



Clinical trial results:

A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Rilonacept for the Prophylaxis of Gout Flares During the Initiation of Allopurinol Therapy

Summary

EudraCT number	2008-007762-39
Trial protocol	DE
Global end of trial date	17 December 2010

Results information

Result version number	v1
This version publication date	31 March 2017
First version publication date	31 March 2017

Trial information

Trial identification

Sponsor protocol code	IL1T-GA-0816
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00958438
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: PRE-SURGE 2

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 10591
Public contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials information, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of 160 mg and 80 mg of weekly subcutaneous (SC) Rilonacept therapy compared to placebo in the prophylaxis of flares in subjects with intercritical gout initiating therapy with allopurinol.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

Subjects received a daily dose of allopurinol 300 mg from Day 1 to the end of the follow-up period. Dose was increased, if needed, every 2 weeks in 100 mg increments to a maximum dose of 800 mg per day until the target serum uric acid level (<6.0 mg/dL) was achieved.

Evidence for comparator: -

Actual start date of recruitment	07 March 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Indonesia: 12
Country: Number of subjects enrolled	South Africa: 186
Country: Number of subjects enrolled	Taiwan: 12
Worldwide total number of subjects	248
EEA total number of subjects	25

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)	213
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 57 study sites in European Union (EU) and rest of the world between 7 March 2009 and 17 December 2010. A total of 471 subjects were screened in the study.

Pre-assignment

Screening details:

Out of 471 subjects, 248 were randomized and treated in the study. Subjects were randomized in 1:1:1 ratio to receive Placebo or Rilonacept 80 mg or Rilonacept 160 mg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Two subcutaneous injections of Placebo (for Rilonacept) as a loading dose on Day 1 followed by a single injection once a week (qw) from Week 1 to Week 15.

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

Dosage and administration details:

Subcutaneous injection in left and right upper arm, the left and right abdomen, and the left and right thigh.

Arm title	Rilonacept 80 mg
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Arm description:

Two subcutaneous injections of Rilonacept 80 mg (for a total of 160 mg) as a loading dose on Day 1, followed by a single 80 mg injection of Rilonacept qw from Week 1 to Week 15.

Arm type	Experimental
Investigational medicinal product name	Rilonacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection in left and right upper arm, the left and right abdomen, and the left and right thigh.

Arm title	Rilonacept 160 mg
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Arm description:

Two subcutaneous injections of Rilonacept 160 mg (for a total of 320 mg) as a loading dose on Day 1, followed by a single 160 mg injection of Rilonacept qw from Week 1 to Week 15.

Arm type	Experimental
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Investigational medicinal product name	Rilonacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection in left and right upper arm, the left and right abdomen, and the left and right thigh.

Number of subjects in period 1	Placebo	Rilonacept 80 mg	Rilonacept 160 mg
Started	82	82	84
Completed	72	72	78
Not completed	10	10	6
Consent withdrawn by subject	4	2	1
Physician decision	1	-	1
Adverse Event	-	3	-
Other than specified	2	3	2
Protocol deviation	3	2	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Two subcutaneous injections of Placebo (for Rilonacept) as a loading dose on Day 1 followed by a single injection once a week (qw) from Week 1 to Week 15.	
Reporting group title	Rilonacept 80 mg
Reporting group description:	
Two subcutaneous injections of Rilonacept 80 mg (for a total of 160 mg) as a loading dose on Day 1, followed by a single 80 mg injection of Rilonacept qw from Week 1 to Week 15.	
Reporting group title	Rilonacept 160 mg
Reporting group description:	
Two subcutaneous injections of Rilonacept 160 mg (for a total of 320 mg) as a loading dose on Day 1, followed by a single 160 mg injection of Rilonacept qw from Week 1 to Week 15.	

Reporting group values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg
Number of subjects	82	82	84
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	51.7	52.6	49
standard deviation	± 12.87	± 11.47	± 11.77
Gender categorical			
Units: Subjects			
Female	5	5	7
Male	77	77	77
Race			
Units: Subjects			
Asian	29	23	30
Black or African American	10	14	10
White	43	45	44
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	82	82	84
Hispanic or Latino	0	0	0

Reporting group values	Total		
Number of subjects	248		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	17		
Male	231		
Race Units: Subjects			
Asian	82		
Black or African American	34		
White	132		
Ethnicity Units: Subjects			
Not Hispanic or Latino	248		
Hispanic or Latino	0		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Two subcutaneous injections of Placebo (for Rilonacept) as a loading dose on Day 1 followed by a single injection once a week (qw) from Week 1 to Week 15.	
Reporting group title	Rilonacept 80 mg
Reporting group description: Two subcutaneous injections of Rilonacept 80 mg (for a total of 160 mg) as a loading dose on Day 1, followed by a single 80 mg injection of Rilonacept qw from Week 1 to Week 15.	
Reporting group title	Rilonacept 160 mg
Reporting group description: Two subcutaneous injections of Rilonacept 160 mg (for a total of 320 mg) as a loading dose on Day 1, followed by a single 160 mg injection of Rilonacept qw from Week 1 to Week 15.	

Primary: Number of Gout Flares Per Subject Assessed From Day 1 to Day 113 (Week 16)

End point title	Number of Gout Flares Per Subject Assessed From Day 1 to Day 113 (Week 16) ^[1]
End point description: Gout flare was defined as acute articular pain typical of a gout attack that required treatment with an anti-inflammatory therapeutic; had at least 3 of the following 4 signs or symptoms: joint swelling, tenderness, redness, and pain; and with at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare. Number of gout flares per participant was reported for this endpoint. Full analysis set (FAS) that included all randomized subjects who received any study medication, and was based on the treatment allocated by the Interactive voice response system (IVRS) at randomization (as randomized). Here, number of subjects analyzed = subjects with available data for this endpoint.	
End point type	Primary
End point timeframe: Day 1 to Day 133 (Week 16)	

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	82	83	
Units: Gout flares				
arithmetic mean (standard deviation)	1.23 (± 1.57)	0.35 (± 0.67)	0.34 (± 0.86)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Modified Gout Flares per Subject From Day 1 to Day 113 (Week 16)

End point title	Number of Modified Gout Flares per Subject From Day 1 to Day 113 (Week 16)
End point description: Modified Gout Flare was defined using modified definition of a gout flare as subject-reported articular pain typical of a gout attack that was deemed to require treatment with anti-inflammatory therapy. Number of modified gout flares per subject were reported for this endpoint. Analysis was performed on FAS population. Here, number of subjects analyzed= subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe: Day 1 to Day 113 (Week 16)	

End point values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	82	83	
Units: modified gout flares				
arithmetic mean (standard deviation)	1.51 (± 1.87)	0.62 (± 1.32)	0.48 (± 0.99)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at Least one Flare From Day 1 to Day 113 (Week 16)

End point title	Percentage of Subjects with at Least one Flare From Day 1 to Day 113 (Week 16)
End point description: Gout flare was defined as acute articular pain typical of a gout attack that required treatment with an anti-inflammatory therapeutic; had at least 3 of the following 4 signs or symptoms: joint swelling, tenderness, redness, and pain; and with at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare. Percentage of subjects with at least one gout flare was reported in this endpoint. Analysis was performed on FAS population.	
End point type	Secondary
End point timeframe: Day 1 to Day 113 (Week 16)	

End point values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	82	84	
Units: Percentage of Participants				
number (not applicable)	56.1	25.6	20.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With at Least two Flares From Day 1 to Day 113 (Week 16)

End point title	Percentage of Subjects With at Least two Flares From Day 1 to Day 113 (Week 16)
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End point description:

Gout flare was defined as acute articular pain typical of a gout attack that required treatment with an anti-inflammatory therapeutic; had at least 3 of the following 4 signs or symptoms: joint swelling, tenderness, redness, and pain; and with at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare. Percentage of subjects with at least two gout flares was reported in this endpoint.

End point type	Secondary
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End point timeframe:

Day 1 to Day 113 (Week 16)

End point values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	82	84	
Units: Percentage of Subjects				
number (not applicable)	32.9	8.5	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gout Flare Days per Subject From Day 1 to Day 113 (Week 16)

End point title	Number of Gout Flare Days per Subject From Day 1 to Day 113 (Week 16)
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End point description:

Gout flare was defined as acute articular pain typical of a gout attack that required treatment with an anti-inflammatory therapeutic; had at least 3 of the following 4 signs or symptoms: joint swelling, tenderness, redness, and pain; and with at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare. Number of gout flare days per subject was reported for this endpoint. Analysis was performed on FAS population. Here, number of subjects analyzed= subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Day 1 to Day 113 (Week 16)

End point values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	82	83	
Units: gout flare days				
arithmetic mean (standard deviation)	11.7 (± 21)	4.3 (± 17.13)	1.86 (± 5.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gout Flare Days with the Subject's Pain Score of 5 or More (From Daily Diary) per Subject From Day 1 to Day 113 (Week 16)

End point title	Number of Gout Flare Days with the Subject's Pain Score of 5 or More (From Daily Diary) per Subject From Day 1 to Day 113 (Week 16)
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End point description:

Subjects were asked to complete a telephone diary by calling the IVRS daily beginning at the baseline visit (Day 1) through the follow-up visit (Day 141) and reported their general well-being, gout symptoms, and weekly study drug administrations. At the onset of pain from a gout flare, subjects were to answer additional diary questions regarding their gout flare and had to continue daily flare assessments until they reported the flare had ended. If a flare occurred just prior to the follow-up visit (Day 141), subjects were to continue completing the daily diary until the flare resolved. Gout flare pain was assessed on a scale from 0 to 10 (with 0=no pain and 10=severe pain) within the past 24 hours. Analysis was performed on FAS population. Here, number of subjects analyzed= subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Day 1 to Day 113 (Week 16)

End point values	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	82	83	
Units: gout flare days				
arithmetic mean (standard deviation)	4.28 (± 7.67)	1.67 (± 8.43)	0.88 (± 2.66)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 20) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (time from the administration of first dose of study drug up to 35 days after the last dose of study drug).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Two subcutaneous injections of Placebo (for Rilonacept) as a loading dose on Day 1 followed by a single injection qw from Week 1 to Week 15.

Reporting group title	Rilonacept 80 mg
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Reporting group description:

Two subcutaneous injections of Rilonacept 80 mg (for a total of 160 mg) as a loading dose on Day 1, followed by a single 80 mg injection of Rilonacept qw from Week 1 to Week 15.

Reporting group title	Rilonacept 160 mg
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Reporting group description:

Two subcutaneous injections of Rilonacept 160 mg (for a total of 320 mg) as a loading dose on Day 1, followed by a single 160 mg injection of Rilonacept qw from Week 1 to Week 15.

Serious adverse events	Placebo	Rilonacept 80 mg	Rilonacept 160 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 82 (4.88%)	5 / 82 (6.10%)	3 / 84 (3.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 84 (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
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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
Fall			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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
Post procedural complication			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 84 (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
Road traffic accident			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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 rupture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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
Upper limb fracture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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
Hypertension			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	0 / 82 (0.00%)	0 / 82 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 82 (0.00%)	0 / 82 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Umbilical hernia, obstructive			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 84 (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 and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 82 (0.00%)	0 / 82 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 84 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 84 (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
Pyelonephritis			

subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 84 (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

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

Non-serious adverse events	Placebo	Rilonacept 80 mg	Rilonacept 160 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 82 (14.63%)	20 / 82 (24.39%)	20 / 84 (23.81%)
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 82 (2.44%)	6 / 82 (7.32%)	4 / 84 (4.76%)
occurrences (all)	3	6	5
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 82 (2.44%)	5 / 82 (6.10%)	1 / 84 (1.19%)
occurrences (all)	2	6	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 82 (0.00%)	6 / 82 (7.32%)	7 / 84 (8.33%)
occurrences (all)	0	21	20
Infections and infestations			
Influenza			
subjects affected / exposed	6 / 82 (7.32%)	5 / 82 (6.10%)	5 / 84 (5.95%)
occurrences (all)	6	5	5
Nasopharyngitis			
subjects affected / exposed	2 / 82 (2.44%)	3 / 82 (3.66%)	6 / 84 (7.14%)
occurrences (all)	2	6	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2009	- Removed the collection of blood samples for proteomics and RNA and information regarding analyses of such samples; - Clarified requirement for collection of study drug injection volume by the subject; - Indicated that this was a phase 3 trial; - Made administrative clarifications and updates to the protocol.
14 October 2009	- Specified that subjects with a purified protein derivative (PPD) tuberculin skin test of ≥ 10 mm in-duration were ineligible for the study; - Specified that human immuno-deficiency virus (HIV) testing was required for sites in South Africa. - Made miscellaneous administrative clarifications and updates to the protocol.
30 November 2009	- Specified that subjects with a history of inadequate urate-lowering response to allopurinol, history of allergic reaction, contraindication, or intolerance to allopurinol, were ineligible for the study; - Specified that subjects who had an absolute or relative contraindication to both naproxen and oral glucocorticoids (e.g., prednisolone, prednisone) were ineligible for the study; - Specified stopping rules for discontinuation of study drug; - Clarified that mandatory immediate termination from the study was required if a subject becomes pregnant during the study; - Made administrative corrections to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported