Clinical trial results:
A double blind, placebo controlled Phase 2 dose ranging study of the effects of ARA 290 on corneal nerve fiber density and neuropathic symptoms of patients with sarcoidosis

Summary

EudraCT number	2013-003016-45
Trial protocol	NL
Global end of trial date	02 February 2015

Results information

Result version number	v1 (current)
This version publication date	11 April 2019
First version publication date	11 April 2019
Summary attachment (see zip file)	Culver et al (2017) IOVS 58(6):BIO52-BIO60 (Culver et al (2017) IOVS, DOSARA study.pdf)

Trial information

Trial identification

Sponsor protocol code	APCP-112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02039687
WHO universal trial number (UTN)	-
Other trial identifiers	P13.173: LUMC protocol number

Notes:

Sponsors

Sponsor organisation name	Araim Pharmaceuticals, Inc.
Sponsor organisation address	580 White Plains Road, Suite 210, Tarrytown, United States, 10591
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Sponsor organisation name	Araim Pharmaceuticals, Inc.
Sponsor organisation address	580 White Plains Road, Suite 210, Tarrytown, United States, 10591
Public contact	Rita Kirk, PhD, Araim Pharmaceuticals, Inc., +1 9147627586, rkirk@araimpharma.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	03 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2015
Global end of trial reached?	Yes
Global end of trial date	02 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of different dose levels of ARA 290 administration on different outcome measures of small fiber neuropathy in subjects with sarcoidosis.

Protection of trial subjects:

Adjustments to or Introduction of additional analgesic medication was allowed.

Background therapy:

n/a

Evidence for comparator:

n/a

Actual start date of recruitment	21 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 32
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	64
EEA total number of subjects	32

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)	59
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Subject Signed the Informed Consent: 24 January 2014
Last Subject Completed Last Examination: 3 February 2015
A total of 74 subjects were enrolled and 64 subjects were randomized in The Netherlands and in The United States.

Pre-assignment

Screening details:

The main inclusion criteria were an established diagnosis of sarcoidosis with pain and reduced nerve fiber density. 74 subjects were assessed for eligibility with 10 excluded due to: nerve fiber score(n=4), lab value (n=2), Brief Pain inventory score (n=1), concomitant medication (n=1), non-compliance (n=1), and investigator decision (n=1).

Period 1

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

Blinding implementation details:

The CRO generated the randomization code to one of the four treatment arms in a block randomization scheme, which directed all sites. At the on-site pharmacy, the study medication vials and 2 sets of boxes each containing 16 vials were labeled with the subject identification number according to the randomization code.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

1 mL placebo administered subcutaneously for 28 consecutive days

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1 mL placebo administered subcutaneously

Arm title	ARA 290 - 1 mg

Arm description:

1 mg ARA 290 administered subcutaneously for 28 consecutive days

Arm type	Experimental
Investigational medicinal product name	ARA 290
Investigational medicinal product code	
Other name	Cibinetide
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1, 4, or 8 mg ARA 290 solution to be administered subcutaneously for 28 consecutive days

Arm title	ARA 290 - 4 mg

Arm description:	
4 mg ARA 290 administered subcutaneously for 28 consecutive days	
Arm type	Experimental
Investigational medicinal product name	ARA 290
Investigational medicinal product code	
Other name	Cibinetide
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
ARA 290 solution to be administered subcutaneously	
Arm title	ARA 290 - 8 mg
Arm description:	
8 mg ARA 290 administered subcutaneously for 28 consecutive days	
Arm type	Experimental
Investigational medicinal product name	ARA 290
Investigational medicinal product code	
Other name	Cibinetide
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
1, 4, or 8 mg ARA 290 solution to be administered subcutaneously for 28 consecutive days	

Number of subjects in period 1	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg
Started	16	16	16
Completed	16	16	15
Not completed	0	0	1
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	ARA 290 - 8 mg
Started	16
Completed	15
Not completed	1
Consent withdrawn by subject	-
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
1 mL placebo administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 1 mg
Reporting group description:	
1 mg ARA 290 administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 4 mg
Reporting group description:	
4 mg ARA 290 administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 8 mg
Reporting group description:	
8 mg ARA 290 administered subcutaneously for 28 consecutive days	

Reporting group values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg
Number of subjects	16	16	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	16	13
From 65-84 years	1	0	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.8	51.4	52.0
standard deviation	± 10.7	± 7.5	± 11.0
Gender categorical Units: Subjects			
Female	7	8	7
Male	9	8	9
Change in Corneal Nerve Fiber Area			
Measurement of corneal nerve fiber area is a non-invasive procedure performed at baseline and at the end of dosing and at 12 weeks follow-up. The nerve fiber area in sarcoidosis patients is reduced compared to normal humans, a measurement of small fiber loss.			
Units: µm^2			
arithmetic mean	2958.2	2941.1	2954.8
standard deviation	± 886.0	± 1050.6	± 629.1
Change in the 6 Minute Walk Test			
Measurement of the distance a patient can walk in 6 minutes			
Units: meters			
arithmetic mean	468	495	445

standard deviation	± 121	± 109	± 88
Change in Intra-epidermal Nerve Fiber Density (IENFD)			
Measurement of small fiber density in skin biopsies. Density is reduced in sarcoidosis patients, an indication of neuropathy.			
Units: fibers/mm			
arithmetic mean	4.7	5.2	6.3
standard deviation	± 2.8	± 2.4	± 3.0
Change in the Scores of the BPI - Pain Severity			
Brief Pain Inventory (BPI), Pain Severity - scale of 0 (no pain) to 10 (worst pain imaginable) in 4 time frames, averaged.			
Units: unit(s)			
arithmetic mean	5.7	6.1	6.2
standard deviation	± 1.6	± 1.9	± 1.4
Change in the Scores of the BPI, Pain Interference			
Brief Pain Inventory (BPI), Pain Interference - scale of 0 (does not interfere) to 10 (completely interferes) how pain interferes with 7 lifestyle parameters, averaged.			
Units: unit(s)			
arithmetic mean	5.6	6.1	5.8
standard deviation	± 2.4	± 2.5	± 2.3
Change in the Scores of the SFNSL			
Small Fiber Neuropathy Screening List (SFNSL) - scale of 0 to 84 (higher score indicates greater neuropathy), sum of 21 questions.			
Units: unit(s)			
arithmetic mean	38.0	41.4	42.5
standard deviation	± 11.0	± 15.1	± 17.8
Change in the Scores of the NPSI			
Neuropathic Pain Symptom Inventory (NPSI) - scale of 0 (least pain) to 10 (most pain) in 10 questions, summed. Total score range from 0 to 100.			
Units: unit(s)			
arithmetic mean	48.9	50.1	58.3
standard deviation	± 20.3	± 20.0	± 20.8
Change in the Scores of the FAS			
Fatigue Assessment Scale (FAS) - scale of 1 (never) to 5 (always) in 10 questions related to fatigue, summed. Total score range from 0 to 50, with 0 being the best possible score and 50 the worst			
Units: unit(s)			
arithmetic mean	32.6	33.4	31.8
standard deviation	± 5.6	± 6.8	± 6.0

Reporting group values	ARA 290 - 8 mg	Total	
Number of subjects	16	64	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	15	59	
From 65-84 years	1	5	

85 years and over	0	0	

Age continuous			
Units: years			
arithmetic mean	52.2		
standard deviation	± 9.2	-	
Gender categorical			
Units: Subjects			
Female	9	31	
Male	7	33	
Change in Corneal Nerve Fiber Area			
Measurement of corneal nerve fiber area is a non-invasive procedure performed at baseline and at the end of dosing and at 12 weeks follow-up. The nerve fiber area in sarcoidosis patients is reduced compared to normal humans, a measurement of small fiber loss.			
Units: µm^2			
arithmetic mean	3191.2		
standard deviation	± 853.2	-	
Change in the 6 Minute Walk Test			
Measurement of the distance a patient can walk in 6 minutes			
Units: meters			
arithmetic mean	416		
standard deviation	± 110	-	
Change in Intra-epidermal Nerve Fiber Density (IENFD)			
Measurement of small fiber density in skin biopsies. Density is reduced in sarcoidosis patients, an indication of neuropathy.			
Units: fibers/mm			
arithmetic mean	5.1		
standard deviation	± 2.7	-	
Change in the Scores of the BPI - Pain Severity			
Brief Pain Inventory (BPI), Pain Severity - scale of 0 (no pain) to 10 (worst pain imaginable) in 4 time frames, averaged.			
Units: unit(s)			
arithmetic mean	5.8		
standard deviation	± 1.2	-	
Change in the Scores of the BPI, Pain Interference			
Brief Pain Inventory (BPI), Pain Interference - scale of 0 (does not interfere) to 10 (completely interferes) how pain interferes with 7 lifestyle parameters, averaged.			
Units: unit(s)			
arithmetic mean	6.1		
standard deviation	± 2.1	-	
Change in the Scores of the SFNSL			
Small Fiber Neuropathy Screening List (SFNSL) - scale of 0 to 84 (higher score indicates greater neuropathy), sum of 21 questions.			
Units: unit(s)			
arithmetic mean	41.2		
standard deviation	± 14.6	-	
Change in the Scores of the NPSI			
Neuropathic Pain Symptom Inventory (NPSI) - scale of 0 (least pain) to 10 (most pain) in 10 questions, summed. Total score range from 0 to 100.			
Units: unit(s)			
arithmetic mean	50.3		

standard deviation	± 17.1	-	
Change in the Scores of the FAS			
Fatigue Assessment Scale (FAS) - scale of 1 (never) to 5 (always) in 10 questions related to fatigue, summed. Total score range from 0 to 50, with 0 being the best possible score and 50 the worst			
Units: unit(s)			
arithmetic mean	32.9		
standard deviation	± 5.1	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
1 mL placebo administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 1 mg
Reporting group description:	
1 mg ARA 290 administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 4 mg
Reporting group description:	
4 mg ARA 290 administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 8 mg
Reporting group description:	
8 mg ARA 290 administered subcutaneously for 28 consecutive days	

Primary: Change in Corneal Nerve Fiber Area

End point title	Change in Corneal Nerve Fiber Area
End point description:	
Measurement of corneal nerve fiber area is a non-invasive procedure performed at baseline and at the end of dosing and at 12 weeks follow-up. The nerve fiber area in sarcoidosis patients is reduced compared to normal humans, a measurement of small fiber loss.	
End point type	Primary
End point timeframe:	
Baseline and 28 days	

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	14[1]
Units: µm^2				
arithmetic mean (standard deviation)	170.0 (± 633.0)	-64.3 (± 759.9)	533.8 (± 1110.02)	203.8 (± 641.2)

Notes:

[1] - Treatment allocation could not be verified due to discrepancy in pharmacy records

Statistical analyses

Statistical analysis title	Copy of Change in corneal nerve fiber density
Statistical analysis description:	
To test the null hypothesis, p-values were provided using a paired t-test analysis within each dose group at the p = 0.05 (two-sided) significance level. The mean, standard error (SE), and 95% confidence interval (CI) for the change from baseline were reported for each treatment group.	
Comparison groups	Placebo v ARA 290 - 8 mg

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.13
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	430.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-130.3
upper limit	992.1
Variability estimate	Standard deviation
Dispersion value	279.9

Statistical analysis title	Change in corneal nerve fiber d...

Statistical analysis description:

To test the null hypothesis, p-values were provided using a paired t-test analysis within each dose group at the p = 0.05 (two-sided) significance level. The mean, standard error (SE), and 95% confidence interval (CI) for the change from baseline were reported for each treatment group.

Comparison groups	Placebo v ARA 290 - 4 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.012
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	697.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	158.8
upper limit	1235.9
Variability estimate	Standard deviation
Dispersion value	268.6

Statistical analysis title	Change in corneal nerve fiber d...

Statistical analysis description:

To test the null hypothesis, p-values were provided using a paired t-test analysis within each dose group at the p = 0.05 (two-sided) significance level. The mean, standard error (SE), and 95% confidence interval (CI) for the change from baseline were reported for each treatment group.

Comparison groups	Placebo v ARA 290 - 1 mg

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.686
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	109.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-429.1
upper limit	647.4
Variability estimate	Standard deviation
Dispersion value	268.5

Secondary: Change in the 6 Minute Walk Test

End point title	Change in the 6 Minute Walk Test
End point description:	
Measurement of the distance a patient can walk in 6 minutes	
End point type	Secondary
End point timeframe:	
Baseline and 28 days	

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	14[2]
Units: meter				
arithmetic mean (standard deviation)	1.2 (± 38.56)	19.3 (± 79.27)	17.7 (± 40.29)	18.2 (± 47.9)

Notes:

[2] - Treatment allocation could not be verified due to discrepancy in pharmacy records

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Intra-epidermal Nerve Fiber Density (IENFD)

End point title	Change in Intra-epidermal Nerve Fiber Density (IENFD)
End point description:	
Measurement of small fiber density in skin biopsies. Density is reduced in sarcoidosis patients, an indication of neuropathy.	
End point type	Secondary
End point timeframe:	
Baseline and 28 days	

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	14[3]
Units: fibers/mm				
arithmetic mean (standard deviation)	0.8 (± 1.13)	0.5 (± 1.58)	0.4 (± 2.28)	-0.3 (± 1.81)

Notes:

[3] - Treatment allocation could not be verified due to discrepancy in pharmacy records (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Scores of the SFNSL

End point title	Change in the Scores of the SFNSL

End point description:

Small Fiber Neuropathy Screening List (SFNSL) - scale of 0 to 84 (higher score indicates greater neuropathy), sum of 21 questions.

End point type	Secondary

End point timeframe:

Baseline to 28 days

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[4]	16	15[5]	13[6]
Units: unit(s)				
arithmetic mean (standard deviation)	-7.3 (± 9.50)	-4.9 (± 8.87)	-8.7 (± 14.17)	-5.5 (± 7.09)

Notes:

[4] - Questionnaires incomplete for some subjects

[5] - Questionnaires incomplete for some subjects

[6] - Questionnaires incomplete for some
Treatment unverifiable (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Scores of the BPI, Pain Severity

End point title	Change in the Scores of the BPI, Pain Severity

End point description:

Change in mean score from baseline to Day 28 is recorded for each outcome. Brief Pain Inventory (BPI), Pain Severity - scale of 0 (no pain) to 10 (worst pain imaginable) in 4 time frames, averaged.

End point type	Secondary

End point timeframe:

Baseline to 28 days

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	15[7]	13[8]
Units: unit(s)				
arithmetic mean (standard deviation)	-0.922 (± 1.4429)	-0.594 (± 1.6680)	-1.167 (± 1.6894)	-1.115 (± 1.7067)

Notes:

[7] - Questionnaires incomplete for some subjects

[8] - Questionnaires incomplete for some
Treatment unverifiable (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Scores of the BPI, Pain Interference

End point title	Change in the Scores of the BPI, Pain Interference

End point description:

BPI, Pain Interference - scale of 0 (does not interfere) to 10 (completely interferes) how pain interferes with 7 lifestyle parameters, averaged.

End point type	Secondary

End point timeframe:

Baseline to 28 days

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	15[9]	13[10]
Units: unit(s)				
arithmetic mean (standard deviation)	-1.732 (± 2.2174)	-1.187 (± 1.9453)	-1.657 (± 1.6482)	-1.308 (± 2.4403)

Notes:

[9] - Questionnaires incomplete for some subjects

[10] - Questionnaires incomplete for some
Treatment unverifiable (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Scores of the NPSI

End point title	Change in the Scores of the NPSI

End point description:

Neuropathic Pain Symptom Inventory (NPSI) - scale of 0 (least pain) to 10 (most pain) in 10 questions, summed. Total score range from 0 to 100.

End point type	Secondary

End point timeframe:

Baseline to 28 days

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	14[11]	13[12]
Units: unit(s)				
arithmetic mean (standard deviation)	-12.88 (± 13.803)	-12.31 (± 16.074)	-14.50 (± 17.887)	-8.38 (± 12.699)

Notes:

[11] - Questionnaires incomplete for some subjects

[12] - Questionnaires incomplete for some
Treatment unverifiable (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Scores of the FAS Questionnaire

End point title	Change in the Scores of the FAS Questionnaire

End point description:

Fatigue Assessment Scale (FAS) - scale of 1 (never) to 5 (always) in 10 questions related to fatigue, summed. Total score range from 0 to 50, with 0 being the best possible score and 50 the worst.

End point type	Secondary

End point timeframe:

Baseline to 28 days

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	15[13]	13[14]
Units: unit(s)				
arithmetic mean (standard deviation)	-2.2 (± 6.00)	-2.6 (± 5.52)	-2.1 (± 5.38)	-3.1 (± 5.27)

Notes:

[13] - Questionnaires incomplete for some subjects

[14] - Questionnaires incomplete for some
Treatment unverifiable (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Adverse Events

End point title	Frequency of Adverse Events

End point description:

Patients reporting at least one treatment emergent adverse event (TEAE)

End point type	Secondary

End point timeframe:

Continuous reporting from baseline through 16 weeks

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	14[15]
Units: patients	12	14	11	12

Notes:

[15] - Treatment allocation could not be verified due to discrepancy in pharmacy records (n=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Serious Adverse Events

End point title	Frequency of Serious Adverse Events

End point description:

Patients reporting at least one serious treatment emergent adverse event (TEAE)

End point type	Secondary

End point timeframe:

Continuous reporting from baseline through 16 weeks

End point values	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg	ARA 290 - 8 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	14[16]
Units: Patients	0	2	0	1

Notes:

[16] - Treatment allocation could not be verified due to discrepancy in pharmacy records (n=2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 28 day treatment with 84 day follow up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0
Reporting groups	
Reporting group title	Placebo
Reporting group description: 1 mL placebo administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 1 mg
Reporting group description: 1 mg ARA 290 administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 4 mg
Reporting group description: 4 mg ARA 290 administered subcutaneously for 28 consecutive days	
Reporting group title	ARA 290 - 8 mg
Reporting group description: 8 mg ARA 290 administered subcutaneously for 28 consecutive days	

Serious adverse events	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Headache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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			
Chest Tightness			

subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Gastrointestinal disorders			
Small Bowel Enteritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Respiratory, thoracic and mediastinal disorders			
Shortness of Breath			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (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
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (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	ARA 290 - 8 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Tightness			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small Bowel Enteritis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Shortness of Breath			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)	14 / 16 (87.50%)	11 / 16 (68.75%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 16 (12.50%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	2	4	2

Injection site pain			
subjects affected / exposed	4 / 16 (25.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Feeling abnormal			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Disease progression			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injection site discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Injection site haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Injection site irritation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Temperature intolerance			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Allergy to arthropod sting			

subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Asthma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Epitaxis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Painful respiration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	3	0
Abnormal dreams			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Agitation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Burnout syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Depressed mood			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tearfulness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Animal bite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Epicondylitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Fibula fracture			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Injection related reaction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Meniscus injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Post procedural haematoma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Procedural pain			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 16 (0.00%)	4 / 16 (25.00%)	3 / 16 (18.75%)
occurrences (all)	0	4	3
Muscle contractions involuntary			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Burning sensation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dizziness exertional			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Mental Impairment			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Presyncope			

subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Retrograde Amnesia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tension headache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Accommodation disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Blepharitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Eye irritation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	2	2	1
Nausea			

subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	0	2	2
Abdominal Pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Abnormal faeces			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Crohn's disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Enteritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eructation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Salivary gland enlargement			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Hyperhidrosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Pruritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rosacea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Sticky skin			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Haematuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Pain in extremity			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Back pain			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Neck pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	3 / 16 (18.75%)
occurrences (all)	2	0	3
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Acute sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Atypical pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Bacterial vaginosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Mastoiditis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Meningitis aseptic			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Orchitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Streptococcal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	ARA 290 - 8 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Feeling abnormal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Disease progression			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Impaired healing subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Injection site discomfort subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site haemorrhage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site irritation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Temperature intolerance subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Immune system disorders Allergy to arthropod sting subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Asthma subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Nasal congestion			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Epitaxis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Painful respiration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Abnormal dreams			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Agitation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Burnout syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tearfulness			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Animal bite			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Epicondylitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fibula fracture			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Injection related reaction			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Meniscus injury			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Post procedural haematoma			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Muscle contractions involuntary			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Paraesthesia			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Burning sensation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dizziness exertional			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Mental Impairment			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Retrograde Amnesia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tension headache			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye disorders			
Vision blurred			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Accommodation disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blepharitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Eye irritation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Abdominal Pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Abnormal faeces			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Crohn's disease			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Enteritis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Eructation			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Gastrointestinal pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Salivary gland enlargement			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Pruritis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Rosacea			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Sticky skin			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Renal failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Acute sinusitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Atypical pneumonia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Bacterial vaginosis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

Mastoiditis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Meningitis aseptic			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Orchitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Streptococcal infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Tooth infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28475703