



## 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
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##### 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.
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Sponsor organisation address	580 White Plains Road, Suite 210, Tarrytown, United States, 10591
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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
<b>Arm title</b>	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

<b>Arm title</b>	ARA 290 - 1 mg
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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

<b>Arm title</b>	ARA 290 - 4 mg
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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

<b>Arm title</b>	ARA 290 - 8 mg
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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

<b>Number of subjects in period 1</b>	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	-	-	-

<b>Number of subjects in period 1</b>	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: $\mu\text{m}^2$			
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

<b>Reporting group values</b>	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	
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Age continuous Units: years arithmetic mean standard deviation	52.2 ± 9.2	-	
Gender categorical Units: Subjects Female Male	9 7	31 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: $\mu\text{m}^2$ arithmetic mean standard deviation	3191.2 ± 853.2	-	
Change in the 6 Minute Walk Test			
Measurement of the distance a patient can walk in 6 minutes			
Units: meters arithmetic mean standard deviation	416 ± 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 standard deviation	5.1 ± 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 standard deviation	5.8 ± 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 standard deviation	6.1 ± 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 standard deviation	41.2 ± 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 <sup>[1]</sup>
Units: $\mu\text{m}^2$				
arithmetic mean (standard deviation)	170.0 ( $\pm$ 633.0)	-64.3 ( $\pm$ 759.9)	533.8 ( $\pm$ 1110.02)	203.8 ( $\pm$ 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

<b>Statistical analysis title</b>	Change in corneal nerve fiber d...
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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

<b>Statistical analysis title</b>	Change in corneal nerve fiber d...
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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
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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 <sup>[2]</sup>
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	

<b>End point values</b>	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 <sup>[3]</sup>
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

<b>End point values</b>	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 <sup>[4]</sup>	16	15 <sup>[5]</sup>	13 <sup>[6]</sup>
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

<b>End point values</b>	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 <sup>[7]</sup>	13 <sup>[8]</sup>
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

<b>End point values</b>	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 <sup>[9]</sup>	13 <sup>[10]</sup>
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

<b>End point values</b>	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 <sup>[11]</sup>	13 <sup>[12]</sup>
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

<b>End point values</b>	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 <sup>[13]</sup>	13 <sup>[14]</sup>
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

<b>End point values</b>	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 <sup>[15]</sup>
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

<b>End point values</b>	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 <sup>[16]</sup>
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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

1 mL placebo administered subcutaneously for 28 consecutive days

Reporting group title	ARA 290 - 1 mg
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Reporting group description:

1 mg ARA 290 administered subcutaneously for 28 consecutive days

Reporting group title	ARA 290 - 4 mg
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Reporting group description:

4 mg ARA 290 administered subcutaneously for 28 consecutive days

Reporting group title	ARA 290 - 8 mg
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Reporting group description:

8 mg ARA 290 administered subcutaneously for 28 consecutive days

<b>Serious adverse events</b>	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
<b>Gastrointestinal disorders</b>			
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
<b>Respiratory, thoracic and mediastinal disorders</b>			
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
<b>Psychiatric disorders</b>			
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

<b>Serious adverse events</b>	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		
<b>Nervous system disorders</b>			
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		
<b>General disorders and administration site conditions</b>			
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		
<b>Gastrointestinal disorders</b>			
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		
<b>Respiratory, thoracic and mediastinal disorders</b>			
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		
<b>Psychiatric disorders</b>			
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 %

<b>Non-serious adverse events</b>	Placebo	ARA 290 - 1 mg	ARA 290 - 4 mg
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	12 / 16 (75.00%)	14 / 16 (87.50%)	11 / 16 (68.75%)
<b>Vascular disorders</b>			
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
<b>General disorders and administration site conditions</b>			
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 occurrences (all)	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 16 (12.50%) 2	0 / 16 (0.00%) 0
Asthma subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Nasal congestion subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1	1 / 16 (6.25%) 1
Epitaxis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Painful respiration subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 16 (12.50%) 3	0 / 16 (0.00%) 0
Abnormal dreams subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Agitation subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0
Burnout syndrome subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Depressed mood			

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

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

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

<b>Non-serious adverse events</b>	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 occurrences (all)	0 / 14 (0.00%) 0		
Hypotension subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injection site pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Feeling abnormal subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Asthenia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Disease progression subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 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			

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

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

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Somnolence subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Tremor subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Burning sensation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Dizziness exertional subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Mental Impairment subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Presyncope subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Retrograde Amnesia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Tension headache subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 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		
<b>Skin and subcutaneous tissue disorders</b>			
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 occurrences (all)	0 / 14 (0.00%) 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 occurrences (all)	0 / 14 (0.00%) 0		
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Neck pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Tendonitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
<b>Infections and infestations</b>			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Acute sinusitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Atypical pneumonia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Bacterial vaginosis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Bronchitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Cellulitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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