



## Clinical trial results:

### Addition of Rituximab to Leflunomide in patients with active rheumatoid arthritis

#### Summary

EudraCT number	2009-015950-39
Trial protocol	DE
Global end of trial date	17 December 2015

#### Results information

Result version number	v1 (current)
This version publication date	11 November 2021
First version publication date	11 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	FFM07-Rtx-Lef
-----------------------	---------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01244958
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Goethe-University Frankfurt
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt am Main, Germany, 6
Public contact	Prof. Dr. Harald Burkhardt, Department of Rheumatology University Hospital Goethe-University of Frankfurt, 0049 69 6301 7302, Harald.Burkhardt@kgu.de
Scientific contact	Prof. Dr. Harald Burkhardt, Department of Rheumatology University Hospital Goethe-University of Frankfurt, 0049 69 6301 7302, Harald.Burkhardt@kgu.de

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	15 December 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Part I

To determine the efficacy and safety at week 24 of rituximab treatment of 1000 mg i.v. versus placebo when used on top of leflunomide in patients with active rheumatoid arthritis that currently have an inadequate response to leflunomide

- Proportion of patients with an ACR 50 response at week 24.

Part II

To determine the efficacy at week 52 of rituximab treatment of two times 1000 mg vs. two times 500 mg rituximab in weeks 24 and 26 respectively in patients who completed Part I and were treated in Part I with 2x1000mg rituximab.

- Mean of DAS28 at week 52

Protection of trial subjects:

Patients who have had an initial response to IMP < 0.6 (DAS28) or less than 20% improvement in both TJC and SJC will receive "rescue treatment" ("standard of care") between week 16 and week 24. "Rescue" treatment with any "standard of care treatment", is at the discretion of the treating investigator.

Background therapy:

All patients will receive concomitant leflunomide 10-20 mg / day at a stable dose as prescribed by the treating physician and in accordance with the local label. In case of toxicity due to leflunomide a reduction to not less than 10 mg is allowed. All patients should continue to receive any background glucocorticoids ( $\leq 10$  mg / day prednisone or equivalent) or oral nonsteroidal anti-inflammatory drugs (NSAIDs) at a stable dose.

Evidence for comparator:

comparison was to Placebo

Actual start date of recruitment	18 August 2010
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	Germany: 149
Worldwide total number of subjects	149
EEA total number of subjects	149

Notes:

<b>Subjects enrolled per age group</b>	
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)	115
From 65 to 84 years	34
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment period from 18.08.2010 until 06.01.2014 in 47 sites in Germany

### Pre-assignment

Screening details:

189 patients were screened. Thereof 41 were screening failure due to withdrawal of informed consent (n=10), 28 that fail to meet inclusion/exclusion criteria in the period until randomization, and 3 due to other reasons. Screening period could be up to 34 before baseline visit including randomization. 149 subjects were randomized only 140 treated

### Pre-assignment period milestones

Number of subjects started	149
Number of subjects completed	140

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	other: 4

### Period 1

Period 1 title	part I
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Rituximab and PLC were blinded and not distinguishable in their vial. Measurement of B-lymphocytes concentration were not provided to investigators and project management to hinder unblinding due to rituximabs ability to deplete the B-lymphocytes

### Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

<b>Arm title</b>	Rituximab
------------------	-----------

Arm description:

Verum arm

Arm type	Experimental
Investigational medicinal product name	MabThera®
Investigational medicinal product code	EU/1/98/067/002
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Infusion on day 1 and 14 - Part I  
two times 1000mg - Part I

<b>Arm title</b>	Control
------------------	---------

Arm description:

Placebo to Rituximab

Arm type	Placebo
----------	---------

Investigational medicinal product name	placebo to rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

twice two vials of Placebo given Day 1 and Day 15

<b>Number of subjects in period 1<sup>[1]</sup></b>	Rituximab	Control
Started	93	47
Completed	75	35
Not completed	18	12
other	18	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 180 subjects were screened, 149 subjects were enrolled but only 140 were randomized and received treatment. That are the subjects treated and analysed in part I of the study.

## Period 2

Period 2 title	part II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject

Blinding implementation details:

Retreatment was consists of two vials - for the lower dosage placebo was added as second vial resulting in a 50% reduced dosage of RTX

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Retreatment 1000 _ P1

Arm description:

Retreatment with twice 1000 mg Rituximab and Placebo in Part 1 of the study

Arm type	Experimental
Investigational medicinal product name	MabThera®
Investigational medicinal product code	EU/1/98/067/002
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

two times 1000mg - Part I separated by 14 days

<b>Arm title</b>	Retreatment 500 _P2
------------------	---------------------

Arm description:

Retreatment starting at week 24 with twice 500 mg Rituximab 14 days apart and Placebo in Part 1 of the study

Arm type	Experimental
----------	--------------

Investigational medicinal product name	MabThera®
Investigational medicinal product code	EU/1/98/067/002
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

two times 500 mg - Part II

<b>Arm title</b>	Retreatment 1000 _V1
------------------	----------------------

Arm description:

Retreatment with twice 1000 mg Rituximab and Verum (RTX) in Part 1 of the study

Arm type	Retreatment
----------	-------------

No investigational medicinal product assigned in this arm

<b>Arm title</b>	Retreatment 500 _V2
------------------	---------------------

Arm description:

Retreatment starting at week 24 with twice 500 mg Rituximab 14 days apart and verum (RTX) in Part 1 of the study

Arm type	Retreatment
----------	-------------

No investigational medicinal product assigned in this arm

<b>Number of subjects in period 2<sup>[2]</sup></b>	Retreatment 1000 _P1	Retreatment 500 _P2	Retreatment 1000 _V1
Started	10	12	30
Completed	8	10	28
Not completed	2	2	2
other	2	2	2

<b>Number of subjects in period 2<sup>[2]</sup></b>	Retreatment 500 _V2
Started	30
Completed	30
Not completed	0
other	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Some of the patients did not continue the part II of the study - they switched to rescue treatment or did not want to continue the study therefore there is a discrepancy between end of part I and beginning of part II of the study

## Baseline characteristics

### Reporting groups

Reporting group title part I

Reporting group description: -

Reporting group values	part I	Total	
Number of subjects	140	140	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	57		
full range (min-max)	22 to 80	-	
Gender categorical			
Units: Subjects			
Female	104	104	
Male	36	36	
ethnic group			
Ethnical group at Screening visit			
Units: Subjects			
caucasian	138	138	
other	2	2	

## End points

### End points reporting groups

Reporting group title	Rituximab
Reporting group description:	
Verum arm	
Reporting group title	Control
Reporting group description:	
Placebo to Rituximab	
Reporting group title	Retreatment 1000 _ P1
Reporting group description:	
Retreatment with twice 1000 mg Rituximab and Placebo in Part 1 of the study	
Reporting group title	Retreatment 500 _P2
Reporting group description:	
Retreatment starting at week 24 with twice 500 mg Rituximab 14 days apart and Placebo in Part 1 of the study	
Reporting group title	Retreatment 1000 _V1
Reporting group description:	
Retreatment with twice 1000 mg Rituximab and Verum (RTX) in Part 1 of the study	
Reporting group title	Retreatment 500 _V2
Reporting group description:	
Retreatment starting at week 24 with twice 500 mg Rituximab 14 days apart and verum (RTX) in Part 1 of the study	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
all subject results are described for the mITT - Modified Intent-to-Treat Population (mITT) The modified Intent-to-treat population (mITT) was defined to include all patients who received at least one dose of study medication and where the ACR Criteria (Part I) or DAS28 (Part II) was measured at least once under study medication. This population was the basis for confirmatory testing.	

### Primary: Proportion of patients with an ACR 50 response at week 24

End point title	Proportion of patients with an ACR 50 response at week 24
End point description:	
To determine the efficacy and safety at week 24 of rituximab treatment of 2x1000 mg i.v. vs. placebo when used on top of leflunomide in patients with active rheumatoid arthritis that currently have an inadequate response to leflunomide	
End point type	Primary
End point timeframe:	
Baseline until week 24	

End point values	Rituximab	Control	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	47		
Units: number	22	7	140	



## Statistical analyses

<b>Statistical analysis title</b>	hypothesis testing
Statistical analysis description: The primary objective of Part I is to prove significant superiority in primary efficacy variable ACR50 response of arm V (LEF + 2×1000 mg Rituximab) as compared to arm P (LEF +2×PLC). i.e. the null hypothesis. H0: Prob (responder at week 24 under RTX+LEF) ≤ Prob (responder at week 24 under PLC+LEF) is to be rejected in favour of H1: Prob (responder at week 24 under RTX+LEF) > Prob (responder at week 24 under PLC+LEF) using a one-sided Cochran-Mantel Haenszel test at the 0.025 level. Types of An	
Comparison groups	Rituximab v Control
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Cochran-Mantel-Haenszel

## Primary: Mean of DAS28 at week 52

End point title	Mean of DAS28 at week 52 <sup>[1]</sup>
End point description: To determine the efficacy at week 52 of rituximab treatment of 1000 mg at week 24 and 1000 mg at week 26 i.v. vs. 500 mg rituximab at week 24 and 500 mg rituximab at week 26 in patients who completed Part I and were treated in Part I with 2x1000 mg rituximab.	
End point type	Primary
End point timeframe: week 52	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: only descriptive analysis done

End point values	Retreatment 1000 _ P1	Retreatment 500 _P2	Retreatment 1000 _V1	Retreatment 500 _V2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	30	30
Units: number				
median (inter-quartile range (Q1-Q3))	2.64 (2.09 to 4.24)	2.47 (2.26 to 3.45)	3.03 (2.32 to 3.90)	2.92 (2.16 to 3.82)

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to week 52

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.1
--------------------	------

### Reporting groups

Reporting group title	Verum Part 1
-----------------------	--------------

Reporting group description:

subjects treated in Part I with 1000 mg Rituximab (RTX)

Reporting group title	Placebo _ P
-----------------------	-------------

Reporting group description:

Subjects treated with Placebo to RTX in part I

Reporting group title	Retreatment 1000 mg _V1
-----------------------	-------------------------

Reporting group description:

subjects retreated in part II with 1000mg Rituximab and verum in part I

Reporting group title	Retreatment 1000 mg _P1
-----------------------	-------------------------

Reporting group description:

subjects retreated in part II with 1000mg Rituximab and placebo in part I

Reporting group title	Retreatment 500 mg _V2
-----------------------	------------------------

Reporting group description:

subjects retreated in part II with 500 mg Rituximab and verum in part I

Reporting group title	Retreatment 500 mg _P2
-----------------------	------------------------

Reporting group description:

subjects retreated in part II with 1000mg Rituximab and placebo in part I

Serious adverse events	Verum Part 1	Placebo _ P	Retreatment 1000 mg _V1
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 93 (20.43%)	1 / 47 (2.13%)	1 / 30 (3.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Investigation abnormal			

subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Weight decreased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric neoplasm			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Skin flap necrosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Joint dislocation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (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			
Hypertensive crisis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (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
Surgical and medical procedures			
Bunion operation			

subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Joint arthroplasty			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Angioplasty			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Intervertebral disc operation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (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
Nasal operation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (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
Nervous system disorders			
Post herpetic neuralgia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Pyrexia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (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
Device dislocation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Diarrhoea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Colitis ulcerative			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Gastritis erosive			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (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
Gastric ulcer			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (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			
Dyspnoea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Muscular weakness			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Osteochondrosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Rotator cuff syndrome			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Tendon calcification			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Osteoarthritis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall abscess			

subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Otitis media			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Urosepsis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Gastroenteritis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (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
Erysipelas			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (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
Metabolism and nutrition disorders			
Arthropathy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Retreatment 1000 mg _P1	Retreatment 500 mg_V2	Retreatment 500 mg_P2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	3 / 30 (10.00%)	3 / 12 (25.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0

Investigations			
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Investigation abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric neoplasm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Skin flap necrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Joint dislocation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			



subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Surgical and medical procedures</b>			
Bunion operation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Joint arthroplasty			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Angioplasty			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Intervertebral disc operation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Nasal operation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Nervous system disorders</b>			
Post herpetic neuralgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>General disorders and administration site conditions</b>			
Impaired healing			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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

Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (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
Device dislocation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Colitis ulcerative			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Gastritis erosive			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Gastric ulcer			

subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Osteochondrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Tendon calcification			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (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
Osteoarthritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Infections and infestations</b> <b>Abdominal wall abscess</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	0 / 12 (0.00%) 0 / 0 0 / 0
<b>Otitis media</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	0 / 12 (0.00%) 0 / 0 0 / 0
<b>Urosepsis</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	0 / 12 (0.00%) 0 / 0 0 / 0
<b>Gastroenteritis</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	0 / 12 (0.00%) 0 / 0 0 / 0
<b>Respiratory tract infection</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	0 / 12 (0.00%) 0 / 0 0 / 0
<b>Erysipelas</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	1 / 12 (8.33%) 1 / 1 0 / 0
<b>Metabolism and nutrition disorders</b> <b>Arthropathy</b> subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 10 (0.00%) 0 / 0 0 / 0	0 / 30 (0.00%) 0 / 0 0 / 0	0 / 12 (0.00%) 0 / 0 0 / 0

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

Non-serious adverse events	Verum Part 1	Placebo _ P	Retreatment 1000 mg _V1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 93 (74.19%)	35 / 47 (74.47%)	22 / 30 (73.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gastric neoplasm			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Haemangioma of liver			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 93 (11.83%)	5 / 47 (10.64%)	2 / 30 (6.67%)
occurrences (all)	14	9	3
Hypotension			
subjects affected / exposed	2 / 93 (2.15%)	1 / 47 (2.13%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Haematoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Hypertensive crisis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	1 / 93 (1.08%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Peripheral venous disease			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Arterial occlusive disease			

subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Surgical and medical procedures			
Bunion operation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dental care			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc operation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nasal operation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Joint arthroplasty			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Synovectomy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Angioplasty			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 93 (2.15%)	2 / 47 (4.26%)	2 / 30 (6.67%)
occurrences (all)	2	2	2
Chills			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Impaired healing			

subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 93 (0.00%)	3 / 47 (6.38%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Peripheral swelling			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	2 / 93 (2.15%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Device dislocation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Death			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Feeling hot			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Device breakage			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Hypersensitivity subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Reproductive system and breast disorders			
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
menorrhagia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Amenorrhoea subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Postmenopausal haemorrhage subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Ovarian cyst subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 2	1 / 47 (2.13%) 1	1 / 30 (3.33%) 1
Cough subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	0 / 47 (0.00%) 0	1 / 30 (3.33%) 1
Throat irritation subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Rales subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Respiratory disorder			



subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Sputum discoloured subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	1 / 30 (3.33%) 1
Emphysema subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 3	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 2	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Enzyme level increased subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	1 / 30 (3.33%) 1
Transaminases increased subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	2 / 47 (4.26%) 2	2 / 30 (6.67%) 2
Blood creatine increased subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	2 / 30 (6.67%) 2
Bacterial test subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
White blood cell count increased			

subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	2
Weight decreased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Investigation abnormal			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Laboratory test abnormal			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Tendon rupture			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Skin flap necrosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 93 (1.08%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Traumatic haematoma			
subjects affected / exposed	2 / 93 (2.15%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Joint dislocation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Upper limb fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Ulna fracture			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Excoriation subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Muscle rupture subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Congenital, familial and genetic disorders Anomalous arrangement of pancreaticobiliary duct subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Tachycardia paroxysmal subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Angina pectoris subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	1 / 30 (3.33%) 1
Bradycardia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Nervous system disorders Syncope subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Post herpetic neuralgia subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 3	1 / 47 (2.13%) 1	1 / 30 (3.33%) 1

Carpal tunnel syndrome subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	2 / 47 (4.26%) 2	0 / 30 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 4	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Cervicobrachial syndrome subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	1 / 30 (3.33%) 1
Dizziness subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	2 / 47 (4.26%) 3	0 / 30 (0.00%) 0
Cubital tunnel syndrome subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Restless legs syndrome subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Blood and lymphatic system disorders Thrombocytosis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Anaemia			

subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Eosinopenia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Anaemia folate deficiency			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 93 (1.08%)	1 / 47 (2.13%)	1 / 30 (3.33%)
occurrences (all)	2	1	2
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Maculopathy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Presbyopia			

subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Gastrointestinal disorders			
Gastric disorder			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	8 / 93 (8.60%)	7 / 47 (14.89%)	2 / 30 (6.67%)
occurrences (all)	9	8	2
Gastric ulcer			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Crohn's disease			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Nausea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Colitis ulcerative			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastritis erosive			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Liver disorder			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Cholestasis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Cholelithiasis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Hepatic steatosis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			



Skin lesion			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Dermatitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 93 (3.23%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Eczema			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Photosensitivity reaction			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Vitiligo			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	2 / 93 (2.15%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pruritus generalised			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1

Alopecia			
subjects affected / exposed	1 / 93 (1.08%)	2 / 47 (4.26%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Acne			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	2
Skin plaque			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dandruff			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Glycosuria			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Renal cyst			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Incontinence			

subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Leukocyturia subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	1 / 30 (3.33%) 1
Dysuria subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Endocrine disorders			
Goitre subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Myxoedema subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	0 / 47 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	1 / 47 (2.13%) 1	1 / 30 (3.33%) 1
Arthralgia subjects affected / exposed occurrences (all)	3 / 93 (3.23%) 3	2 / 47 (4.26%) 2	0 / 30 (0.00%) 0
Osteoarthritis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	1 / 47 (2.13%) 2	0 / 30 (0.00%) 0
Rheumatoid arthritis subjects affected / exposed occurrences (all)	9 / 93 (9.68%) 9	2 / 47 (4.26%) 2	0 / 30 (0.00%) 0
Bursitis subjects affected / exposed occurrences (all)	1 / 93 (1.08%) 1	1 / 47 (2.13%) 1	0 / 30 (0.00%) 0
Osteopenia			

subjects affected / exposed	2 / 93 (2.15%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Spinal pain			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Sacroiliitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Synovial cyst			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Osteochondrosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Enthesopathy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Rotator cuff syndrome			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tendon calcification			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tenosynovitis			

subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Arthropathy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	1 / 93 (1.08%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Joint swelling			
subjects affected / exposed	1 / 93 (1.08%)	2 / 47 (4.26%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Osteonecrosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Joint effusion			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 93 (11.83%)	6 / 47 (12.77%)	7 / 30 (23.33%)
occurrences (all)	12	6	9
Gastroenteritis			
subjects affected / exposed	2 / 93 (2.15%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Herpes zoster			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1

Cystitis			
subjects affected / exposed	3 / 93 (3.23%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	5	0	0
Urinary tract infection			
subjects affected / exposed	8 / 93 (8.60%)	2 / 47 (4.26%)	2 / 30 (6.67%)
occurrences (all)	9	2	2
Paronychia <sup>1</sup>			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 93 (3.23%)	2 / 47 (4.26%)	1 / 30 (3.33%)
occurrences (all)	3	2	2
Oral herpes			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Abdominal wall abscess			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	4 / 93 (4.30%)	2 / 47 (4.26%)	5 / 30 (16.67%)
occurrences (all)	5	2	6
Rhinitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Pulpitis dental			
subjects affected / exposed	3 / 93 (3.23%)	1 / 47 (2.13%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Fungal skin infection			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	2 / 93 (2.15%)	2 / 47 (4.26%)	2 / 30 (6.67%)
occurrences (all)	5	2	2
Febrile infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Erysipelas			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Localised infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Breast abscess			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Acute sinusitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Urosepsis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
lung infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 93 (0.00%)	2 / 47 (4.26%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Erythema migrans			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Conjunctivitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Arthritis infective			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Onychomycosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Lymphangitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 93 (2.15%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Hypokalaemia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			



subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Glucose tolerance impaired			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Vitamin B complex deficiency			
subjects affected / exposed	0 / 93 (0.00%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 47 (2.13%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 47 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

<b>Non-serious adverse events</b>	Retreatment 1000 mg_P1	Retreatment 500 mg_V2	Retreatment 500 mg_P2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	21 / 30 (70.00%)	10 / 12 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastric neoplasm			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Haemangioma of liver subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 30 (3.33%) 1	1 / 12 (8.33%) 1
Hypotension subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	1 / 12 (8.33%) 1
Haematoma subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Hypertensive crisis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Lymphoedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 2	0 / 12 (0.00%) 0
Peripheral venous disease subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Flushing subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Arterial occlusive disease subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Surgical and medical procedures			
Bunion operation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Dental care			

subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc operation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Nasal operation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Joint arthroplasty			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Synovectomy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Angioplasty			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Chills			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Impaired healing			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			

subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Device dislocation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Death			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Device breakage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
menorrhagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Amenorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ovarian cyst			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 10 (10.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Throat irritation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sputum discoloured			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Emphysema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Enzyme level increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Transaminases increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Blood creatine increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Bacterial test subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Weight decreased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Investigation abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Weight increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Laboratory test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urine analysis abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fall			

subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Foot fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tendon rupture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin flap necrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Traumatic haematoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Joint dislocation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Upper limb fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ulna fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Excoriation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Muscle rupture			



subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Congenital, familial and genetic disorders Anomalous arrangement of pancreaticobiliary duct subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Tachycardia paroxysmal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Angina pectoris subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Nervous system disorders Syncope subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Post herpetic neuralgia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Carpal tunnel syndrome subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Migraine			

subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cubital tunnel syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Eosinopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Anaemia folate deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Maculopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Presbyopia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Gastric disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	2 / 10 (20.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Gastric ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Crohn's disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Colitis ulcerative			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastritis erosive			

subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Liver disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cholestasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cholelithiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hepatic steatosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			

subjects affected / exposed	0 / 10 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 10 (0.00%)	2 / 30 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin plaque			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eczema asteatotic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dandruff			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Glycosuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Incontinence			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Leukocyturia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Myxoedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rheumatoid arthritis			
subjects affected / exposed	1 / 10 (10.00%)	3 / 30 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	4	1
Bursitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			



subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sacroiliitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Synovial cyst			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Osteochondrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Enthesopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tendon calcification			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tenosynovitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Arthropathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Joint swelling			

subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Osteonecrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Joint effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 10 (20.00%)	13 / 30 (43.33%)	2 / 12 (16.67%)
occurrences (all)	2	14	2
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Paronychia <sup>1</sup>			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 30 (3.33%) 1	1 / 12 (8.33%) 2
Oral herpes subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Abdominal wall abscess subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Pulpitis dental subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 30 (6.67%) 2	0 / 12 (0.00%) 0
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Febrile infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	0 / 12 (0.00%) 0
Erysipelas subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 30 (0.00%) 0	1 / 12 (8.33%) 1
Localised infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0
Breast abscess subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	0 / 12 (0.00%) 0

Otitis media			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Acute sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urosepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
lung infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Erythema migrans			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Tonsillitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Arthritis infective			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lymphangitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			

subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vitamin B complex deficiency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 30 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2011	Patients with anti-TNF-inhibitor pre-treatment to be allowed
07 May 2012	Protocol was to be amended due to update in safety information to mabthera
16 September 2013	Due to insufficient recruitment sample size was adjusted
26 January 2015	Changes in data management procedures to be updated in protocol

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33738492>