Clinical trial results:
A Randomized, Placebo-Controlled, Double Blind, Multicenter Phase 2 Study to Explore Tolerability, Safety, Pharmacokinetics, Pharmacodynamics and Efficacy of Intravenous Multiple Infusions of NI-0101, an anti-Toll Like Receptor 4 Monoclonal Antibody in Patients with Rheumatoid Arthritis

Summary

EudraCT number	2016-005017-45
Trial protocol	HU BG PL GB
Global end of trial date	17 May 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	NI-0101-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	NovImmune S.A.
Sponsor organisation address	14 Chemin des Aulx, 1228 Plan-les-Ouates, Switzerland,
Public contact	Emmanuel Monnet, NovImmune S.A., +41 22593 82 33, emonnet@novimmune.com
Scientific contact	Emmanuel Monnet, NovImmune S.A., +41 22593 82 33, emonnet@novimmune.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2018
Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine the preliminary tolerability and safety profile of multiple intravenous (i.v.) administrations of NI-0101
- To describe the Pharmacokinetic/Pharmacodynamic (PK/PD) profiles of NI-0101
- To determine NI-0101 preliminary efficacy
- To explore specific biomarkers as predictors of treatment response
- To explore the impact of the FcyRIIa genotype on the response to treatment
- To assess the immunogenicity of NI-0101

Protection of trial subjects:

The study protocol, patient information sheet, Informed Consent Form (ICF) and all other relevant study documentation and amendments were reviewed by Independent Ethics Committees in the United Kingdom (UK), Bulgaria, Hungary, Serbia, Bosnia, Poland, Moldova and Georgia. The study did not commence until formal approval had been granted.

Background therapy:

Methotrexate

Evidence for comparator:

No active comparator - placebo controlled

Actual start date of recruitment	01 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Georgia: 36
Country: Number of subjects enrolled	Moldova, Republic of: 11
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Worldwide total number of subjects	90
EEA total number of subjects	30

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)	65
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 250 patients with RA screened for eligibility, 90 were randomized into the treatment phase of the study. A total of 86 patients completed the study.

Pre-assignment

Screening details:

Subjects attended a screening visit within 4 weeks prior to the first treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	NI-0101

Arm description:

Subjects treated with NI-0101

Arm type	Experimental
Investigational medicinal product name	NI-0101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NI-0101 was administered by intravenous infusion, over a period of one hour, at a dose of 5 mg/kg. Infusions were performed every two weeks

Arm title	Placebo

Arm description:

Subject received a placebo

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

Dosage and administration details:

Placebo was administered by intravenous infusion, over a period of one hour, at a dose of 5 mg/kg. Infusions were performed every two weeks

Number of subjects in period 1	NI-0101	Placebo
Started	61	29
Completed	57	29
Not completed	4	0
Consent withdrawn by subject	2	-
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	NI-0101
Reporting group description:	
Subjects treated with NI-0101	
Reporting group title	Placebo
Reporting group description:	
Subject received a placebo	

Reporting group values	NI-0101	Placebo	Total
Number of subjects	61	29	90
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)	48	17	65
From 65-84 years	13	12	25
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	54.6	57.1	
standard deviation	± 11.10	± 13.07	-
Gender categorical			
Units: Subjects			
Female	50	23	73
Male	11	6	17
Steroids dose category (mg)			
Units: Subjects			
No steroid given	20	9	29
1mg - 5mg	6	8	14
5mg - 10mg	35	12	47
MTX dose category (mg/week)			
Units: Subjects			
3.5mg - 10mg	2	2	4
10mg - 20mg	55	25	80
2mg - 25mg	4	2	6
Duration of RA			
Length of time since RA diagnosis			
Units: Years			
arithmetic mean	8.5	5.4	
standard deviation	± 7.86	± 4.82	-
Age at RA diagnosis			

Age of participant when they were diagnosed with RA			
Units: Years			
arithmetic mean	45.7	51.2	
standard deviation	± 11.56	± 13.62	-
CRP			
Units: (mg/L)			
arithmetic mean	18.3	13.4	
standard deviation	± 26.63	± 14.03	-
ESR			
Units: (mm/hr)			
arithmetic mean	45.3	43.1	
standard deviation	± 24.26	± 16.51	-

End points

End points reporting groups	
Reporting group title	NI-0101
Reporting group description: Subjects treated with NI-0101	
Reporting group title	Placebo
Reporting group description: Subject received a placebo	

Primary: Change in DAS28-CRP Score from Baseline Visit to W12	
End point title	Change in DAS28-CRP Score from Baseline Visit to W12
End point description:	
End point type	Primary
End point timeframe: Baseline to week 12	

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	5.9 (± 0.90)	5.8 (± 0.82)		
SD14 (W2)	-0.3 (± 0.63)	-0.4 (± 0.52)		
SD28 (W4)	-0.7 (± 0.86)	-0.6 (± 0.73)		
SD42 (W6)	-1.1 (± 0.95)	-0.8 (± 0.89)		
SD56 (W8)	-1.3 (± 1.02)	-1.1 (± 1.03)		
SD70 (W10)	-1.4 (± 1.18)	-1.3 (± 1.07)		
SD84 (W12)	-1.5 (± 1.35)	-1.3 (± 1.07)		

Statistical analyses

Statistical analysis title	Treatment effect NI-0101 - Placebo
Comparison groups	NI-0101 v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4666
Method	Least Square Means (SE)
Parameter estimate	Mean difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.28

Secondary: Change in DAS28-ESR Score from Baseline Visit to W12

End point title	Change in DAS28-ESR Score from Baseline Visit to W12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 12	

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	6.6 (± 0.89)	6.6 (± 0.88)		
SD14 (W2)	-0.4 (± 0.65)	-0.4 (± 0.52)		
SD28 (W4)	-0.9 (± 0.88)	-0.7 (± 0.67)		
SD42 (W6)	-1.2 (± 0.94)	-1.0 (± 0.87)		
SD56 (W8)	-1.4 (± 1.05)	-1.3 (± 1.02)		
SD70 (W10)	-1.6 (± 1.33)	-1.5 (± 1.11)		
SD84 (W12)	-1.7 (± 1.41)	-1.4 (± 1.09)		

Statistical analyses

Statistical analysis title	Treatment effect NI-0101 – Placebo
Comparison groups	NI-0101 v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3395
Method	Least Square Means (SE)
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.3

Secondary: Proportions of Patients with EULAR Response Criteria

End point title	Proportions of Patients with EULAR Response Criteria
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 12	

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: Participants				
Response	45	24		
No response	11	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Tender or Swollen 28-Joint Counts Change from Baseline to W12

End point title	Tender or Swollen 28-Joint Counts Change from Baseline to W12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 12	

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: units on a scale				
arithmetic mean (standard deviation)				
Tender 28-Joint Counts SD84 (W12)	-8.1 (± 7.67)	-6.3 (± 6.65)		
Swollen 28-Joint Counts SD84 (W12)	-7.1 (± 6.87)	-6.1 (± 5.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving ACR20 response

End point title	Proportion of patients achieving ACR20 response

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: Patients				
SD14 (W2)	5	1		
SD28 (W4)	15	5		
SD42 (W6)	22	10		
SD56 (W8)	24	14		
SD70 (W10)	25	14		
SD84 (W12)	33	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving ACR50 response

End point title	Proportion of patients achieving ACR50 response

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: Patients				
SD14 (W2)	0	0		
SD28 (W4)	1	1		
SD42 (W6)	6	2		
SD56 (W8)	8	5		
SD70 (W10)	9	5		
SD84 (W12)	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving ACR70 response

End point title	Proportion of patients achieving ACR70 response

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	NI-0101	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: Patients				
SD14 (W2)	0	0		
SD28 (W4)	0	0		
SD42 (W6)	0	1		
SD56 (W8)	1	1		
SD70 (W10)	3	2		
SD84 (W12)	6	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event within the date of the start of treatment until the end-of-study visit has been reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	NI-0101
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	NI-0101	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 61 (4.92%)	1 / 29 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NI-0101	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 61 (50.82%)	15 / 29 (51.72%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 61 (3.28%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Baker's cyst excision			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	5 / 61 (8.20%)	0 / 29 (0.00%)	
occurrences (all)	5	0	
Asthenia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Influenza like illness			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 61 (4.92%)	0 / 29 (0.00%)	
occurrences (all)	3	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Fibrin D dimer increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Aortic valve stenosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Palpitations			

subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 29 (3.45%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 0 / 61 (0.00%) 0	 2 / 29 (6.90%) 2	
Blood and lymphatic system disorders Iron deficiency anemia subjects affected / exposed occurrences (all)	 2 / 61 (3.28%) 2	 0 / 29 (0.00%) 0	
Eye disorders Eye hemorrhage subjects affected / exposed occurrences (all)	 1 / 61 (1.64%) 1	 0 / 29 (0.00%) 0	
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	 2 / 61 (3.28%) 2	 0 / 29 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	 1 / 61 (1.64%) 1	 0 / 29 (0.00%) 0	
Chronic gastritis subjects affected / exposed occurrences (all)	 1 / 61 (1.64%) 1	 0 / 29 (0.00%) 0	
Duodenitis subjects affected / exposed occurrences (all)	 1 / 61 (1.64%) 1	 0 / 29 (0.00%) 0	
Food poisoning subjects affected / exposed occurrences (all)	 1 / 61 (1.64%) 1	 0 / 29 (0.00%) 0	
Gastritis subjects affected / exposed occurrences (all)	 0 / 61 (0.00%) 0	 1 / 29 (3.45%) 1	
Hiatus hernia subjects affected / exposed occurrences (all)	 1 / 61 (1.64%) 1	 0 / 29 (0.00%) 0	
Nausea			

subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Arthritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 61 (4.92%)	3 / 29 (10.34%)	
occurrences (all)	3	3	
Upper respiratory tract infection			
subjects affected / exposed	4 / 61 (6.56%)	1 / 29 (3.45%)	
occurrences (all)	4	1	

Asymptomatic bacteriuria			
subjects affected / exposed	3 / 61 (4.92%)	0 / 29 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	2 / 61 (3.28%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Bacteriuria			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Enterococcal infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	

Tracheitis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 29 (0.00%) 0	
Tracheobronchitis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 29 (0.00%) 0	
Metabolism and nutrition disorders Hyperglycemia subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	1 / 29 (3.45%) 1	
Hyperlipidemia subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 29 (3.45%) 1	
Hyperuricemia subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 29 (3.45%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2017	The following amendments were made to protocol V1.0: - Typographical corrections - ECG to be carried out at the end of treatment visit (SD84) only if either physical examination or vital signs or cardiac monitoring showed abnormalities - Clarification of frequency of vital signs assessments
06 October 2017	The following amendments were made to protocol V1.1 dated 6 February 2017: - Addition of anti-RANKL as a prohibited concomitant medication within three months prior to screening; added to exclusion criteria and list of prohibited concomitant medications, as anti-RANKL therapy in the NI-0101-04 study could potentially confound the evaluation of potential effects of NI-0101. - Clarification of vital signs assessments to align the main body text with the schedule of assessment table and further describe vital signs assessments across visits. - Removal of the requirement to stratify patients across both arms of the study for FcRIIa genotype in a 2:1 ratio for RR/RH:HH. The FcRIIa genotype stratification was retained, but without a defined ratio to be achieved for the RR/RH and HH groups, to better match the frequency of the genotype in the population while maintaining stratification of the groups across treatment arms. - Clarification regarding class 2 analgesics (authorized for use to treat mild to moderate pain) as authorized concomitant therapies - Clarification that CRP is measured in a central laboratory and ESR is measured locally - Clarification that the pre-enrolment visit could occur within four weeks after the screening visit (rather than between three and four weeks after the screening visit) - Clarification of SAE reporting email address

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported