post-dosing safety assessment). Safety events that occurred during the Booster procedure in Cohort 3 are listed separately in the table. Categorical data are presented with the number of patients with at least one event for the following selections:
- Treatment-emergent adverse events (TEAEs)
- Deaths
- Serious TEAEs
- TEAEs leading to withdrawal of IMP
- Severe and life threatening adverse events (AEs)
- TEAEs possibly/probably related to IMP
- Serious TEAEs possibly/probably related to IMP

End point type	Primary

End point timeframe:

The safety reporting period was defined as the interval between the time of first dosing and the end of the designated Follow-up period. Adverse events falling into this time window were classified as treatment-emergent Adverse Events (TEAEs).

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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	9	9
Units: Number of patients				
Treatment-emergent adverse events (TEAEs)	8	9	9	9
Deaths	0	1	0	1
Serious TEAEs	2	1	0	3
TEAEs leading to withdrawal of IMP	0	0	0	1
Severe and life threatening AEs	1	1	0	3
TEAEs possibly/probably related to IMP	5	4	5	8
Serious TEAEs possibly/probably related to IMP	0	0	0	0

End point values	Placebo	Cohort 3 Booster (Safety Analysis Set)	Placebo in Cohort 3 Booster (Safety Analysis Set)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	3	1	
Units: Number of patients				
Treatment-emergent adverse events (TEAEs)	12	2	1	
Deaths	1	0	0	
Serious TEAEs	4	0	0	

TEAEs leading to withdrawal of IMP	0	0	0	
Severe and life threatening AEs	3	0	0	
TEAEs possibly/probably related to IMP	6	0	1	
Serious TEAEs possibly/probably related to IMP	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Global assessment of tolerability in Cohorts 1-4 and Placebo (Safety Analysis Set)

End point title	Global assessment of tolerability in Cohorts 1-4 and Placebo (Safety Analysis Set)[2]

End point description:

No hypothesis testing performed. Results are reported for the safety population (all randomized patients who received at least one dose of ACI-24 or placebo and who have at least one post-dosing safety assessment). Data for Cohorts 1-4 and Placebo until week 52 are reported in this table. Tolerability data are tabulated with descriptive statistics and counts. For each visit, the count of patients in the tolerability categories "very good", "good", and "moderate" are given. Tolerability was never assessed as "poor" and this category is therefore not listed.

Note: The number of patients provided in the table ("number of subjects analysed") shows the number of patients planned to be analyzed. The actual number of patients analyzed per data point (week) is the sum of listed patients per data point (week).
Data for patients of Cohort 3 and 4 who received dose 8 are reported in separate tables.

End point type	Primary

End point timeframe:

Tolerability was assessed at weeks 2, 4, 6, 8, 10, 12, 14, 18, 24, 26, 30, 36, 38, 42, 48 & 52. In addition, Cohort 4 patients receiving dose 8 were assessed at weeks 74 & 76 and Cohort 3 patients receiving dose 8 at weeks 2, 4 & 12 after boosting dose.

Notes:

[2] - 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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	9	9
Units: Number of patients				
Week 2 – Very Good	8	8	7	5
Week 2 – Good	1	1	2	4
Week 2 – Moderate	0	0	0	0
Week 4 – Very Good	9	8	7	3
Week 4 – Good	0	1	2	6
Week 4 – Moderate	0	0	0	0
Week 6 – Very Good	8	9	8	5
Week 6 – Good	1	0	1	4
Week 6 – Moderate	0	0	0	0
Week 8 – Very Good	8	7	7	6
Week 8 – Good	1	2	2	3
Week 8 – Moderate	0	0	0	0

Week 10 – Very Good	9	6	7	2
Week 10 – Good	0	3	1	4
Week 10 – Moderate	0	0	1	0
Week 12 – Very Good	9	6	7	4
Week 12 – Good	0	3	2	5
Week 12 – Moderate	0	0	0	0
Week 14 – Very Good	8	6	7	4
Week 14 – Good	1	2	1	5
Week 14 – Moderate	0	1	1	0
Week 18 – Very Good	7	5	6	4
Week 18 – Good	1	2	3	5
Week 18 – Moderate	1	2	0	0
Week 24 – Very Good	7	7	7	4
Week 24 – Good	2	0	2	5
Week 24 – Moderate	0	2	0	0
Week 26 – Very Good	4	7	8	4
Week 26 – Good	5	0	1	5
Week 26 – Moderate	0	2	0	0
Week 30 – Very Good	6	7	5	4
Week 30 – Good	3	1	2	4
Week 30 – Moderate	0	1	1	1
Week 36 – Very Good	4	7	5	3
Week 36 – Good	4	1	4	5
Week 36 – Moderate	1	1	0	1
Week 38 – Very Good	5	6	6	3
Week 38 – Good	4	1	3	6
Week 38 – Moderate	0	2	0	0
Week 42 – Very Good	6	7	5	3
Week 42 – Good	3	1	2	6
Week 42 – Moderate	0	1	1	0
Week 48 – Very Good	3	6	7	1
Week 48 – Good	6	1	2	7
Week 48 – Moderate	0	2	0	0
Week 52 – Very Good	4	6	8	3
Week 52 – Good	5	3	1	6
Week 52 – Moderate	0	0	0	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of patients				
Week 2 – Very Good	7			
Week 2 – Good	5			
Week 2 – Moderate	0			
Week 4 – Very Good	9			
Week 4 – Good	3			
Week 4 – Moderate	0			
Week 6 – Very Good	9			
Week 6 – Good	3			

Week 6 – Moderate	0			
Week 8 – Very Good	8			
Week 8 – Good	4			
Week 8 – Moderate	0			
Week 10 – Very Good	6			
Week 10 – Good	5			
Week 10 – Moderate	0			
Week 12 – Very Good	8			
Week 12 – Good	4			
Week 12 – Moderate	0			
Week 14 – Very Good	8			
Week 14 – Good	3			
Week 14 – Moderate	0			
Week 18 – Very Good	5			
Week 18 – Good	6			
Week 18 – Moderate	0			
Week 24 – Very Good	6			
Week 24 – Good	5			
Week 24 – Moderate	0			
Week 26 – Very Good	6			
Week 26 – Good	4			
Week 26 – Moderate	1			
Week 30 – Very Good	7			
Week 30 – Good	4			
Week 30 – Moderate	0			
Week 36 – Very Good	3			
Week 36 – Good	8			
Week 36 – Moderate	0			
Week 38 – Very Good	6			
Week 38 – Good	4			
Week 38 – Moderate	0			
Week 42 – Very Good	4			
Week 42 – Good	5			
Week 42 – Moderate	0			
Week 48 – Very Good	3			
Week 48 – Good	7			
Week 48 – Moderate	0			
Week 52 – Very Good	3			
Week 52 – Good	6			
Week 52 – Moderate	1			

Statistical analyses

No statistical analyses for this end point

Primary: Global assessment of tolerability in Cohort 3 Booster and Placebo in Cohort 3 Booster (Safety Analysis Set)

End point title	Global assessment of tolerability in Cohort 3 Booster and Placebo in Cohort 3 Booster (Safety Analysis Set)[3]

End point description:

Please refer to the description for the end point "Global assessment of tolerability in Cohorts 1-4 and Placebo (Safety Analysis Set)".

End point type	Primary

End point timeframe:

As stated above (end point "Global assessment of tolerability in Cohorts 1-4 and Placebo (Safety Analysis Set)"), tolerability in Cohort 3 Booster patients who received dose 8 (ACI-24 or placebo) was assessed at weeks 2, 4 & 12 after boosting dose.

Notes:

[3] - 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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 3 Booster (Safety Analysis Set)	Placebo in Cohort 3 Booster (Safety Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	1		
Units: Number of patients				
Week 2 – Very Good	2	0		
Week 2 – Good	0	0		
Week 2 – Moderate	1	1		
Week 4 – Very Good	3	0		
Week 4 – Good	0	1		
Week 4 – Moderate	0	0		
Week 12 – Very Good	3	0		
Week 12 – Good	0	1		
Week 12 – Moderate	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Global assessment of tolerability in Cohort 4 Booster and Placebo in Cohort 4 Booster (Safety Analysis Set)

End point title	Global assessment of tolerability in Cohort 4 Booster and Placebo in Cohort 4 Booster (Safety Analysis Set)[4]

End point description:

Please refer to the description for the end point "Global assessment of tolerability in Cohorts 1-4 and Placebo (Safety Analysis Set)".

End point type	Primary

End point timeframe:

As stated above (end point "Global assessment of tolerability in Cohorts 1-4 and Placebo (Safety Analysis Set)"), tolerability in Cohort 4 patients who received dose 8 (ACI-24 or placebo) was assessed at weeks 74 & 76.

Notes:

[4] - 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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 4 Booster (Safety Analysis Set)	Placebo in Cohort 4 Booster (Safety Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	1		
Units: Number of patients				
Week 74 – Very Good	2	0		
Week 74 – Good	3	1		
Week 74 – Moderate	0	0		
Week 76 – Very Good	2	0		
Week 76 – Good	4	0		
Week 76 – Moderate	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Descriptive measures of anti-Abeta1-42 IgG in serum: Responder analysis (Full Analysis Set)

End point title	Descriptive measures of anti-Abeta1-42 IgG in serum: Responder analysis (Full Analysis Set)[5]

End point description:

The Aβ1-42 IgG antibody response in serum was studied in patients at the prespecified timepoints of Week 26 and Week 52 by enzyme-linked immunosorbent assay (ELISA) detecting the free fraction of IgG response. A patient was defined as a responder if the antibody response at 26 and/or 52 weeks of treatment was at least doubled compared to the Baseline value of antibody response. The Baseline value was defined as the mean of the anti-Aβ1-42 IgG titer values at the Screening Visit (Week -4 to 0) and visit 1 (Week 0).

Note: The number of patients provided in the table ("number of subjects analysed") shows the number of patients planned to be analyzed. Table does not allow entering the number of patients analyzed per data point (actual numbers are recorded below).
Actual number of patients analyzed (n):
- at Week 26: n = 9 (Cohort 1, Cohort 2, Cohort 3, Cohort 4), n = 11 (Placebo)
- at Week 52: n = 9 (Cohort 1, Cohort 2, Cohort 4), n = 8 (Cohort 3, Placebo)

End point type	Primary

End point timeframe:

End point was assessed at weeks 26 and 52 after first dose.

Notes:

[5] - 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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	9	9
Units: Number of patients				
Week 26 – IgG Responder	0	0	0	0
Week 52 – IgG Responder	0	0	1	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of patients				
Week 26 – IgG Responder	0			
Week 52 – IgG Responder	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive measures of brain Aβ levels assessed by Positron Emission Tomography (PET) in Cohorts 1-4 and Placebo (Full Analysis Set)

End point title	Descriptive measures of brain Aβ levels assessed by Positron Emission Tomography (PET) in Cohorts 1-4 and Placebo (Full Analysis Set)[6]

End point description:

The brain Aβ levels were quantified by Amyloid Positron Emission Tomography (PET) using Florbetaben as the PET tracer at 3 different time points (Baseline or Screening (weeks -4 or week 0) and 2 later timepoints (weeks 26 & 52 or weeks 52 & 76) depending on the cohort/patient). The change from Baseline in composite summary (CompSum) Standardized Uptake Value Ratio (SUVR) using the Mean Cerebellum Gray (MCG) as reference region is tabulated.

Note: The number of patients provided in the table ("number of subjects analysed") shows the number of patients planned to be analyzed. Table does not allow entering the number of patients analyzed per data point (actual numbers are recorded below).
Actual number of patients analyzed (n):
- at Week 26: n = 9 (Cohort 2-3), n = 3 (Cohort 4), n = 7 (Placebo)
- at Week 52: n = 9 (Cohort 2-3), n = 7 (Cohort 4), n = 8 (Placebo)
Data of patients in Cohort 4 Booster is listed in a separate table.
PET Imaging was not done in Cohort 1.

End point type	Secondary

End point timeframe:

Cohorts 2-3 patients were planned to be scanned at weeks 0, 26 & 52.
Patients 1-4 in Cohort 4 were planned to be scanned at weeks -4 (Screening), 26 & 52.
Patients 5-12 in Cohort 4 were planned to be scanned at weeks -4 (Screening), 52 & 76.

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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 2	Cohort 3	Placebo	Cohort 4 (before/without Booster) (Full Analysis Set)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	9	9	12	9
Units: Composite Summary SUVR (MCG)				
arithmetic mean (standard deviation)				

Change from Baseline (CompSum SUVR) – Week 26	0.02 (± 0.21)	0.02 (± 0.19)	0.02 (± 0.28)	-0.10 (± 0.10)
Change from Baseline (CompSum SUVR) – Week 52	0.08 (± 0.25)	-0.03 (± 0.22)	0.06 (± 0.22)	-0.07 (± 0.07)

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive measures of brain Aβ levels assessed by Positron Emission Tomography (PET) in Cohort 4 Booster and Placebo in Cohort 4 Booster at Week 76 (Full Analysis Set)

End point title	Descriptive measures of brain Aβ levels assessed by Positron Emission Tomography (PET) in Cohort 4 Booster and Placebo in Cohort 4 Booster at Week 76 (Full Analysis Set)

End point description:

Please refer to the description for the end point "Descriptive measures of brain Aβ levels assessed by Positron Emission Tomography (PET) in Cohorts 1-4 and Placebo (Full Analysis Set)".

Note: The number of patients in the table ("number of subjects analysed") shows the actual number of patients analyzed at week 76.
As data for only 1 placebo patient is available, a standard deviation (SD) is not applicable. Since the table does not allow to enter "not applicable", a "0.0" was entered as SD for the placebo patient.

End point type	Secondary

End point timeframe:

As stated above (end point "Descriptive measures of brain Aβ levels assessed by Positron Emission Tomography (PET) in Cohorts 1-4 and Placebo (Full Analysis Set)", Cohort 4 patients 5-12 were planned to be scanned at Week 76.

End point values	Cohort 4 Booster (Full Analysis Set)	Placebo in Cohort 4 Booster (Full Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	1		
Units: Composite Summary SUVR (MCG)				
arithmetic mean (standard deviation)				
Change from Baseline (CompSum SUVR) – Week 76	0.06 (± 0.11)	-0.17 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of global function as measured by the Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) in Cohorts 1-4 and Placebo (Full Analysis Set)

End point title	Assessment of global function as measured by the Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) in Cohorts

	1-4 and Placebo (Full Analysis Set)[7]

End point description:

The CDR was assessed in 6 categories: memory, orientation, judgement/problem solving, community affairs, home/hobbies, personal care. It is based on a semi-structured interview conducted with the patient and caregiver, by a rater without access to the results of the cognitive tests. Each category has scores from 0 (no symptoms) to 3 (severe), and the sum of these items (sum of boxes) may range from 0 to 18 points. An increase in the CDR - SB indicates a decline in functioning. The change from Baseline in CDR - SB is tabulated.

Note: The number of patients provided in the table ("number of subjects analysed") shows the number of patients planned to be analyzed. Table does not allow entering the number of patients analyzed per data point, for the actual number of patients analyzed per data point refer to the attachment.
Data for Cohort 4 Booster is presented in a separate table.
Data for Cohort 3 Booster is not presented due to the small sample size.

End point type	Secondary

End point timeframe:

The Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) was assessed at weeks 0, 26, 36, 52, 76, 100 & 152 (Cohorts 1-3 and 4 (before/without Booster)). Patients in Cohort 4 Booster were assessed at weeks 76, 87, 100 & 126.

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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 1	Cohort 2	Cohort 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	9	12
Units: CDR – SB				
arithmetic mean (standard deviation)				
Change from Baseline (CDR-SB) – Week 26	1.8 (± 1.7)	0.6 (± 1.5)	0.8 (± 1.3)	1.1 (± 1.3)
Change from Baseline (CDR-SB) – Week 36	2.3 (± 1.6)	1.3 (± 2.7)	0.7 (± 0.8)	1.4 (± 2.4)
Change from Baseline (CDR-SB) – Week 52	2.9 (± 2.0)	2.6 (± 3.6)	0.9 (± 1.7)	2.0 (± 2.9)
Change from Baseline (CDR-SB) – Week 76	3.5 (± 3.0)	3.4 (± 4.2)	1.9 (± 1.8)	3.9 (± 4.3)
Change from Baseline (CDR-SB) – Week 100	5.7 (± 2.5)	3.6 (± 3.9)	3.1 (± 2.5)	4.4 (± 4.7)
Change from Baseline (CDR-SB) – Week 152	7.2 (± 3.5)	4.4 (± 2.9)	5.4 (± 4.0)	4.4 (± 3.7)

End point values	Cohort 4 (before/without Booster) (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: CDR – SB				
arithmetic mean (standard deviation)				
Change from Baseline (CDR-SB) – Week 26	0.1 (± 0.5)			
Change from Baseline (CDR-SB) – Week 36	0.3 (± 0.8)			

Change from Baseline (CDR-SB) – Week 52	1.0 (± 1.0)			
Change from Baseline (CDR-SB) – Week 76	1.7 (± 0.8)			
Change from Baseline (CDR-SB) – Week 100	3.0 (± 2.1)			
Change from Baseline (CDR-SB) – Week 152	8.5 (± 0.0)			

Attachments (see zip file)	Attachment_CDR-Sum of boxes (FAS)/ACI-24-0701_CDR-Sum

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of global function as measured by the Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) in Cohort 4 Booster and Placebo in Cohort 4 Booster (Full Analysis Set)

End point title	Assessment of global function as measured by the Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) in Cohort 4 Booster and Placebo in Cohort 4 Booster (Full Analysis Set)

End point description:

Please refer to the description for the end point "Assessment of global function as measured by the Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) in Cohorts 1-4 and Placebo (Full Analysis Set)".

Note: As data for only 1 placebo patient is available, a standard deviation (SD) is not applicable. Since the table does not allow to enter "not applicable", a "0.0" was entered as SD for the placebo patient.

End point type	Secondary

End point timeframe:

As stated above (end point "Assessment of global function as measured by the Clinical Dementia Rating (CDR) Scale - sum of boxes (SB) in Cohorts 1-4 and Placebo (Full Analysis Set)", patients in Cohort 4 Booster were assessed at weeks 76, 87, 100 & 126.

End point values	Cohort 4 Booster (Full Analysis Set)	Placebo in Cohort 4 Booster (Full Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	1		
Units: CDR – SB				
arithmetic mean (standard deviation)				
Change from Baseline (CDR-SB) – Week 76	1.0 (± 1.4)	5.0 (± 0.0)		
Change from Baseline (CDR-SB) – Week 87	1.1 (± 1.2)	4.0 (± 0.0)		
Change from Baseline (CDR-SB) – Week 100	1.4 (± 1.7)	6.0 (± 0.0)		
Change from Baseline (CDR-SB) – Week 126	3.1 (± 3.4)	7.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of cognitive function as measured by Mini-Mental State Examination (MMSE) in Cohorts 1-4 and Placebo (Full Analysis Set)

End point title	Assessment of cognitive function as measured by Mini-Mental State Examination (MMSE) in Cohorts 1-4 and Placebo (Full Analysis Set)[8]

End point description:

The MMSE was performed to evaluate cognitive function, assessing memory, orientation, and praxis in a short series of tests. The score is from 0 to 30 with 30 being the best possible and 0 being the worst possible score. The change from Baseline in MMSE total scores is tabulated.

Note: The number of patients provided in the table ("number of subjects analysed") shows the number of patients planned to be analyzed. Table does not allow entering the number of patients analyzed per data point, for the actual number of patients analyzed per data point refer to the attachment.
Data for Cohort 4 Booster is presented in a separate table.
Data for Cohort 3 Booster is not presented due to the small sample size.

End point type	Secondary

End point timeframe:

The Mini-Mental State Examination (MMSE) was performed at weeks -4, 0, 26, 36, 52, 76, 100 & 152 (Cohorts 1-3 and 4 (before/without Booster)). Patients in Cohort 4 Booster were assessed at weeks 76, 87, 100 & 126.

Notes:

[8] - 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: All data obtained in this study are listed and summarized with descriptive statistics or frequency tables where appropriate. No hypothesis testings have been performed as per the statistical analysis plan.

End point values	Cohort 1	Cohort 2	Cohort 3	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	9	12
Units: MMSE total score				
arithmetic mean (standard deviation)				
Change from Baseline (MMSE total score) – Week 26	-2.9 (± 2.0)	-2.1 (± 3.6)	-1.3 (± 1.2)	-1.3 (± 3.3)
Change from Baseline (MMSE total score) – Week 36	-4.5 (± 3.4)	-2.0 (± 2.8)	-2.1 (± 1.9)	-1.5 (± 3.3)
Change from Baseline (MMSE total score) – Week 52	-3.0 (± 4.4)	-2.9 (± 5.6)	-3.0 (± 3.3)	-2.9 (± 2.1)
Change from Baseline (MMSE total score) – Week 76	-4.4 (± 4.3)	-3.9 (± 2.3)	-5.1 (± 3.4)	-4.4 (± 2.5)
Change from Baseline (MMSE total score) – Week 100	-6.4 (± 4.0)	-4.3 (± 2.3)	-5.9 (± 2.6)	-7.1 (± 3.8)
Change from Baseline (MMSE total score) – Week 152	-10.0 (± 4.7)	-8.5 (± 4.1)	-6.2 (± 4.2)	-9.1 (± 3.2)

End point values	Cohort 4 (before/without Booster) (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: MMSE total score				
arithmetic mean (standard deviation)				
Change from Baseline (MMSE total score) – Week 26	0.8 (± 1.4)			
Change from Baseline (MMSE total score) – Week 36	0.8 (± 1.4)			
Change from Baseline (MMSE total score) – Week 52	0.2 (± 1.9)			
Change from Baseline (MMSE total score) – Week 76	-1.7 (± 2.9)			
Change from Baseline (MMSE total score) – Week 100	-2.5 (± 2.1)			
Change from Baseline (MMSE total score) – Week 152	-11 (± 0.0)			

Attachments (see zip file)	Attachment_MMSE (FAS)/ACI-24-0701_MMSE_FAS_20190510.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of cognitive function as measured by Mini-Mental State Examination (MMSE) in Cohort 4 Booster and Placebo in Cohort 4 Booster (Full Analysis Set)

End point title	Assessment of cognitive function as measured by Mini-Mental State Examination (MMSE) in Cohort 4 Booster and Placebo in Cohort 4 Booster (Full Analysis Set)

End point description:

Please refer to the description for the end point "Assessment of cognitive function as measured by Mini-Mental State Examination (MMSE) in Cohorts 1-4 and Placebo (Full Analysis Set)".

Note: As data for only 1 placebo patient is available, a standard deviation (SD) is not applicable. Since the table does not allow to enter "not applicable", a "0.0" was entered as SD for the placebo patient.

End point type	Secondary

End point timeframe:

As stated above (end point "Assessment of cognitive function as measured by Mini-Mental State Examination (MMSE) in Cohorts 1-4 and Placebo (Full Analysis Set)", patients in Cohort 4 Booster were assessed at weeks 76, 87, 100 & 126.

End point values	Cohort 4 Booster (Full Analysis Set)	Placebo in Cohort 4 Booster (Full Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	1		
Units: MMSE total score				

arithmetic mean (standard deviation)				
Change from Baseline (MMSE total score) – Week 76	-0.2 (± 1.9)	-2.0 (± 0.0)		
Change from Baseline (MMSE total score) – Week 87	-1.8 (± 4.0)	-3.0 (± 0.0)		
Change from Baseline (MMSE total score) – Week 100	-0.8 (± 2.6)	1.0 (± 0.0)		
Change from Baseline (MMSE total score) – Week 126	-3.0 (± 4.4)	-9.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the purpose of safety reporting, the study period was defined as the interval between the time of first dosing and the end of the designated Follow-up period.

Adverse event reporting additional description:

Determination of AEs was based on:
- the signs or symptoms detected during the physical examination and on clinical evaluation of the patient
- the interview of the patient and their caregiver

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Cohort 1 (Safety Analysis Set)

Reporting group description:

Cohort 1 Safety Analysis Set (9 patients who received at least 1 dose of ACI-24 at 10µg)

Reporting group title	Cohort 2 (Safety Analysis Set)

Reporting group description:

Cohort 2 Safety Analysis Set (9 patients who received at least 1 dose of ACI-24 at 100µg)

Reporting group title	Cohort 3 (Safety Analysis Set)

Reporting group description:

Cohort 3 Safety Analysis Set (9 patients who received at least 1 dose of ACI-24 at 300µg)

Reporting group title	Cohort 4 (Safety Analysis Set)

Reporting group description:

Cohort 4 Safety Analysis Set (9 patients who received at least 1 dose of ACI-24 at 1000µg).

Note: For 1 patient the SAE "Neoplasm malignant" was reported during the study. This patient completed the study but died shortly (arround 1 month) after the last safety Follow-up visit. Although this event (Death) did not occur in the official safety reporting period of the study, this outcome is however reported in the table for SAEs.

Reporting group title	Placebo (pooled) (Safety Analysis Set)

Reporting group description:

Placebo (pooled) Safety Analysis Set (12 patients who received at least 1 dose of placebo)

Reporting group title	Cohort 3 Booster (Safety Analysis Set)

Reporting group description:

Cohort 3 Booster (Safety Analysis Set) (3 patients who received a boosting dose (dose 8) of ACI-24 at 300µg 2.5 to 3.25 years after the last injection received at week 48). Events that occurred after booster injection are reported.

Reporting group title	Placebo in Cohort 3 Booster (Safety Analysis Set)

Reporting group description:

Placebo in Cohort 3 Booster (Safety Analysis Set) (1 patient who received a boosting dose (dose 8) of placebo 2.5 to 3.25 years after the last injection received at week 48). Events that occurred after booster injection are reported.

Serious adverse events	Cohort 1 (Safety Analysis Set)	Cohort 2 (Safety Analysis Set)	Cohort 3 (Safety Analysis Set)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	0 / 9 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac death			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4 (Safety Analysis Set)	Placebo (pooled) (Safety Analysis Set)	Cohort 3 Booster (Safety Analysis Set)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	4 / 12 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	1	1	0

number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chest pain			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo in Cohort 3 Booster (Safety Analysis Set)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neoplasm malignant				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Compression fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Cardiac death				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Death			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1 (Safety Analysis Set)	Cohort 2 (Safety Analysis Set)	Cohort 3 (Safety Analysis Set)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	9 / 9 (100.00%)	9 / 9 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Colon cancer			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Keratoacanthoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Leiomyoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neoplasm malignant			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Prostate cancer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vein disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hip arthroplasty			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Tooth extraction			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Death			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Feeling cold			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injection site haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injection site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Injection site swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Irritability			

subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Malaise			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nodule			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rales			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Affective disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Aggression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Anger			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	2	2	1
Delirium			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Delusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 9 (0.00%)	3 / 9 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Depressive symptom			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1

Erectile dysfunction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Hallucination, auditory			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hallucination, visual			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	2
Rapid eye movements sleep abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Sleep disorder			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood acid phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Compression fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 9 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Radius fracture			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Wound			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Wrist fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Cognitive disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Dyskinesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Head titubation			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	3
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Lacunar infarction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Parkinson's disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Sensory disturbance			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Vertigo positional			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Accommodation disorder			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Macular degeneration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Vitreous detachment			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Diarrhoea			
subjects affected / exposed	3 / 9 (33.33%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	4	1	0
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 9 (22.22%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Pancreatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Vomiting projectile			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Blepharitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Eczema asteatotic			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Rosacea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Staphylococcal skin infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Arthropathy			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	4	0	1
Costochondritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Monarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Periarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Tendonitis			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Erythema migrans			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gingival infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Herpes virus infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 9 (22.22%)	2 / 9 (22.22%)
occurrences (all)	0	3	3
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1

Tooth infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Wound infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 4 (Safety Analysis Set)	Placebo (pooled) (Safety Analysis Set)	Cohort 3 Booster (Safety Analysis Set)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	12 / 12 (100.00%)	2 / 3 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Colon cancer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

Keratoacanthoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leiomyoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Neoplasm malignant			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Prostate cancer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vein disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hip arthroplasty			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Tooth extraction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Cardiac death			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Death			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	5 / 9 (55.56%)	3 / 12 (25.00%)	0 / 3 (0.00%)
occurrences (all)	10	4	0
Feeling cold			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Injection site haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Irritability			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0

Nodule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Dysphonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0

Affective disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Aggression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Anger			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Confusional state			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Delirium			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Delusion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 9 (11.11%)	3 / 12 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Depressive symptom			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Erectile dysfunction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Hallucination, auditory			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hallucination, visual			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Rapid eye movements sleep abnormal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Restlessness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood acid phosphatase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
C-reactive protein increased			

subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Compression fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thermal burn			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wrist fracture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Cognitive disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dementia Alzheimer's type			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	3 / 12 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Dyskinesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Head titubation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	4 / 9 (44.44%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	14	1	0
Hypoaesthesia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lacunar infarction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Parkinson's disease			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sensory disturbance			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vertigo positional			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Accommodation disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Macular degeneration			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Visual acuity reduced			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	3 / 12 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Nausea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	4	1	0
Pancreatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	2 / 12 (16.67%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Vomiting projectile			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blepharitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			

subjects affected / exposed	1 / 9 (11.11%)	2 / 12 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Hyperhidrosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rosacea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Staphylococcal skin infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Arthropathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Costochondritis			

subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Monarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Pain in jaw			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Periarthritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0

Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema migrans			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gingival infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 9 (44.44%)	2 / 12 (16.67%)	0 / 3 (0.00%)
occurrences (all)	6	2	0
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0

Wound infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Diabetes mellitus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo in Cohort 3 Booster (Safety Analysis Set)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Colon cancer			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Keratoacanthoma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Leiomyoma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Neoplasm malignant subjects affected / exposed occurrences (all) Prostate cancer subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Thrombophlebitis superficial subjects affected / exposed occurrences (all) Vein disorder subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Surgical and medical procedures Hernia repair subjects affected / exposed occurrences (all) Hip arthroplasty subjects affected / exposed occurrences (all) Tooth extraction subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
General disorders and administration site conditions Cardiac death subjects affected / exposed occurrences (all) Chest discomfort subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

Chest pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Death				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Feeling cold				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site erythema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site haemorrhage				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site reaction				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site swelling				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Irritability				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Malaise				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nodule				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Oedema peripheral				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Pyrexia subjects affected / exposed occurrences (all) Ulcer subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 1 / 1 (100.00%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rales subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all) Affective disorder subjects affected / exposed occurrences (all) Aggression subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

Agitation				
subjects affected / exposed	1 / 1 (100.00%)			
occurrences (all)	1			
Anger				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Anxiety				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Confusional state				
subjects affected / exposed	1 / 1 (100.00%)			
occurrences (all)	1			
Delirium				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Delusion				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Depression				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Depressive symptom				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Erectile dysfunction				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hallucination				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hallucination, auditory				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hallucination, visual				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Insomnia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rapid eye movements sleep abnormal			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Restlessness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood acid phosphatase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
C-reactive protein increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural			

complications				
Arthropod bite				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Compression fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Contusion				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fall				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ligament sprain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Limb injury				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Post lumbar puncture syndrome				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Radius fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Road traffic accident				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Thermal burn				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Wound				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Wrist fracture				

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Cardiac disorders Extrasystoles subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Nervous system disorders Balance disorder subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Cognitive disorder subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Dementia Alzheimer's type subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Dyskinesia subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Head titubation subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Lacunar infarction subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Memory impairment			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Parkinson's disease			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sensory disturbance			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vertigo positional			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eye disorders			
Accommodation disorder			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Macular degeneration			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vitreous detachment			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Inguinal hernia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pancreatitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Paraesthesia oral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vomiting projectile			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blepharitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ecchymosis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eczema asteatotic			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Night sweats			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Papule			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rosacea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin ulcer			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Staphylococcal skin infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Arthropathy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Costochondritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Monarthritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Muscle spasms			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain in jaw			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Periarthritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Erythema migrans			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Gastroenteritis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Gingival infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Herpes virus infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Influenza subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Laryngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Pneumonia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Tooth infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Wound infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0			
Metabolism and nutrition disorders Decreased appetite				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gout			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2009	Amendment 2: Major Changes • Added a requirement for 24 hours of hospitalization after first IMP injection • Added the requirement to obtain approval before commencement of Step 2 Minor Changes • Updated study contact details and Sponsor Medical Director • Clarification on planned interim analysis provided
25 September 2009	Amendment 1: Major Changes • Added DSMB meetings for safety evaluation • Added T-cell measurement at V4 (Week 6) • Additional description of the Informed Consent procedure added • Added patient safety supervision and monitoring after injections • Included coagulation assessment prior to lumbar puncture • Defined randomization process (eg, the 4 first patients of each dose-cohort [Step 1], were randomized in an interval of more or equal (≥) than 7 days) • Removed cross-reactivity measurement • Removed PET imaging in the case of dose-Cohort 1 (10 µg) (Step 1) Minor Changes • Included additional investigational medicinal product storage information • Updated study contact details • Updated site personnel responsibilities regarding psychometric tests and Clinical rating scales • Re-organized psychometric test battery • Updated visits time window • Updated laboratory assessments and schedule
10 September 2010	Amendment 3: Major Changes • Removed EEG recording • Changed the ligand to be used for PET imaging
22 March 2011	Amendment 4: Major Changes • Added additional T-cell measurements at V2 (Week 2), V6 (Week 10), V11 (Week 26), and V14 (Week 38) • Addition of TLR4 expression assessments at V1 (Week 0) and 17 (Week 52) • Updated blood sample volumes to be taken Minor Changes • Added clarifications on wording • Updated study plan with new laboratory assessments • Updated study contact details

23 September 2011	Amendment 5: Major Changes • Addition of TLRs and NLRs expression assessments at V1 (Week 0) and 17 (Week 52) • Added clarification that vital signs were measured at every visit • Allowed the use of Memantine in the Follow-up period (after Week 52) • Addition of coagulation indices measurement at Screening visit • Updated blood sample volumes to be taken (10 mL for biomarkers assessments instead of 20 mL and 20 mL for T-cell profile assessment instead of 10 mL) Minor Changes • Added clarifications on wording
17 January 2012	Amendment 6: Minor Changes • Listed the changes of responsible persons/organizations and contact details
04 May 2012	Amendment 7: Minor Changes • Listed the changes of responsible persons/organizations and contact details
10 July 2012	Amendment 8: Major Changes • Added an interim analysis in Step 1 to see antibody anti-Aβ1-42 titers for all patients in Cohort 1 and patients of Cohort 2 up to 6 months of treatment • Updated patient information with additional details that further described the use of Florbetaben as radiolabeled agent in PET imaging
04 October 2013	Amendment 9: Major Changes • Replacement of PET imaging by measurement of Aβ1-42 in blood in the interim analysis at 26 weeks of treatment in the highest dose group and in all corresponding sections • Added clarification that the unblinding could have been done using the IVRS and there were no sealed code break envelops on site • Added a clarification on the SAE reporting procedure and safety officer email address • Updated the Data Handling section after the change of system from Oracle Clinical to Omnicomm Minor Changes • Included changes on the background information related to the IB update • Added clarification on the responsibilities on the packaging and labeling of investigational medicinal product • Added clarification that MRI was part of the Screening visit and not Baseline visit • Added clarifications on wording
18 March 2014	Amendment 10: Major Changes • Added Cohort 4 to assess the immunogenicity of a higher dose (1000 µg) of ACI-24 • Added PET imaging as an inclusion criterion • Added performance of Baseline CSF sampling at least 3 days prior to administration of investigational medicinal product Minor Changes • Change of safety reporting company to Product Life Ltd
04 July 2014	Amendment 11: Major Changes • Changed inclusion criterion number 2 with raising the MMSE upper limit from 26 to 28

02 April 2015	Amendment 12: Major Changes • Added analysis of additional testing in the first 4 patients of Cohort 4: Aβ1-42 and Aβ1-40 in plasma and Aβ1-42 in CSF; IgM anti-Aβ; inflammatory markers
26 June 2015	Amendment 13: Major Changes • Added analysis of additional testing in the 12 patients of Cohort 3: Aβ1-42 and Aβ1-40 in plasma and Aβ1-42 in CSF; IgM anti-Aβ in serum; inflammatory markers (cytokines)
30 November 2015	Amendment 14: Major Changes • Expanded Cohort 4 from 4 to 12 patients • Added a late booster injection at 18 months for patients in Cohort 4 • Added an inclusion criterion as requested by the Swedish MPA in order to comply with Swedish law 1992:859 13b §. This additional criterion was only applicable in Sweden. Minor Changes • Updated study contact details
03 March 2016	Amendment 15: Major Changes • Added a late booster injection at 2.5 to 3.25 years after last dose for patients in Cohort 3 Minor Changes • Corrected the visit schedule for Study Plan number 2 for Cohort 4 to state that PET imaging was done at the Screening Visit, not at V1
17 October 2016	Amendment 16: Major Changes • Clarified content for the full interim analysis of Step 1 data, namely: - to specify that subsequent Interim analyses could have been conducted if needed at later timepoints than V11 (Week 26) for all patients enrolled in Cohort 4 - planned to unblind data of patients participating in Cohort 1, 2, 3, and 4 after booster after data for these cohorts had been locked - all data available for any visit in all cohorts up to the data-cut date (ie, the last patient completing Week 26 in Cohort 4) was to be included in the full interim analysis • Implemented changes to improve consistency between sections of the study protocol, by clarifying the study objectives and endpoints classifications in Sections 7.1 and 7.2 of the study protocol • Clarified the term "Inflammatory marker" to delineate between collection of cytokines alone or cytokines and CRP • Clarified that the version of ADAS-Cog to be used was ADAS-Cog12 Minor Changes • A number of administrative changes were added, including modification of the contact list to include additional vendors and update information, modification of the headers in some pages to align with the section concerned, modification of the signature page, an update of Section 6.2, and clarification of what procedure/analysis was to be performed for each cohort when the wording was confusing
17 July 2017	Amendment 17: Minor Changes • Reduced the safety Follow-up period of patients in Cohort 4 who received a booster injection at 18 months from 2 years to 1 year

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small sample size allowed only descriptive statistics.

Notes: