Clinical trial results:
Stratification of Biologic Therapies for RA by Pathobiology (STRAP): A randomised, open-labelled biopsy-driven stratification trial in DMARD inadequate responder patients randomised to Etanercept, Tocilizumab or Rituximab.

Summary

EudraCT number	2014-003529-16
Trial protocol	GB
Global end of trial date	23 January 2021

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	STRAP_ReDA_010104

Additional study identifiers

ISRCTN number	ISRCTN10618686
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London (QMUL)
Sponsor organisation address	Joint Research Management Office (JRMO), Empire House, 67-75 New Road, London, United Kingdom, E1 1HH
Public contact	Professor Costantino Pitzalis, Centre for Experimental Medicine and Rheumatology, QMUL, QMUL, emrclinicaltrials@qmul.ac.uk
Scientific contact	Professor Costantino Pitzalis, Centre for Experimental Medicine and Rheumatology, QMUL, QMUL, emrclinicaltrials@qmul.ac.uk

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	23 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2021
Global end of trial reached?	Yes
Global end of trial date	23 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of this study is to test the utility of analysing synovial B cell infiltrates as a potential biomarker to guide therapeutic decisions in patients failing DMARD therapy. We hypothesise that stratification of patients according to their synovial B cell infiltrate into the B cellpoor/rich pathotype by histomorphology and/or a B cell specific gene expression module derived from FANTOM5 (Functional ANnoTation Of Mammalian Genome) will better define response rates. Specifically, we hypothesise that the other two treatment options (Tocilizumab and Etanercept, treated together for analysis) are superior to Rituximab in B-cell-poor patients.

As documented in the protocol and statistical analyses plan, data from the STRAP trial will be analysed together with the data from the STRAP-EU trial (identical trial running in the EU) for all endpoints and submitted as one clinical study report at the end of the trials.

Protection of trial subjects:

The drugs used in this trial are all approved for use in this patient population.
Infusions of Rituximab may be associated with infusion reactions of varying severity in up to 15% of patients. Most are mild and managed by slowing the rate of the Rituximab infusion. Occasionally, more severe reactions necessitate stopping the infusion and rarely, anaphylaxis has been reported. Patients will be given corticosteroids (methylprednisolone 100mg intravenous), antihistamines (chlorphenamine 10mg intravenous) and paracetamol (1000mg orally) before the infusion to minimise the risk of reactions. The risk of infection will be discussed with the patient prior to enrolment in the study however patients would be at no greater risk than routine care within the NHS.

Injection-site reactions with Tocilizumab and Etanercept may also occur. The risk of such reactions as well as of infection will be discussed with the patient prior to enrolment in the study however patients would be at no greater risk than routine care within the NHS.

Ultrasound-guided synovial biopsy is a quick, safe and well tolerated procedure; patients who consent to the study and therefore synovial biopsy will have a longer appointment in hospital and may experience discomfort from the local anaesthetic and biopsy procedure. However, published data on this procedure confirms that it is well tolerated, safe, and patients are agreeable to multiple biopsies.

The risks of venepuncture may include fainting, pain and/or bruising at the site of the needle puncture. Every possible effort will be taken to minimise the potential of these risks occurring.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 June 2015
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	Spain: 6
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United Kingdom: 184
Worldwide total number of subjects	223
EEA total number of subjects	39

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)	173
From 65 to 84 years	49
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patient with rheumatoid arthritis were recruited from rheumatology clinics at 20 sites in the United Kingdom, 3 sites in Italy, and 1 site in each of Belgium, Spain, and Portugal. Recruitment began in June 2015 and ended in May 2019.

Pre-assignment

Screening details:

294 patients provided informed consent, however only 228 of these underwent synovial biopsy. 2 were subsequently found to be inelegibile, prior to randomisation, therefore a total of 226 patients were randomised onto the trial. 3 were excluded from the ITT analyses as they received steroid injections <4 weeks prior to screening (exclusion criteria)

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Only the joint assessor who assessed the patients swollen and tender joints at each visit was blinded to treatment. The patient and investigator were not blinded to treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Patients randomised to Rituximab

Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks who continues to have active disease or flares will be re-treated at 24 weeks, as per the SmPC

Arm title	Tocilizumab

Arm description:

Patients randomised to tocilizumab.

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Tocilizumab for adult patients with RA is 162mg administered as a weekly subcutaneous injection and it was self-administered by patients.

Arm title	Etanercept

Arm description:

Patients randomised to Etanercept.

Arm type	Active drug
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it was self-administered by patients.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only the joint assessor who assessed the patients swollen and tender joints at each visit was blinded to treatment. The patient and investigator were not blinded to treatment.

Number of subjects in period 1	Rituximab	Tocilizumab	Etanercept
Started	78	73	72
Completed	78	73	72

Period 2

Period 2 title	Baseline to Week 16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Blinding implementation details:

Only the joint assessor who assessed the patients swollen and tender joints at each visit was blinded to treatment. The patient and investigator were not blinded to treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Patients randomised to rituximab completing the period up to week 16.

Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a

responder at 16 weeks who continues to have active disease or flares will be re-treated at 24 weeks, as per the SmPC

Arm title	Tocilizumab
Arm description:	
Patients randomised to tocilizumab and completing the period up to week 16.	
Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
The recommended dose of Tocilizumab for adult patients with RA is 162mg administered as a weekly subcutaneous injection and it was self-administered by patients.	
Arm title	Etanercept
Arm description:	
Patients randomised to etanercept and compelting the period up to week 16.	
Arm type	Active drug
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details:	
The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it was self-administered by patients.	

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only the joint assessor who assessed the patients swollen and tender joints at each visit was blinded to treatment. The patient and investigator were not blinded to treatment.

Number of subjects in period 2	Rituximab	Tocilizumab	Etanercept
Started	78	73	72
Completed	72	72	69
Not completed	6	1	3
Consent withdrawn by subject	4	-	-
Adverse event, non-fatal	2	1	3

Period 3

Period 3 title	Week 16 to week 48
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind

Roles blinded	Assessor[3]

Blinding implementation details:

Only the joint assessor who assessed the patients swollen and tender joints at each visit was blinded to treatment. The patient and investigator were not blinded to treatment.

Arms

Are arms mutually exclusive?	No
Arm title	Rituximab

Arm description:

Patients randomsied to rituximab and receiving rituximab at the start of the period week 16-48.

Arm type	Active drug
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks who continues to have active disease or flares will be re-treated at 24 weeks, as per the SmPC

Arm title	Tocilizumab

Arm description:

Patients randomsied to tocilizumab and receiving tocilizumab at the start of the period week 16-48.

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Tocilizumab for adult patients with RA is 162mg administered as a weekly subcutaneous injection and it was self-administered by patients.

Arm title	Etanercept

Arm description:

Patients randomsied to etanercept and receiving etanercept at the start of the period week 16-48.

Arm type	Active drug
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it was self-administered by patients.

Arm title	Rituximab + Etanercept

Arm description:

Patients who were randomized to rituximab but switched to etanercept at week 16 or later.

Arm type	Active drug

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks who continues to have active disease or flares will be re-treated at 24 weeks, as per the SmPC

Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it was self-administered by patients.

Arm title	Tocilizumab + Rituximab

Arm description:

Patient who was randomized to Tocilizumab but switched to rituximab at week 24 (protocol deviation).

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Tocilizumab for adult patients with RA is 162mg administered as a weekly subcutaneous injection and it was self-administered by patients.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks who continues to have active disease or flares will be re-treated at 24 weeks, as per the SmPC

Arm title	Tocilizumab + Etanercept

Arm description:

Patients who were randomized to tocilizumab but switched to etanercept at week 16 or later.

Arm type	Active drug
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Tocilizumab for adult patients with RA is 162mg administered as a weekly subcutaneous injection and it was self-administered by patients.

Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it was self-administered by patients.

Arm title	Etanercept + Rituximab

Arm description:

Patients randomised to etanercept and switched to rituximab at week 16 or later.

Arm type	Active drug
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it was self-administered by patients.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to Rituximab will have an infusion cycle at baseline consisting of two infusions given 2 weeks apart (Day 0 and Day 15). A patient initially randomised to Rituximab, deemed a responder at 16 weeks who continues to have active disease or flares will be re-treated at 24 weeks, as per the SmPC

Notes:

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only the joint assessor who assessed the patients swollen and tender joints at each visit was blinded to treatment. The patient and investigator were not blinded to treatment.

Number of subjects in period 3[4]	Rituximab	Tocilizumab	Etanercept
Started	64	62	61
Completed	46	56	37
Not completed	18	6	24
Physician decision	2	-	1
Consent withdrawn by subject	3	-	2
Adverse event, non-fatal	-	-	5
Transferred to other arm/group	13	6	15
Pregnancy	-	-	1
Lost to follow-up	-	-	-
Joined	0	0	0
Transferred in from other group/arm	-	-	-

Number of subjects in period 3[4]	Rituximab + Etanercept	Tocilizumab + Rituximab	Tocilizumab + Etanercept
Started	8	1	10
Completed	17	1	13
Not completed	4	0	2
Physician decision	1	-	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	2	-	-
Transferred to other arm/group	-	-	-
Pregnancy	-	-	-
Lost to follow-up	1	-	-
Joined	13	0	5
Transferred in from other group/arm	13	-	5

Number of subjects in period 3[4]	Etanercept + Rituximab
Started	8
Completed	22
Not completed	1
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Transferred to other arm/group	-
Pregnancy	-
Lost to follow-up	-
Joined	15
Transferred in from other group/arm	15

Notes:

[4] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: The reason is due to the system not allowing the starting number of a group to be 0. The patient in Tocilizumab + Rituximab group transfered out of Tocilizumab group however I could not record them as a transfer into the Tocilizumab + Rituximab group since they are recorded in the starting number for this group. Ideally the starting number for the Tocilizumab + Rituximab group would have been 0, the completed number 1, & transfer in number 1, which would have given a net of zero transfers.

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
Patients randomised to Rituximab	
Reporting group title	Tocilizumab
Reporting group description:	
Patients randomised to tocilizumab.	
Reporting group title	Etanercept
Reporting group description:	
Patients randomised to Etanercept.	

Reporting group values	Rituximab	Tocilizumab	Etanercept
Number of subjects	78	73	72
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)	59	55	59
From 65-84 years	19	18	12
85 years and over	0	0	1
Age continuous Units: years			
median	55.1	53.5	52.2
standard deviation	± 13.1	± 14.0	± 13.1
Gender categorical Units: Subjects			
Female	60	54	54
Male	18	19	18
Pathotype Units: Subjects			
Diffuse Myeloid	22	18	20
Lympho-Myeloid	42	41	35
Pauci-immune Fibroid	14	12	13
Myeloid–Lymphoid	0	1	0
Ungradable	0	1	4
Study (UK or EU)			
Study patient was recruited to (STRAP-UK or STRAP-EU)			
Units: Subjects			
EU	14	13	12
UK	64	60	60
Rheumatoid factor (RF) OR Anti–citrullinated protein antibody			

positive Units: Subjects			
negative	10	14	12
positive	68	59	60
Rheumatoid factor (RF) positive Units: Subjects			
negative	21	25	23
positive	57	48	49
Anti–citrullinated protein antibody (ACPA) positive Units: Subjects			
negative	15	16	18
positive	61	57	54
Not reported	2	0	0
Current methotrexate use Units: Subjects			
No	24	26	31
Yes	54	47	41
Current prednisolone use Units: Subjects			
No	63	65	58
Yes	15	8	14
Number of current DMARDs Units: Subjects			
None	30	19	22
One	32	40	36
Two	15	13	13
Three+	1	1	1
Alcohol consumption Units: Subjects			
Yes	36	31	31
No	37	42	41
Not reported	5	0	0
Smoking (ever) Units: Subjects			
Yes	41	42	35
No	37	31	37
BMI Units: kg/m²			
median	25.0	25.0	25.7
inter-quartile range (Q1-Q3)	22.4 to 29.5	22.4 to 31.1	23.5 to 30.5
Disease duration Units: years			
median	3.0	3.0	5.0
inter-quartile range (Q1-Q3)	1.0 to 8.0	1.0 to 8.0	2.0 to 8.2
Clinical disease activity index (CDAI) Units: score			
median	31.3	33.8	33.8
inter-quartile range (Q1-Q3)	24.6 to 41.2	25.9 to 41.8	26.0 to 44.2
Erythrocyte sedimentation rate (ESR) Units: mm/h			

median	27.0	28.0	25.0
inter-quartile range (Q1-Q3)	16.0 to 45.8	15.0 to 45.0	16.0 to 37.0
C-reactive protein (CRP)			
Units: mg/L			
median	11.5	13.0	10.0
inter-quartile range (Q1-Q3)	4.5 to 29.2	5.0 to 28.0	3.5 to 26.0
Haemoglobin (Hb)			
Units: g/L			
median	123.5	113.0	125.5
inter-quartile range (Q1-Q3)	117.2 to 134.8	101.2 to 120.5	119.0 to 130.0
Number of tender joints, 0-28			
Units: Score 0-28			
median	10.0	11.0	13.5
inter-quartile range (Q1-Q3)	7.0 to 17.8	7.0 to 19.0	8.0 to 20.0
Number of swollen joints, 0-28			
Units: Score 0-28			
median	7.0	7.0	7.0
inter-quartile range (Q1-Q3)	4.0 to 11.0	5.0 to 10.0	4.0 to 10.2
Number of tender joints (0-68)			
Units: Score 0-68			
median	17.5	16.0	20.0
inter-quartile range (Q1-Q3)	11.0 to 30.8	11.0 to 27.0	14.0 to 31.0
Number of swollen joints (0-68)			
Units: Score 0-68			
median	9.0	9.0	9.0
inter-quartile range (Q1-Q3)	5.0 to 14.0	6.0 to 13.0	5.0 to 13.0
VAS Patient’s global assessment—arthritis, 0–100			
Units: Score 0-100			
median	71.5	75.0	72.5
inter-quartile range (Q1-Q3)	46.2 to 84.8	55.0 to 89.0	60.8 to 87.2
VAS Physician’s global assessment, 0–100			
Units: Score 0-100			
median	55.5	61.0	66.5
inter-quartile range (Q1-Q3)	38.2 to 75.5	46.0 to 82.0	45.8 to 79.2
28 joint count Disease Activity Score (DAS-28), ESR			
Units: Score			
arithmetic mean	5.8	6.0	6.0
standard deviation	± 1.3	± 1.3	± 0.9
28 joint count Disease Activity Score (DAS-28), CRP			
Units: Score			
arithmetic mean	5.4	5.6	5.5
standard deviation	± 1.1	± 1.1	± 1.0
Health assessment questionnaire (HAQ) score			
Units: Score			
median	1.6	1.8	1.7
inter-quartile range (Q1-Q3)	1.0 to 2.1	1.2 to 2.2	1.1 to 2.1
van der Heijde modified Sharp score (SHSS), Total			
Units: Score			

median	5.0	5.0	4.0
inter-quartile range (Q1-Q3)	2.0 to 11.0	1.0 to 14.8	0.0 to 12.0
van der Heijde modified Sharp score (SHSS), Erosion			
Units: Score			
median	3.0	1.0	2.0
inter-quartile range (Q1-Q3)	0.2 to 7.0	0.0 to 6.0	0.0 to 6.0
van der Heijde modified Sharp score (SHSS), Joint Space Narrowing			
Units: Score			
median	1.0	3.0	0.5
inter-quartile range (Q1-Q3)	0.0 to 6.0	0.0 to 11.0	0.0 to 6.5
Ultrasound 12-max score (Power Doppler)			
Units: Score			
median	7.5	7.0	7.0
inter-quartile range (Q1-Q3)	3.8 to 12.2	3.0 to 11.0	4.0 to 11.0
Ultrasound 12-max score (Synovial Thickening)			
Units: Score			
arithmetic mean	23.8	22.7	22.3
standard deviation	± 5.7	± 6.1	± 6.7

Reporting group values	Total		
Number of subjects	223		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	173		
From 65-84 years	49		
85 years and over	1		
Age continuous			
Units: years			
median			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	168		
Male	55		
Pathotype			
Units: Subjects			
Diffuse Myeloid	60		
Lympho-Myeloid	118		
Pauci-immune Fibroid	39		
Myeloid–Lymphoid	1		
Ungradable	5		

Study (UK or EU)			
Study patient was recruited to (STRAP-UK or STRAP-EU)			
Units: Subjects			
EU	39		
UK	184		
Rheumatoid factor (RF) OR Anti–citrullinated protein antibody (ACPA) positive Units: Subjects			
negative	36		
positive	187		
Rheumatoid factor (RF) positive Units: Subjects			
negative	69		
positive	154		
Anti–citrullinated protein antibody (ACPA) positive Units: Subjects			
negative	49		
positive	172		
Not reported	2		
Current methotrexate use Units: Subjects			
No	81		
Yes	142		
Current prednisolone use Units: Subjects			
No	186		
Yes	37		
Number of current DMARDs Units: Subjects			
None	71		
One	108		
Two	41		
Three+	3		
Alcohol consumption Units: Subjects			
Yes	98		
No	120		
Not reported	5		
Smoking (ever) Units: Subjects			
Yes	118		
No	105		
BMI Units: kg/m²			
median			
inter-quartile range (Q1-Q3)	-		
Disease duration Units: years			
median			
inter-quartile range (Q1-Q3)	-		

Clinical disease activity index (CDAI) Units: score median inter-quartile range (Q1-Q3)	- -		
Erythrocyte sedimentation rate (ESR) Units: mm/h median inter-quartile range (Q1-Q3)	- -		
C-reactive protein (CRP) Units: mg/L median inter-quartile range (Q1-Q3)	- -		
Haemoglobin (Hb) Units: g/L median inter-quartile range (Q1-Q3)	- -		
Number of tender joints, 0-28 Units: Score 0-28 median inter-quartile range (Q1-Q3)	- -		
Number of swollen joints, 0-28 Units: Score 0-28 median inter-quartile range (Q1-Q3)	- -		
Number of tender joints (0-68) Units: Score 0-68 median inter-quartile range (Q1-Q3)	- -		
Number of swollen joints (0-68) Units: Score 0-68 median inter-quartile range (Q1-Q3)	- -		
VAS Patient’s global assessment—arthritis, 0–100 Units: Score 0-100 median inter-quartile range (Q1-Q3)	- -		
VAS Physician’s global assessment, 0–100 Units: Score 0-100 median inter-quartile range (Q1-Q3)	- -		
28 joint count Disease Activity Score (DAS-28), ESR Units: Score arithmetic mean standard deviation	- -		
28 joint count Disease Activity Score (DAS-28), CRP Units: Score arithmetic mean standard deviation	- -		
Health assessment questionnaire (HAQ)			

score Units: Score median inter-quartile range (Q1-Q3)	-		
van der Heijde modified Sharp score (SHSS), Total Units: Score median inter-quartile range (Q1-Q3)	-		
van der Heijde modified Sharp score (SHSS), Erosion Units: Score median inter-quartile range (Q1-Q3)	-		
van der Heijde modified Sharp score (SHSS), Joint Space Narrowing Units: Score median inter-quartile range (Q1-Q3)	-		
Ultrasound 12-max score (Power Doppler) Units: Score median inter-quartile range (Q1-Q3)	-		
Ultrasound 12-max score (Synovial Thickening) Units: Score arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description: Patients randomised to Rituximab	
Reporting group title	Tocilizumab
Reporting group description: Patients randomised to tocilizumab.	
Reporting group title	Etanercept
Reporting group description: Patients randomised to Etanercept.	
Reporting group title	Rituximab
Reporting group description: Patients randomised to rituximab completing the period up to week 16.	
Reporting group title	Tocilizumab
Reporting group description: Patients randomised to tocilizumab and completing the period up to week 16.	
Reporting group title	Etanercept
Reporting group description: Patients randomised to etanercept and compelting the period up to week 16.	
Reporting group title	Rituximab
Reporting group description: Patients randomsied to rituximab and receiving rituximab at the start of the period week 16-48.	
Reporting group title	Tocilizumab
Reporting group description: Patients randomsied to tocilizumab and receiving tocilizumab at the start of the period week 16-48.	
Reporting group title	Etanercept
Reporting group description: Patients randomsied to etanercept and receiving etanercept at the start of the period week 16-48.	
Reporting group title	Rituximab + Etanercept
Reporting group description: Patients who were randomized to rituximab but switched to etanercept at week 16 or later.	
Reporting group title	Tocilizumab + Rituximab
Reporting group description: Patient who was randomized to Tocilizumab but switched to rituximab at week 24 (protocol deviation).	
Reporting group title	Tocilizumab + Etanercept
Reporting group description: Patients who were randomized to tocilizumab but switched to etanercept at week 16 or later.	
Reporting group title	Etanercept + Rituximab
Reporting group description: Patients randomised to etanercept and switched to rituximab at week 16 or later.	
Subject analysis set title	ITT week 16 - B cell poor - Rituximab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell poor by RNA-seq classification, randomised to rituximab and analysed as ITT at week 16.	
Subject analysis set title	ITT week 16 - B cell poor - Tocilizumab/Etanercept
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subgroup of patients classified as B cell poor by RNA-seq classification, randomised to tocilizumab OR	

etanercept, and analysed as ITT at week 16.

Subject analysis set title	ITT week 16 - B cell rich - Rituximab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subgroup of patients classified as B cell rich by RNA-sequencing classification, randomised to rituximab, and analysed as ITT at week 16.

Subject analysis set title	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subgroup of patients classified as B cell rich by RNA-sequencing classification, randomised to either tocilizumab OR etanercept, and analysed as ITT at week 16.

Subject analysis set title	PP week 16 - B cell poor - Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by RNA-seq classification, randomised to rituximab and analysed as per protocol at week 16.

Subject analysis set title	PP week 16 - B cell poor - Tocilizumab/Etanercept
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell poor by RNA-seq classification, randomised to tocilizumab OR etanercept, and analysed as per protocol at week 16.

Subject analysis set title	PP week 16 - B cell rich - Rituximab
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by RNA-seq classification, randomised to rituximab and analysed as ITT at week 16.

Subject analysis set title	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject analysis set type	Per protocol

Subject analysis set description:

Subgroup of patients classified as B cell rich by RNA-seq classification, randomised to tocilizumab OR etanercept, and analysed as per protocol at week 16.

Subject analysis set title	Week 16 - B cell poor - Rituximab - MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell poor - Rituximab: Patients on methotrexate at baseline

Subject analysis set title	Week 16 - B cell poor - TOC/ETN - MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell poor - tocilizumab or etanercept: Patients on methotrexate at baseline

Subject analysis set title	Week 16 - B cell poor - Rituximab - NO MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell poor - Rituximab: Patient NOT on methotrexate at baseline

Subject analysis set title	Week 16 - B cell poor - TOC/ETN - NO MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell poor - tocilizumab or etanercept: Patient NOT on methotrexate at baseline

Subject analysis set title	Week 16 - B cell rich - Rituximab - MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell rich - Rituximab: Patients on methotrexte at baseline

Subject analysis set title	Week 16 - B cell rich - TOC/ETN - MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell rich - tocilizumab or etanercept: Patient on methotrexate at baseline

Subject analysis set title	Week 16 - B cell rich - Rituximab - NO MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell rich - rituximab: Patients not on methotrexate at baseline

Subject analysis set title	Week 16 - B cell rich - TOC/ETN - NO MTX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Week 16 - B cell rich - tocilizumab or etanercept: Patients not on methotrexate at baseline

Subject analysis set title	Switchers to Rituximab - Week 16 (+16)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients deemed treatment failures at 16 weeks from baseline were switched to another therapeutic option and their response was evaluated 16 weeks after that

Subject analysis set title	Switchers to Etanercept - Week 16 (+16)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients deemed treatment failures at 16 weeks from baseline were switched to another therapeutic option and their response was evaluated 16 weeks after that

Primary: ACR20

End point title	ACR20

End point description:

ACR20 was used to identify responders/non-responders to determine treatment switches. Participants who fulfil the following criteria are considered responders: 20% or more improvement in tender and swollen joint counts and 20% or more improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments (both 10 cm VAS), pain (VAS), disability as measured by HAQ, and an acute-phase reactant. Particpants who do not reach this criteria are considered non-responders.

End point type	Primary

End point timeframe:

16 weeks

End point values	ITT week 16 - B cell poor - Rituximab	ITT week 16 - B cell poor - Tocilizumab/Etanercept	ITT week 16 - B cell rich - Rituximab	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	77	32	66
Units: Patients				
Responder	23	46	21	49

End point values	PP week 16 - B cell poor - Rituximab	PP week 16 - B cell poor - Tocilizumab/Etanercept	PP week 16 - B cell rich - Rituximab	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	57	30	59
Units: Patients				
Responder	20	33	19	43

End point values	Week 16 - B cell poor - Rituximab - MTX	Week 16 - B cell poor - TOC/ETN - MTX	Week 16 - B cell poor - Rituximab - NO MTX	Week 16 - B cell poor - TOC/ETN - NO MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	50	16	27
Units: Patients				
Responder	17	32	9	14

End point values	Week 16 - B cell rich - Rituximab - MTX	Week 16 - B cell rich - TOC/ETN - MTX	Week 16 - B cell rich - Rituximab - NO MTX	Week 16 - B cell rich - TOC/ETN - NO MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	36	8	30
Units: Patients				
Responder	18	28	5	21

End point values	Switchers to Rituximab - Week 16 (+16)	Switchers to Etanercept - Week 16 (+16)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	36		
Units: Patients				
Responder	8	7		

Statistical analyses

Statistical analysis title	RTX vs TOC/ETN, B cell poor, ITT
Statistical analysis description:	
ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.66

Statistical analysis title	RTX vs TOC/ETN, B cell rich, ITT
Statistical analysis description:	
ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	5.07

Statistical analysis title	RTX vs TOC/ETN, B cell poor, PP
Statistical analysis description:	
Per protocol week 16 - B cell poor - Rituximab v Per protocol week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	PP week 16 - B cell poor - Rituximab v PP week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.4

Statistical analysis title	RTX vs TOC/ETN, B cell rich, PP
Statistical analysis description:	
Per protocol week 16 - B cell rich - Rituximab v Per protocol week 16 - B cell rich - Tocilizumab/Etanercept	
Comparison groups	PP week 16 - B cell rich - Rituximab v PP week 16 - B cell rich - Tocilizumab/Etanercept

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	4.47

Statistical analysis title	Interaction: Treatment*B cell status, ITT
Statistical analysis description:	
Analysis conducted on the whole ITT population	
Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept v ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.46
Method	Likelihood ratio test

Notes:

[1] - Interaction test conducted through 2 nested logistic regression models

Statistical analysis title	Interaction: MTX use*Study, ITT
Statistical analysis description:	
Analysis conducted on the whole ITT cohort	
Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept v ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.96
Method	Likelihood ratio test

Notes:

[2] - Analysis conducted through 2 nested logistic regression models

Statistical analysis title	RTX vs. TOC/ETN, B cell rich, ITT
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2.06

Statistical analysis title	Meta-analysis, TOC/ETA vs. RTX, B cell poor, ITT
Comparison groups	ITT week 16 - B cell poor - Tocilizumab/Etanercept v ITT week 16 - B cell poor - Rituximab
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority[3]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.14

Notes:

[3] - A fixed-effects Mantel-Haenszel meta-analysis was performed on the two studies (STRAP and STRAP-EU) to obtain a unified adjusted odds ratio and 95% CI, as an alternative way of adjusting for site. This was carried as a repetitio of the primary analysis on the B cell POOR population.

Statistical analysis title	B poor, MTX: RTX vs TOC/ETN
Comparison groups	Week 16 - B cell poor - Rituximab - MTX v Week 16 - B cell poor - TOC/ETN - MTX
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	3.03

Statistical analysis title	B poor, NO MTX: RTX vs TOC/ETN
Comparison groups	Week 16 - B cell poor - Rituximab - NO MTX v Week 16 - B cell poor - TOC/ETN - NO MTX

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	2.85

Statistical analysis title	B rich, MTX: RTX vs TOC/ETN
Comparison groups	Week 16 - B cell rich - Rituximab - MTX v Week 16 - B cell rich - TOC/ETN - MTX
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	5.53

Statistical analysis title	B rich, NO MTX: RTX vs TOC/ETN
Comparison groups	Week 16 - B cell rich - Rituximab - NO MTX v Week 16 - B cell rich - TOC/ETN - NO MTX
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	7.88

Statistical analysis title	RTX vs. ETA - 16 weeks after treatment switch
Comparison groups	Switchers to Etanercept - Week 16 (+16) v Switchers to Rituximab - Week 16 (+16)

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	7.9

Secondary: ACR50

End point title	ACR50

End point description:

Participants who fulfil the following criteria are considered responders according to ACR50: 50% or more improvement in tender and swollen joint counts and 50% or more improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments (both 10 cm VAS), pain (VAS), disability as measured by HAQ, and an acute-phase reactant.

End point type	Secondary

End point timeframe:

16 weeks

End point values	ITT week 16 - B cell poor - Rituximab	ITT week 16 - B cell poor - Tocilizumab/Etanercept	ITT week 16 - B cell rich - Rituximab	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	77	32	66
Units: Patients				
Responder	12	35	9	33

End point values	PP week 16 - B cell poor - Rituximab	PP week 16 - B cell poor - Tocilizumab/Etanercept	PP week 16 - B cell rich - Rituximab	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	57	30	59
Units: Patients				
Responder	9	25	9	30

Statistical analyses

Statistical analysis title	RTX vs TOC/ETN, B cell poor, ITT
Statistical analysis description:	
ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	5.18

Statistical analysis title	RTX vs TOC/ETN, B cell rich, ITT
Statistical analysis description:	
ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	8.41

Statistical analysis title	RTX vs TOC/ETN, B cell poor, PP
Statistical analysis description:	
Per protocol week 16 - B cell poor - Rituximab v Per protocol week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	PP week 16 - B cell poor - Rituximab v PP week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	5.94

Statistical analysis title	RTX vs TOC/ETN, B cell rich, PP

Statistical analysis description:

Per protocol week 16 - B cell rich - Rituximab v Per protocol week 16 - B cell rich - Tocilizumab/Etanercept

Comparison groups	PP week 16 - B cell rich - Tocilizumab/Etanercept v PP week 16 - B cell rich - Rituximab
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	6.97

Secondary: ACR70

End point title	ACR70

End point description:

Participants who fulfil the following criteria are considered responders according to ACR70: 70% or more improvement in tender and swollen joint counts and 70% or more improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments (both 10 cm VAS), pain (VAS), disability as measured by HAQ, and an acute-phase reactant.

End point type	Secondary

End point timeframe:

16 weeks

End point values	ITT week 16 - B cell poor - Rituximab	ITT week 16 - B cell poor - Tocilizumab/Etanercept	ITT week 16 - B cell rich - Rituximab	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	77	32	66
Units: Patients				
Responder	6	18	4	20

End point values	PP week 16 - B cell poor - Rituximab	PP week 16 - B cell poor - Tocilizumab/Etanercept	PP week 16 - B cell rich - Rituximab	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	57	30	59
Units: Patients				
Responder	5	13	4	18

Statistical analyses

Statistical analysis title	RTX vs TOC/ETN, B cell poor, ITT
Statistical analysis description:	
ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell poor - Tocilizumab/Etanercept v ITT week 16 - B cell poor - Rituximab
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	5.73

Statistical analysis title	RTX vs TOC/ETN, B cell rich, ITT
Statistical analysis description:	
ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	13.89

Statistical analysis title	RTX vs TOC/ETN, B cell poor, PP
Statistical analysis description:	
Per protocol week 16 - B cell poor - Rituximab v Per protocol week 16 - B cell poor -	

Tocilizumab/Etanercept

Comparison groups	PP week 16 - B cell poor - Rituximab v PP week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	5.92

Statistical analysis title	RTX vs TOC/ETN, B cell rich, PP

Statistical analysis description:

Per protocol week 16 - B cell rich - Rituximab v Per protocol week 16 - B cell rich - Tocilizumab/Etanercept

Comparison groups	PP week 16 - B cell rich - Rituximab v PP week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	10.71

Secondary: DAS28(ESR) <= 2.6

End point title	DAS28(ESR) <= 2.6

End point description:

Number of patients with DAS28 (calculated using ESR) less than or equal to 2.6.

End point type	Secondary

End point timeframe:

16 weeks

End point values	ITT week 16 - B cell poor - Rituximab	ITT week 16 - B cell poor - Tocilizumab/Etanercept	ITT week 16 - B cell rich - Rituximab	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	77	32	66
Units: Patients				
Responder	6	29	8	35

End point values	PP week 16 - B cell poor - Rituximab	PP week 16 - B cell poor - Tocilizumab/Etanercept	PP week 16 - B cell rich - Rituximab	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	57	30	59
Units: Patients				
Responder	6	22	7	32

Statistical analyses

Statistical analysis title	RTX vs TOC/ETN, B cell poor, ITT
Statistical analysis description:	
ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	11.17

Statistical analysis title	RTX vs TOC/ETN, B cell rich, ITT
Statistical analysis description:	
ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept	
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	6.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	19.89

Statistical analysis title	RTX vs TOC/ETN, B cell poor, PP
Statistical analysis description:	
Per protocol week 16 - B cell poor - Rituximab v Per protocol week 16 - B cell poor - Tocilizumab/Etanercept	
Comparison groups	PP week 16 - B cell poor - Rituximab v PP week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	9.12

Statistical analysis title	RTX vs TOC/ETN, B cell rich, PP
Statistical analysis description:	
Per protocol week 16 - B cell rich - Rituximab v Per protocol week 16 - B cell rich - Tocilizumab/Etanercept	
Comparison groups	PP week 16 - B cell rich - Rituximab v PP week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	5.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.79
upper limit	19.23

Secondary: CDAI <10.1

End point title	CDAI <10.1
End point description: Clinical Disease Activity Index (CDAI) score of less than 10.1	
End point type	Secondary
End point timeframe: 16 weeks	

End point values	ITT week 16 - B cell poor - Rituximab	ITT week 16 - B cell poor - Tocilizumab/Etanercept	ITT week 16 - B cell rich - Rituximab	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	77	32	66
Units: Patients				
Responder	16	35	16	38

End point values	PP week 16 - B cell poor - Rituximab	PP week 16 - B cell poor - Tocilizumab/Etanercept	PP week 16 - B cell rich - Rituximab	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	57	30	59
Units: Patients				
Responder	14	25	14	35

Statistical analyses

Statistical analysis title	RTX vs TOC/ETN, B cell poor, ITT
Statistical analysis description: ITT week 16 - rituximab - B cell poor vs ITT week 16 - tocilizumab/etanercept - B cell poor	
Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	3.01

Statistical analysis title	RTX vs TOC/ETN, B cell rich, ITT
Statistical analysis description:	
ITT week 16 - rituximab - B cell rich vs ITT week 16 - tocilizumab/etanercept - B cell rich	
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	4.96

Statistical analysis title	RTX vs TOC/ETN, B cell poor, PP
Statistical analysis description:	
Per protocol week 16 - rituximab - B cell poor vs Per protocol week 16 - tocilizumab/etanercept - B cell poor	
Comparison groups	PP week 16 - B cell poor - Rituximab v PP week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2.77

Statistical analysis title	RTX vs TOC/ETN, B cell rich, PP
Statistical analysis description:	
Per protocol week 16 - rituximab - B cell rich vs Per protocol week 16 - tocilizumab/etanercept - B cell rich	
Comparison groups	PP week 16 - B cell rich - Rituximab v PP week 16 - B cell rich - Tocilizumab/Etanercept

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	5.31

Secondary: CDAI

End point title	CDAI
End point description:	
Mean % change in CDAI score at 16 weeks.	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	ITT week 16 - B cell poor - Rituximab	ITT week 16 - B cell poor - Tocilizumab/Etanercept	ITT week 16 - B cell rich - Rituximab	ITT week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	77	32	66
Units: Value				
least squares mean (confidence interval 95%)	-18.3 (-22.9 to -13.7)	-21.4 (-25.2 to -17.5)	-19.6 (-23.5 to -15.7)	-24.0 (-26.7 to -21.3)

End point values	PP week 16 - B cell poor - Rituximab	PP week 16 - B cell poor - Tocilizumab/Etanercept	PP week 16 - B cell rich - Rituximab	PP week 16 - B cell rich - Tocilizumab/Etanercept
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	57	30	59
Units: Value				
least squares mean (confidence interval 95%)	-18.2 (-23.1 to -13.3)	-22.3 (-26.4 to -18.2)	-20.1 (-24.3 to -15.9)	-24.4 (-27.3 to -21.5)

Statistical analyses

Statistical analysis title	RTX vs TOC/ETN, B cell poor, ITT
Statistical analysis description:	
ITT week 16 - Rituximab - B cell poor VS ITT week 16 - tocilizumab/etanercept - B cell poor	

Comparison groups	ITT week 16 - B cell poor - Rituximab v ITT week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	7.7

Statistical analysis title	RTX vs TOC/ETN, B cell rich, ITT
Statistical analysis description:	
ITT week 16 - Rituximab - B cell rich VS ITT week 16 - tocilizumab/etanercept - B cell rich	
Comparison groups	ITT week 16 - B cell rich - Rituximab v ITT week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	8.7

Statistical analysis title	RTX vs TOC/ETN, B cell poor, PP
Statistical analysis description:	
Per protocol week 16 - Rituximab - B cell poor VS Per protocol week 16 - tocilizumab/etanercept - B cell poor	
Comparison groups	PP week 16 - B cell poor - Rituximab v PP week 16 - B cell poor - Tocilizumab/Etanercept
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	9.1

Statistical analysis title	RTX vs TOC/ETN, B cell rich, PP
Statistical analysis description:	
Per protocol week 16 - Rituximab - B cell rich VS Per protocol week 16 - tocilizumab/etanercept - B cell rich	
Comparison groups	PP week 16 - B cell rich - Rituximab v PP week 16 - B cell rich - Tocilizumab/Etanercept
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	9

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs were recorded from the time of the first trial specific assessment/procedure was undertaken (at the screening visit) until the end of the trial period at 48 weeks + 30 days.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
Participants who received at least one dose of rituximab during the trial.	
Reporting group title	Tocilizumab
Reporting group description:	
Participants who received at least one dose of tocilizumab during the trial.	
Reporting group title	Etanercept
Reporting group description:	
Participants who received at least one dose of etanercept during the trial.	
Reporting group title	No IMP
Reporting group description:	
Patient who did not received any IMP but experienced an SAE during particpation in the trial.	

Serious adverse events	Rituximab	Tocilizumab	Etanercept
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 99 (5.05%)	3 / 73 (4.11%)	9 / 107 (8.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of the right ovary			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture of thoracic spine			

subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (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
Left wrist ring finger extension tendon rupture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	0 / 107 (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
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
pacemaker insertion - elective			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Elective ovariectomy			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenic sepsis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Profound neutropenia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial thickening			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain relating to ovarian cyst			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Xanthogranulomatous cholecystitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (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			
Lower respiratory tract infection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity pneumonitis with superadditive viral lower respiratory tract infection			

subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral lower respiratory tract infection, RSV +			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right hand abscess secondary to insect bite			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza A Neutropenia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	No IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of the right ovary			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fracture of thoracic spine			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left wrist ring finger extension tendon rupture			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			

pacemaker insertion - elective				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Elective ovariectomy				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Neutropenic sepsis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Profound neutropenia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Endometrial thickening				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain relating to ovarian cyst				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Appendicitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Xanthogranulomatous cholecystitis				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute hepatitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Lower respiratory tract infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity pneumonitis with superadditive viral lower respiratory tract infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral lower respiratory tract infection, RSV +				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Pyelonephritis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Labyrinthitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right hand abscess secondary to insect bite				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza A Neutropenia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Rituximab	Tocilizumab	Etanercept
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 99 (90.91%)	63 / 73 (86.30%)	96 / 107 (89.72%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0

Baker's cyst			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Genital cyst			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Malignant melanoma			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Ovarian cyst NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Skin tags			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Vascular disorders			
Blood pressure high			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Deep thrombophlebitis of the leg			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Dizziness and giddiness			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	4 / 107 (3.74%)
occurrences (all)	1	0	4
Fainting			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Giant cell arteritis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Haemorrhage			

subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	1	0	2
Hypertension arterial			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Light headedness			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Nose bleed			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Post-menopausal bleeding			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Raynaud's syndrome			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Rectal bleeding			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Subconjunctival hemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Systolic hypertension			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
TIA			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Vaso vagal attack			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Surgical and medical procedures			

Appendectomy			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	2
Cataract extraction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Cataract operation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	2
Cholecystectomy			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Hernia repair			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Hip replacement			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Knee replacement			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Knee total replacement			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Ovariectomy			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Pacemaker insertion (cardiac)			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Toe nail removal			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tooth extraction NOS			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	1	1	2

Transvaginal tape procedure			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tympanoplasty			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Administration site bruise			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Adverse drug reaction NOS			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Appetite lost			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Burning foot			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	2	1	0
Chest pain NEC			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Chronic pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Cyst rupture NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Drug intolerance NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Facial flushing			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	3 / 99 (3.03%)	1 / 73 (1.37%)	3 / 107 (2.80%)
occurrences (all)	5	1	3
Fever			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	3 / 107 (2.80%)
occurrences (all)	1	0	3
Flu like symptoms			
subjects affected / exposed	6 / 99 (6.06%)	1 / 73 (1.37%)	7 / 107 (6.54%)
occurrences (all)	6	1	9
Flushing			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
General malaise			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Hot flushes NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Injection related reaction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Injection site discomfort			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Injection site irritation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Injection site lump			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Injection site reaction NOS			

subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	8 / 107 (7.48%)
occurrences (all)	0	1	9
Injection site redness			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	4 / 107 (3.74%)
occurrences (all)	1	0	4
Intermittent fever			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Lethargy			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Mass NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Nodule			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Other chest pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain aggravated			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Pitting leg oedema			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	2	0
Retrosternal pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Sickness			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Swelling of feet			

subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Swelling of fingers			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Swelling of hands			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Swelling of legs			
subjects affected / exposed	0 / 99 (0.00%)	2 / 73 (2.74%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Tenderness NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Tired all the time			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Tiredness			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	2	0	2
Immune system disorders			
Hay fever			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Hypersensitivity reaction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Infection induced asthma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Uveitis NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			

Adnexal mass			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Menstrual cycle shortened			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute bronchitis			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Acute nasopharyngitis (common cold)			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Asthmatic attack			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Bronchitis NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Burning in throat			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Catarrh			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Chest pain (non-cardiac)			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Chest tightness			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Cough			

subjects affected / exposed	5 / 99 (5.05%)	3 / 73 (4.11%)	7 / 107 (6.54%)
occurrences (all)	5	3	7
Difficulty breathing			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Disturbances of sensation of smell and taste			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Dry cough			
subjects affected / exposed	1 / 99 (1.01%)	3 / 73 (4.11%)	5 / 107 (4.67%)
occurrences (all)	1	3	5
Dry throat			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	2	0	2
Exacerbation of asthma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Hiccups			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Hoarseness of voice			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Hypersensitivity pneumonitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Itchy throat			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Laryngeal discomfort			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Loss of smell			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1

Nasal congestion			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Nasal discharge			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Nasal obstruction			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Pain throat			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Persistent dry cough			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Phlegm			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	3 / 99 (3.03%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	3	1	0
Rhinorrhea			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Runny nose			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Shortness of breath			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Sore throat			
subjects affected / exposed	8 / 99 (8.08%)	7 / 73 (9.59%)	4 / 107 (3.74%)
occurrences (all)	8	7	7
Sore throat NOS			
subjects affected / exposed	1 / 99 (1.01%)	2 / 73 (2.74%)	0 / 107 (0.00%)
occurrences (all)	1	2	0

Wheezes			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Crying			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Feeling down			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Feeling irritated			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Low mood			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	3 / 107 (2.80%)
occurrences (all)	0	1	3
Memory impaired			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Panic attack			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Investigations			
Abnormal LFTs			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Alanine aminotransferase abnormal NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	3 / 107 (2.80%)
occurrences (all)	0	1	3
Alanine aminotransferase increased			

subjects affected / exposed	3 / 99 (3.03%)	3 / 73 (4.11%)	3 / 107 (2.80%)
occurrences (all)	3	3	3
ALP increased			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Arthrocentesis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Bilirubin elevated			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Bilirubin increased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Blood neutrophils abnormal			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Blood sugar decreased			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Cholesterol high			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Cholesterol levels raised			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Cholesterol total increased			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Creatinine increased			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1

LFTs raised			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Liver function tests abnormal NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Liver function tests raised			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Lymphocyte count low			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
MCV abnormal			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Neutrophil count low			
subjects affected / exposed	2 / 99 (2.02%)	3 / 73 (4.11%)	0 / 107 (0.00%)
occurrences (all)	2	4	0
Neutrophils reduced			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Platelet count low			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Raised liver enzymes			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Serum calcium			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Transaminase glutamic-pyruvic increased			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	2	0	1
Transaminitis			

subjects affected / exposed	0 / 99 (0.00%)	2 / 73 (2.74%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Urine abnormal NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Urine culture positive			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Vitamin D low			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Weight gain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Ankle sprain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Blister rupture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Broken elbow			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Cat scratch			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Fall			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Falling			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Falling down			
subjects affected / exposed	2 / 99 (2.02%)	4 / 73 (5.48%)	2 / 107 (1.87%)
occurrences (all)	2	7	3
Finger injury			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Fracture of anatomical neck of humerus, closed			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Golfer's elbow			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Insect bite NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Laceration of finger			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Laceration of leg			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Mosquito bite			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Muscle strain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Perforated eardrum			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1

Rash at site of injection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Skin laceration			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Sprain of interphalangeal (joint) of hand			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Superficial injury of hand(s) except finger(s) alone			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Wrong injection technique			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Cardiac disorders			
Chest pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Chest tightness			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Fibrillation atrial			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Heart fluttering			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Palpitation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Palpitations			

subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	1	1	3
Tachycardia NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Nervous system disorders			
Aura			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Faintness			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	6 / 99 (6.06%)	4 / 73 (5.48%)	7 / 107 (6.54%)
occurrences (all)	7	4	7
Headache temporal			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Loss of sensation			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	2	1	0
Migraine type headaches			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
R sciatica			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tremor of hands			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Leucopenia			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	2	1	0
Leukopenia NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 99 (0.00%)	6 / 73 (8.22%)	1 / 107 (0.93%)
occurrences (all)	0	7	1
Neutropenia aggravated			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Swollen lymph nodes			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear ache			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Ear disorder NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Ear pain			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Otitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Vertigo			

subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Eye disorders			
Bloodshot eye			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Decreased night vision			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Degeneration macular			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Dry eyes			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Floaters in eye			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Gritty eyes			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Near vision disturbance			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Panuveitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Red eye			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
bdomincal hernia NOS			

subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Abdominal pain generalised			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Acid indigestion			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Appendicitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Blistering of mouth			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Bloating			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Burning mouth syndrome			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Churning of stomach			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	2	0	1
Constipation			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	0	1	2
Dental abscess			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Dental disorder NOS			

subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	3 / 99 (3.03%)	6 / 73 (8.22%)	4 / 107 (3.74%)
occurrences (all)	7	6	4
Diarrhoea NOS			
subjects affected / exposed	1 / 99 (1.01%)	2 / 73 (2.74%)	2 / 107 (1.87%)
occurrences (all)	1	2	2
Dry mouth			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Dyspepsia			
subjects affected / exposed	1 / 99 (1.01%)	2 / 73 (2.74%)	1 / 107 (0.93%)
occurrences (all)	1	2	1
Emesis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Epigastric discomfort			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Epigastric pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Gas in stomach			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Increased stool frequency			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Loose bowel			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Loose stools			

subjects affected / exposed	0 / 99 (0.00%)	2 / 73 (2.74%)	2 / 107 (1.87%)
occurrences (all)	0	2	2
Lower abdominal pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Mouth ulcer			
subjects affected / exposed	3 / 99 (3.03%)	5 / 73 (6.85%)	1 / 107 (0.93%)
occurrences (all)	3	6	1
Nausea			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	3 / 107 (2.80%)
occurrences (all)	2	0	3
Nausea alone			
subjects affected / exposed	3 / 99 (3.03%)	5 / 73 (6.85%)	2 / 107 (1.87%)
occurrences (all)	3	5	2
Nausea and vomiting			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Nausea vomiting and diarrhoea			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	1	1	2
Oesophagitis NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Oral thrush			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Oral ulceration			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain gum			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Stomach ache			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Stomach cramps			

subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	3
Stomach discomfort			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Taste changed			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Tongue erythema			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Tongue ulceration			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Tooth ache			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Toothache			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Ulceration of mouth			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Upper abdominal pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Vomited			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Vomiting NOS			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	3	1	2
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0

Xanthogranulomatous cholecystitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Actinic keratosis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Ankle ulcer			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Bruise			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	1	0	2
Bruise of head			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	3 / 107 (2.80%)
occurrences (all)	2	0	3
Eczema exacerbated			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Eczema NOS			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Erythema ear			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Erythema NOS			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	4 / 107 (3.74%)
occurrences (all)	1	0	4
Erythematous rash			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Erythematous skin rash			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Facial hair increased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Generalised itching			
subjects affected / exposed	1 / 99 (1.01%)	3 / 73 (4.11%)	0 / 107 (0.00%)
occurrences (all)	1	3	0
Generalized itching			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Hair loss			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	0	1	2
Herpes simplex aggravated			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Infected nail bed			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Itching papule			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Itchy			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Itchy skin			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Localised itching			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Macular rash			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Malar rash			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Nail dystrophy			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Nail thinning			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Numbness in leg			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Numbness in toes			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Papular rash			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Paraesthesia lower limb			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Paraesthesia skin			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Petechial rash			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Photosensitivity (NOS)			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Pins and needles			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	2
Pityriasis rosea			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Psoriasis aggravated			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Rash both legs			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Rash face			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	2	1	0
Rash NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Rash over arms			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Red rash			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Redness			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Redness of face			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Scalp folliculitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Shingles			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	2	0	1
Skin abrasion			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Skin fragility			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Skin lesion NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Skin rash			
subjects affected / exposed	1 / 99 (1.01%)	2 / 73 (2.74%)	2 / 107 (1.87%)
occurrences (all)	1	2	2
Skin ulcer NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Skin wound			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Sun blister			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Swollen lips			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tendency to bruise easily			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tinea corporis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Tingling feet/hands			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Unspecified pruritic disorder			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Yeast infection of the skin			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	3
Kidney stone			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Microscopic haematuria			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Urinary incontinence			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Endocrine disorders			
Type II diabetes mellitus			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Arthralgia aggravated			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	3 / 99 (3.03%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	3	1	0
Bursitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Calf pain			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Coccyx pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Coxalgia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Cramps			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Cramps of extremities			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Early morning stiffness			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Fibromyalgia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Foot pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Ganglion			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Ganglion of joint			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Generalised joint pains			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Golfer's elbow			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Groin pain			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Hand pain			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Joint inflammation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Knee lock			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Knee pain			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	2	1	1
Leg cramps			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Low back pain			
subjects affected / exposed	3 / 99 (3.03%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	3	1	2
Muscle cramps			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Muscle fatigue			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Muscle weakness lower limb			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Neck pain			
subjects affected / exposed	3 / 99 (3.03%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	3	1	0
Necrotising fasciitis			

subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Nocturnal leg muscle cramps			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
OA hip			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Osteoarthritis shoulders			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Pain back			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Pain in (l) shoulder			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Pain in (r) arm			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain in (r) foot			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Pain in (r) hip			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Pain in (r) knee			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Pain in (r) shoulder			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Pain in elbow			

subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain in hand			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain in hip			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain in joint, site unspecified			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Pain in knee			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Pain in leg			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Painful hand			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Painful knee			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Periarticular disorder			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	2	0	0
Plantar fasciitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Restless legs			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Rheumatoid arthritis aggravated			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Rheumatoid arthritis flare up			

subjects affected / exposed	2 / 99 (2.02%)	4 / 73 (5.48%)	7 / 107 (6.54%)
occurrences (all)	3	4	10
Rheumatoid nodule			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	5 / 107 (4.67%)
occurrences (all)	1	0	5
Shoulder fracture			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Shoulder pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2
Stiffness			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Swan-neck deformity			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Swelling of knees			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Swelling of wrists			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	2	0	2
Temporomandibular joint disorder NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Tenderness muscle			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Thoracic spine compression fracture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1

Trigger finger			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Upper back pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Wrist arthropathy			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Wrist pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Tendon rupture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abdominal abscess NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Abdominal infection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Abscess dental			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Abscess hand			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Abscess of vulva, other			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Abscess on buttock			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Acute posterior ganglionitis			

subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Bladder infection NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Blister infected			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Boil on face			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Bronchitis NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	2
Cellulitis of toe			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Chest infection			
subjects affected / exposed	12 / 99 (12.12%)	5 / 73 (6.85%)	10 / 107 (9.35%)
occurrences (all)	13	6	10
Chlamydial proctitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Cold			
subjects affected / exposed	6 / 99 (6.06%)	5 / 73 (6.85%)	5 / 107 (4.67%)
occurrences (all)	6	6	7
Cold sores			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	2	1
Cold sores lip			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Colitis, enteritis, and gastroenteritis			

of presumed infectious origin			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Common cold			
subjects affected / exposed	5 / 99 (5.05%)	6 / 73 (8.22%)	9 / 107 (8.41%)
occurrences (all)	5	7	12
Conjunctivitis NOS			
subjects affected / exposed	1 / 99 (1.01%)	2 / 73 (2.74%)	1 / 107 (0.93%)
occurrences (all)	1	2	1
Coronavirus infection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Coryza			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Coryzal symptoms			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Cystitis (NOS)			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	2 / 99 (2.02%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	2	0	1
Ear infection NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Flu			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Food poisoning			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 99 (0.00%)	2 / 73 (2.74%)	2 / 107 (1.87%)
occurrences (all)	0	2	2

Gastroenteritis NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Groin abscess			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Head cold			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	1	0	1
Herpes simplex			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Infected bites			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Infected finger			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Infected thumb			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Infection respiratory			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Influenza with other manifestations			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Joint abscess			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Keratitis viral NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0

Labyrinthitis NOS			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Laryngitis NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Laryngopharyngitis			
subjects affected / exposed	0 / 99 (0.00%)	3 / 73 (4.11%)	0 / 107 (0.00%)
occurrences (all)	0	3	0
Lower respiratory tract infection NOS			
subjects affected / exposed	1 / 99 (1.01%)	2 / 73 (2.74%)	2 / 107 (1.87%)
occurrences (all)	1	2	3
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
LRTI			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	0	1	1
Nail fungal infection NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Otitis media NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Parainfluenzae virus infection NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Pilonidal cyst			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pilonidal sinus			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pneumonia NOS			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0

Pyelonephritis NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Rhinitis NOS			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Rhinopharyngitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Sepsis NOS			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Sinusitis NOS			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	2	1	0
Skin fungal infection NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Skin infection NOS			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Thigh abscess			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Throat infection			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	0	1	2
Thrush NOS			
subjects affected / exposed	0 / 99 (0.00%)	2 / 73 (2.74%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Thrush vaginal			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	0	0	2

Tooth abscess			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	1	1	1
Upper respiratory tract infection NOS			
subjects affected / exposed	2 / 99 (2.02%)	2 / 73 (2.74%)	5 / 107 (4.67%)
occurrences (all)	2	3	8
Upper respiratory tract infection viral NOS			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	2	1	0
Urinary tract infection NOS			
subjects affected / exposed	2 / 99 (2.02%)	3 / 73 (4.11%)	6 / 107 (5.61%)
occurrences (all)	3	3	8
URTI (upper respiratory tract infection)			
subjects affected / exposed	2 / 99 (2.02%)	1 / 73 (1.37%)	2 / 107 (1.87%)
occurrences (all)	3	1	2
UTI			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	2 / 107 (1.87%)
occurrences (all)	1	0	5
Vaginal candida			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Vaginal candidiasis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Viral infection NOS			
subjects affected / exposed	4 / 99 (4.04%)	1 / 73 (1.37%)	1 / 107 (0.93%)
occurrences (all)	4	1	2
Viral pharyngitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Whooping cough			

subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Wound infection NEC			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Food intolerance			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 99 (1.01%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	1	1	0
Hypercholesterolemia			
subjects affected / exposed	0 / 99 (0.00%)	2 / 73 (2.74%)	0 / 107 (0.00%)
occurrences (all)	0	2	0
Hypertriglyceridemia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 99 (0.00%)	0 / 73 (0.00%)	1 / 107 (0.93%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Lipoatrophy			
subjects affected / exposed	0 / 99 (0.00%)	1 / 73 (1.37%)	0 / 107 (0.00%)
occurrences (all)	0	1	0
Pain in (l) hip			
subjects affected / exposed	1 / 99 (1.01%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	3 / 99 (3.03%)	0 / 73 (0.00%)	0 / 107 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	No IMP		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	1 / 1 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Baker's cyst			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Genital cyst			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Malignant melanoma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ovarian cyst NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin tags			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Blood pressure high			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Deep thrombophlebitis of the leg			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dizziness and giddiness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Fainting			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Giant cell arteritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Haemoptysis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Haemorrhage				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hypertension				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hypertension arterial				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Light headedness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nose bleed				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Post-menopausal bleeding				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Raynaud's syndrome				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rectal bleeding				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Subconjunctival hemorrhage				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Systolic hypertension				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
TIA				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Vaso vagal attack			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Appendectomy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cataract extraction			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cataract operation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cholecystectomy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hernia repair			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hip replacement			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Knee replacement			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Knee total replacement			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ovariectomy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pacemaker insertion (cardiac)			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Toe nail removal			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tooth extraction NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Transvaginal tape procedure			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tympanoplasty			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Administration site bruise			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Adverse drug reaction NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Appetite lost			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Burning foot			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chest pain NEC			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chronic pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cyst rupture NOS			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Drug intolerance NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Facial flushing				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fever				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Flu like symptoms				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Flushing				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
General malaise				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hot flushes NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection related reaction				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site discomfort				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site irritation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site lump				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site reaction NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Injection site redness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Intermittent fever				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Lethargy				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Mass NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Night sweats				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nodule				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Other chest pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain aggravated				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pitting leg oedema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Retrosternal pain				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sickness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Swelling of feet			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Swelling of fingers			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Swelling of hands			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Swelling of legs			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tenderness NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tired all the time			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tiredness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hay fever			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypersensitivity reaction			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Infection induced asthma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Uveitis NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Adnexal mass			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Menstrual cycle shortened			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Acute bronchitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Acute nasopharyngitis (common cold)			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Asthmatic attack			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Bronchitis NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Burning in throat			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Catarrh			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chest pain (non-cardiac)			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Chest tightness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cough				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Difficulty breathing				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Disturbances of sensation of smell and taste				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dry cough				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dry throat				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Exacerbation of asthma				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hiccups				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hoarseness of voice				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hypersensitivity pneumonitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Itchy throat				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Laryngeal discomfort				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Loss of smell				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nasal congestion				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nasal discharge				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nasal obstruction				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain throat				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Persistent dry cough				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Phlegm				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Productive cough				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rhinorrhea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Runny nose				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Shortness of breath				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Sore throat				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sore throat NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Wheezes			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Crying			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Feeling down			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Feeling irritated			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Low mood			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Memory impaired			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Panic attack			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Investigations			
Abnormal LFTs			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Alanine aminotransferase abnormal NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Alanine aminotransferase increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
ALP increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Arthrocentesis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Bilirubin elevated				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Bilirubin increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Blood neutrophils abnormal				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Blood sugar decreased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cholesterol high				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cholesterol levels raised				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cholesterol total increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Creatinine increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
LFTs raised				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Liver function tests abnormal NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Liver function tests raised				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Lymphocyte count low				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
MCV abnormal				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Neutrophil count low				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Neutrophils reduced				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Platelet count low				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Raised liver enzymes				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Serum calcium				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Transaminase glutamic-pyruvic increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Transaminitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Urine abnormal NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Urine culture positive			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vitamin D low			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Weight gain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ankle sprain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blister rupture			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Broken elbow			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cat scratch				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fall				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Falling				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Falling down				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Finger injury				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fracture of anatomical neck of humerus, closed				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Golfer's elbow				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Insect bite NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Laceration of finger				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Laceration of leg				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Mosquito bite				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Muscle strain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Perforated eardrum			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rash at site of injection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Sprain of interphalangeal (joint) of hand			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Superficial injury of hand(s) except finger(s) alone			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Wrong injection technique			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Chest tightness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Fibrillation atrial			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Heart fluttering			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Palpitation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tachycardia NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Aura			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Carpal tunnel syndrome			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Faintness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Headache temporal			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Loss of sensation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Migraine			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Migraine type headaches			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

R sciatica			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tremor of hands			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Leucopenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Leukopenia NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Neutropenia aggravated			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Swollen lymph nodes			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear ache			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ear disorder NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Otitis			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eye disorders			
Bloodshot eye			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Decreased night vision			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Degeneration macular			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dry eyes			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Floaters in eye			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gritty eyes			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Near vision disturbance			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Panuveitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Red eye			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
bdomincal hernia NOS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain generalised			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Abdominal pain lower			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Acid indigestion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Appendicitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blistering of mouth			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Bloating			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Burning mouth syndrome			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Churning of stomach			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Constipation			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dental abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dental disorder NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Diarrhoea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Diarrhoea NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dry mouth				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Emesis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Epigastric discomfort				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Epigastric pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Gas in stomach				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Gastritis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Increased stool frequency				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Loose bowel				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Loose stools				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Lower abdominal pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Mouth ulcer				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nausea alone				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nausea and vomiting				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nausea vomiting and diarrhoea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Oesophagitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Oral thrush				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Oral ulceration				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain gum				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Stomach ache				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Stomach cramps				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Stomach discomfort				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Taste changed				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tongue erythema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tongue ulceration				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tooth ache				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Toothache				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ulceration of mouth				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Upper abdominal pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Vomited				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Vomiting NOS				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Xanthogranulomatous cholecystitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Actinic keratosis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ankle ulcer			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Bruise			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Bruise of head			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eczema exacerbated			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eczema NOS			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Erythema ear				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Erythema NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Erythematous rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Erythematous skin rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Facial hair increased				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Generalised itching				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Generalized itching				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hair loss				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Herpes simplex aggravated				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hyperhidrosis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Infected nail bed				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Itching papule				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Itchy				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Itchy skin				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Localised itching				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Macular rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Malar rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nail dystrophy				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nail thinning				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Numbness in leg				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Numbness in toes				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Papular rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Paraesthesia lower limb				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Paraesthesia skin				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Petechial rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Photosensitivity (NOS)				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pins and needles				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pityriasis rosea				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Psoriasis aggravated				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rash both legs				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rash face				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rash NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rash over arms				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Red rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Redness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Redness of face				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Scalp folliculitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Shingles				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin abrasion				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin fragility				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin lesion NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin rash				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin ulcer NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin wound				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Sun blister				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Swollen lips				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tendency to bruise easily				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tinea corporis				

subjects affected / exposed occurrences (all) Tingling feet/hands subjects affected / exposed occurrences (all) Unspecified pruritic disorder subjects affected / exposed occurrences (all) Yeast infection of the skin subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Kidney stone subjects affected / exposed occurrences (all) Microscopic haematuria subjects affected / exposed occurrences (all) Urinary incontinence subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Endocrine disorders Type II diabetes mellitus subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthralgia aggravated subjects affected / exposed occurrences (all) Back pain	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Bursitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Calf pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Coccyx pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Coxalgia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cramps				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cramps of extremities				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Early morning stiffness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Fibromyalgia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Foot pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ganglion				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ganglion of joint				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Generalised joint pains				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Golfer's elbow				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Groin pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hand pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Joint inflammation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Knee lock				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Knee pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Leg cramps				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Low back pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Muscle cramps				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Muscle fatigue				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Muscle weakness lower limb				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Musculoskeletal chest pain				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Necrotising fasciitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nocturnal leg muscle cramps				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
OA hip				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Osteoarthritis shoulders				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Osteopenia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain back				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in (l) shoulder				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in (r) arm				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in (r) foot				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in (r) hip				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in (r) knee				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in (r) shoulder				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in elbow				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in hand				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in hip				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in joint, site unspecified				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in knee				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pain in leg				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Painful hand				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Painful knee				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Periarticular disorder				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Plantar fasciitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Restless legs				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rheumatoid arthritis aggravated				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rheumatoid arthritis flare up				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rheumatoid nodule				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Sciatica				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Shoulder fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Shoulder pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Stiffness				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Swan-neck deformity				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Swelling of knees				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Swelling of wrists				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Temporomandibular joint disorder NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Tenderness muscle				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Thoracic spine compression fracture				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Trigger finger				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Upper back pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Wrist arthropathy				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Wrist pain				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tendon rupture				
subjects affected / exposed	1 / 1 (100.00%)			
occurrences (all)	1			
Infections and infestations				
Abdominal abscess NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Abdominal infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Abscess dental				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Abscess hand				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Abscess of vulva, other				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Abscess on buttock				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Acute posterior ganglionitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Bladder infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Blister infected				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Boil on face				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Bronchitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Bronchitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cellulitis of toe				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Chest infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Chlamydial proctitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cold				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cold sores				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cold sores lip				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Colitis, enteritis, and gastroenteritis of presumed infectious origin				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Common cold				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Conjunctivitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Coronavirus infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Coryza				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Coryzal symptoms				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cystitis (NOS)				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ear infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ear infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Flu				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Food poisoning				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Gastroenteritis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Groin abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Head cold				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Herpes simplex				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Infected bites				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Infected finger				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Infected thumb				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Infection respiratory				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Influenza with other manifestations				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Joint abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Keratitis viral NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Labyrinthitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Laryngitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Laryngopharyngitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection viral				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
LRTI				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Nail fungal infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Otitis media NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Parainfluenzae virus infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pilonidal cyst				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Pilonidal sinus				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pneumonia NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Pyelonephritis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rhinitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Rhinopharyngitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Sepsis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Sinusitis NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin fungal infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Thigh abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Throat infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			

Thrush NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Thrush vaginal				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tooth abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tooth infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection viral NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Urinary tract infection NOS				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
URTI (upper respiratory tract infection)				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
UTI				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Vaginal candida				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Vaginal candidiasis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Viral infection NOS				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Viral pharyngitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Whooping cough			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Wound infection NEC			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Food intolerance			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypercholesterolemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypertriglyceridemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Iron deficiency			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Lipoatrophy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain in (l) hip			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2015	1. Queen Mary University of London has a new appointed Sponsor representative. 2. Addition of optional MRI scans (applicable only for patients at Barts Health Trust and Leeds Teaching Hospitals NHS Trust) for a sub-set of the main study (minimum 60, maximum 90). 3. Additional post-treatment study/call at week 54-56 to record AEs/SAEs after the trial treatment period (0-48 weeks) 4. Clarifications to existing inclusion/exclusion criteria 5. Additional pre- and post- biopsy assessment forms at visits: at visit 2 (week -3 - -1) and visit 3 and at week 16 biopsy (if done) at visit 7 (week 16) and visit 8 (week 20). 6. Clarification/expansion of safety reporting requirements (incl. pregnancy) to IMP providers (Roche/Pfizer) in line with contractual agreements. 7. Creation of additional optional MRI scans combined PIS and ICF. 8. Additional study specific time point at Visit 10 (week 28) in line with planned peripheral blood analyses. 9. Amendment to Main study PIS 10. Additional secondary endpoint efficacy analysis endpoint added in line with Statistical Analysis Plan 11. Other changes to the protocol deemed minor
27 February 2017	Addition of two more inclusion criteria: Patients must have a minimum of 3 swollen joints – the joint selected for biopsy and a minimum of 2 from 28 joint count set, as assessed at biopsy visit AND selected joint for biopsy must be minimum grade 2 synovial thickening, as assessed at the biopsy visit. Other non-substantial changes.
05 March 2018	Changes to protocol: • Change of Sponsor representative to Dr Mays Jawad • Update to Statistician's address and job role • Page 7, 34 and 85- addition that recruitment targets will be combined for STRAP and STRAP-EU trials. • Page 44-added sentence to refer to current Rituximab SmPC for shelf life of prepared infusion solution of Rituximab. • Page 49- Clarification that a translator must be made available for non-English speaking, potential STRAP participants. This should be clearly documented in the patient notes • Page 84- removal of requirement for Sponsor to send line listings of all AEs to Roche. • Page 87- Added that data from the STRAP and STRAP-EU trials will be analysed together for all endpoints and combined and submitted as one clinical study report at the end of the trial (both EudraCT numbers will be referenced in the report). • Page 91- the DMEC will review both STRAP and STRAP-EU data. • Removal of reference to R4RA trial as this has now finished recruitment (patients were previously able to go on to the R4RA trial if they were a non-responder to etanercept at week 16). Also: -SmPCs have recently been updated and submitted with this amendment - Addition of one new Trust within the UK (NHS Lothian Trust).
27 November 2018	1. Change of follow up period from 48 weeks to 24 weeks for patients recruited from January 2019 onwards. 2. Minor correction to sample size 3. GDPR updates to patient information sheet 4. Other minor corrections/clarifications to the PIS, consent form and end of trial letter 5. Update to sponsor e-mail address

13 March 2020	• Integration of RNA-seq molecular analysis into the original biopsy histopathology classification method • 4 exploratory endpoints (week 16 timepoint) moved to secondary endpoints • Modification to exploratory endpoints • Removal of RAMRIQ analysis • Roche has changed the legal representation from UK to Germany. The Marketing Authorization Holder has been changed from Roche Registration Ltd. Welwyn UK to Roche Registration GmbH (RRG), Grenzach, Germany. • The end of study definition changed from 6 months to 12 months after LPLV. • Reference Safety Information has been updated for Etanercept and Tocilizumab

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported