Clinical trial results:
Efficacy and safety of CD5024 1% cream versus metronidazole 0.75% cream in subjects with papulopustular rosacea over 16 weeks treatment, followed by a 36-week extension period

These results have been removed from public view whilst they are reviewed and may need to be corrected before being returned to public view

Summary

EudraCT number	2011-004791-11
Trial protocol	CZ GB DE HU BG
Global end of trial date	19 December 2013

Results information

Result version number	v1 (current)
This version publication date	16 March 2016
First version publication date	16 March 2016

Trial information

Trial identification

Sponsor protocol code	RD.03.SPR.40173CZ

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Galderma R&D SNC
Sponsor organisation address	Les Templiers, 2400 Route des Colles, BIOT, France,
Public contact	CTA Coordinator, Galderma R&D SNC, +33 (0)493-95-70-85, cta.coordinator@galderma.com
Scientific contact	CTA Coordinator, Galderma R&D SNC, +33 (0)493-95-70-85, cta.coordinator@galderma.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	21 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Period A:
To compare efficacy and safety of CD5024 1% cream applied once daily versus metronidazole 0.75% cream applied twice daily in subjects with papulopustular rosacea after 16-week topical treatment.
Period B:
To compare, for subjects initially successfully treated by 16 weeks treatment, CD5024 1% cream versus metronidazole 0.75% cream during a 36-week extension period by assessing:
- The time of first relapse,
- The relapse rate,
- And the number of days free of treatment
The safety objective of this study for Period A and Period B was to assess the overall safety of CD5024 1% Cream applied once daily up to 16 weeks during Period A and up to 28 weeks during Period B compared to Metronidazole 0.75% Cream.

Protection of trial subjects:

Safety was documented by recording AEs, rosacea signs and symptoms, physical examinations, and vital signs and blood hematology and biochemistry on an ongoing basis.
Furthermore, an IDMC was established in order to ensure subject safety by reviewing any hematology laboratory results or SAE reports that they received after subject randomization.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2012
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	Romania: 109
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Ukraine: 60
Country: Number of subjects enrolled	Poland: 114
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Czech Republic: 80
Country: Number of subjects enrolled	France: 67
Country: Number of subjects enrolled	Germany: 226
Country: Number of subjects enrolled	Hungary: 160

Worldwide total number of subjects	962
EEA total number of subjects	828

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)	792
From 65 to 84 years	168
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 1034 subjects were screened in 64 centers in 10 countries (Bulgaria, Czech Republic,France, Germany, Great-Britain, Hungary, Poland, Romania, Russia, and Ukraine), among which 962 were randomized to receive Ivermectin 1% Cream (N=478) or Metronidazole 0.75% Cream (N=484).

Pre-assignment

Screening details:

In Period A, 962 subjects were randomized to receive Ivermectin 1% Cream (N=478) or Metronidazole 0.75% Cream (N=484) in 64 centers .
In total, 762 subjects were eligible for entering in Period B and 757 out of these subjects decided to continue in Period B: 399 subjects in the Ivermectin 1% Cream group and 358 subjects in the Metronidazole 0.75%

Pre-assignment period milestones

Number of subjects started	962
Number of subjects completed	962

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivermectin 1% cream

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ivermectin 1% Cream
Investigational medicinal product code	CD5024
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

one small pea size applied on right and left cheeks, forehead, chin and nose) at bedtime

Arm title	Metronidazole 0.75% Cream

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Metronidazole 0.75% Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Approximately one small pea size amount per facial region (right and left cheeks, forehead, chin and nose).
Twice daily at morning and bedtime
7 days a week

Investigational medicinal product name	Ivermectin 1% cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Approximately one small pea size amount per facial region (right and left cheeks, forehead, chin and nose)
7 days a week
Once daily at bedtime

Notes:

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

Justification: Patients not considered blinded as difference in regimen between active controlled arm and CD5024 (BID versus QD)

Number of subjects in period 1	Ivermectin 1% cream	Metronidazole 0.75% Cream
Started	478	484
Completed	446	456
Not completed	32	28
Consent withdrawn by subject	21	9
Adverse event, non-fatal	6	13
Pregnancy	1	1
other	-	1
Lost to follow-up	3	2
Protocol deviation	1	2

Period 2

Period 2 title	Period B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[2]

Blinding implementation details:

Randomisation was the same as period A

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivermectin 1% cream

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ivermectin 1% Cream
Investigational medicinal product code	CD5024
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details: one small pea size applied on right and left cheeks, forehead, chin and nose) at bedtime

Arm title	Metronidazole 0.75% Cream
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Ivermectin 1% Cream
Investigational medicinal product code	CD5024
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use
Dosage and administration details: one small pea size applied on right and left cheeks, forehead, chin and nose) at bedtime	
Investigational medicinal product name	Ivermectin 1% Cream
Investigational medicinal product code	CD5024
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use
Dosage and administration details: one small pea size applied on right and left cheeks, forehead, chin and nose) at bedtime	
Investigational medicinal product name	Metronidazole 0.75% Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use
Dosage and administration details: approximately one small pea size amount per facila region (right and left cheeks, forehead, chin and nose). Twice daily at morning and bedtime. 7 days a week	

Notes:

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

Justification: Patients not considered blinded as difference in regimen between active controlled arm and CD5024 (BID versus QD)

Number of subjects in period 2[3]	Ivermectin 1% cream	Metronidazole 0.75% Cream
Started	399	358
Completed	366	326
Not completed	33	32
Consent withdrawn by subject	23	18
Adverse event, non-fatal	2	4
Pregnancy	2	1
other	2	2
Lost to follow-up	2	4
Protocol deviation	2	3

Notes:

[3] - 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: In total, 762 subjects were eligible for entering in Period B (they were considered as "success" i.e. IGA equal to 0 or 1) and 757 out of these subjects decided to continue in Period B.

Baseline characteristics

Reporting groups	
Reporting group title	Ivermectin 1% cream
Reporting group description: -	
Reporting group title	Metronidazole 0.75% Cream
Reporting group description: -	

Reporting group values	Ivermectin 1% cream	Metronidazole 0.75% Cream	Total
Number of subjects	478	484	962
Age categorical			
age			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	394	398	792
From 65-84 years	83	85	168
85 years and over	1	1	2
Age continuous			
Units: years			
arithmetic mean	51.22	51.87	
standard deviation	± 13.4	± 13.24	-
Gender categorical			
Units: Subjects			
Female	311	316	627
Male	167	168	335

End points

End points reporting groups	
Reporting group title	Ivermectin 1% cream
Reporting group description: -	
Reporting group title	Metronidazole 0.75% Cream
Reporting group description: -	
Reporting group title	Ivermectin 1% cream
Reporting group description: -	
Reporting group title	Metronidazole 0.75% Cream
Reporting group description: -	

Primary: % change reduction in inflammatory lesion	
End point title	% change reduction in inflammatory lesion
End point description:	
End point type	Primary
End point timeframe:	
Inflammatory lesion counts were to be performed at Screening, Baseline, Week 3, Week 6, Week 9, Week 12, and Week 16/ ET visits.	

End point values	Ivermectin 1% cream	Metronidazole 0.75% Cream		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	484		
Units: reduction of inflammatory lesions				
number (not applicable)				
% change reduction nber of lesions	83	74		

Statistical analyses

Statistical analysis title	% change in inflammatory lesions counts ITT
Statistical analysis description:	
% change in inflammatory lesions counts ITT - LOCF	
Comparison groups	Ivermectin 1% cream v Metronidazole 0.75% Cream
Number of subjects included in analysis	962
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Primary: time to first relapse	
End point title	time to first relapse

End point description:

End point type	Primary

End point timeframe:

Time to first relapse defined as time to IGA > or = to 2

End point values	Ivermectin 1% cream	Metronidazole 0.75% Cream		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	399	358		
Units: days	115	85		

Statistical analyses

Statistical analysis title	Time to relapse (days)
Comparison groups	Ivermectin 1% cream v Metronidazole 0.75% Cream
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Logrank test

Statistical analysis title	Time to relapse (days)
Comparison groups	Metronidazole 0.75% Cream v Ivermectin 1% cream
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Logrank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The study RD.03.SPR.40173 consisted of an initial 16-week treatment period (Period A) followed by a 36-week extension period (Period B).

Adverse event reporting additional description:

The ratio subjects affected / exposed is calculated by EudraCT database and does not necessarily reflects ratios in clinical study reports taking into consideration other reporting threshold.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Ivermectin 1% cream period A
Reporting group description: -	
Reporting group title	Metronidazole 0.75% cream period A
Reporting group description: -	
Reporting group title	Ivermectin 1% cream period B
Reporting group description: -	
Reporting group title	Metronidazole 0.75% cream period B
Reporting group description: -	

Serious adverse events	Ivermectin 1% cream period A	Metronidazole 0.75% cream period A	Ivermectin 1% cream period B
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 478 (1.67%)	5 / 484 (1.03%)	10 / 399 (2.51%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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
Breast cancer			
subjects affected / exposed	0 / 478 (0.00%)	1 / 484 (0.21%)	0 / 399 (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
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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
Femoral artery occlusion			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic pregnancy			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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			
Chronic sinusitis			
subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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
Pneumonia			
subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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			
Brain herniation			

subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
whiplash injury			
subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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
Congenital, familial and genetic disorders			
Vitello-intestinal duct remnant			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: MedDRA 12			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 478 (0.00%)	1 / 484 (0.21%)	0 / 399 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic stroke			

subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 478 (0.00%)	1 / 484 (0.21%)	0 / 399 (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			
Ileus			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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
Abdominal pain			
subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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
Inguinal hernia			
subjects affected / exposed	1 / 478 (0.21%)	1 / 484 (0.21%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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 chest pain			
subjects affected / exposed	0 / 478 (0.00%)	1 / 484 (0.21%)	0 / 399 (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
Spinal column stenosis			
subjects affected / exposed	1 / 478 (0.21%)	0 / 484 (0.00%)	0 / 399 (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
Infections and infestations			
Eczema infected			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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
Paronychia			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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 tract infection bacterial			
subjects affected / exposed	0 / 478 (0.00%)	0 / 484 (0.00%)	0 / 399 (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

Serious adverse events	Metronidazole 0.75% cream period B		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 359 (3.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	2 / 359 (0.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femoral artery occlusion			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ectopic pregnancy			

subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic sinusitis			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
whiplash injury			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Vitello-intestinal duct remnant			

subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: MedDRA 12			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ischaemic stroke			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract			

subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psoriatic arthropathy			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal chest pain			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal column stenosis			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Eczema infected			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paronychia			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 359 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ivermectin 1% cream period A	Metronidazole 0.75% cream period A	Ivermectin 1% cream period B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	252 / 478 (52.72%)	262 / 484 (54.13%)	118 / 399 (29.57%)
Vascular disorders			
Hypertension			

subjects affected / exposed	6 / 478 (1.26%)	4 / 484 (0.83%)	4 / 399 (1.00%)
occurrences (all)	6	4	4
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 478 (3.14%)	11 / 484 (2.27%)	5 / 399 (1.25%)
occurrences (all)	18	17	7
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 478 (0.21%)	5 / 484 (1.03%)	4 / 399 (1.00%)
occurrences (all)	1	5	4
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 478 (1.05%)	1 / 484 (0.21%)	0 / 399 (0.00%)
occurrences (all)	6	1	0
Rhinitis			
subjects affected / exposed	2 / 478 (0.42%)	3 / 484 (0.62%)	4 / 399 (1.00%)
occurrences (all)	2	4	4
Cough			
subjects affected / exposed	3 / 478 (0.63%)	2 / 484 (0.41%)	3 / 399 (0.75%)
occurrences (all)	4	2	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 478 (0.21%)	5 / 484 (1.03%)	3 / 399 (0.75%)
occurrences (all)	1	5	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 478 (1.46%)	4 / 484 (0.83%)	6 / 399 (1.50%)
occurrences (all)	10	4	8
Arthralgia			
subjects affected / exposed	1 / 478 (0.21%)	6 / 484 (1.24%)	4 / 399 (1.00%)
occurrences (all)	1	7	4
Arthritis			
subjects affected / exposed	1 / 478 (0.21%)	1 / 484 (0.21%)	4 / 399 (1.00%)
occurrences (all)	1	1	7
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	32 / 478 (6.69%)	29 / 484 (5.99%)	37 / 399 (9.27%)
occurrences (all)	34	34	39
Influenza			
subjects affected / exposed	9 / 478 (1.88%)	10 / 484 (2.07%)	12 / 399 (3.01%)
occurrences (all)	9	10	12
Bronchitis			
subjects affected / exposed	6 / 478 (1.26%)	4 / 484 (0.83%)	4 / 399 (1.00%)
occurrences (all)	6	4	6
Upper respiratory tract infection			
subjects affected / exposed	6 / 478 (1.26%)	4 / 484 (0.83%)	1 / 399 (0.25%)
occurrences (all)	7	4	2
Oral herpes			
subjects affected / exposed	3 / 478 (0.63%)	5 / 484 (1.03%)	7 / 399 (1.75%)
occurrences (all)	3	5	8
Pharyngitis			
subjects affected / exposed	3 / 478 (0.63%)	4 / 484 (0.83%)	5 / 399 (1.25%)
occurrences (all)	3	4	5
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 478 (0.00%)	1 / 484 (0.21%)	5 / 399 (1.25%)
occurrences (all)	0	1	5
Urinary tract infection			
subjects affected / exposed	0 / 478 (0.00%)	1 / 484 (0.21%)	2 / 399 (0.50%)
occurrences (all)	0	1	2

Non-serious adverse events	Metronidazole 0.75% cream period B		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 359 (31.48%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 359 (1.95%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 359 (1.11%)		
occurrences (all)	6		

Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 1 / 359 (0.28%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 1 / 359 (0.28%) 1 2 / 359 (0.56%) 6 4 / 359 (1.11%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 0 / 359 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all)	 5 / 359 (1.39%) 6 2 / 359 (0.56%) 2 1 / 359 (0.28%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Bronchitis	 39 / 359 (10.86%) 44 6 / 359 (1.67%) 6		

subjects affected / exposed	3 / 359 (0.84%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	0 / 359 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	3 / 359 (0.84%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	6 / 359 (1.67%)		
occurrences (all)	6		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 359 (0.56%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	5 / 359 (1.39%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported