Clinical trial results:
Multicenter, randomised, double-blind clinical trial on the efficacy and safety of medicinal products containing Diclofenac in patients with actinic keratosis

Summary

EudraCT number	2014-001621-33
Trial protocol	DE
Global end of trial date	25 June 2015

Results information

Result version number	v1
This version publication date	20 July 2016
First version publication date	20 July 2016

Trial information

Trial identification

Sponsor protocol code	14-01/AK-Diclo

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dermapharm AG
Sponsor organisation address	Lil-Dagover-Ring 7, Gruenwald, Germany, 82031
Public contact	Head of Clinical Department, Dermapharm AG, 0049 08964186-0,
Scientific contact	Head of Clinical Department, Dermapharm AG, 0049 08964186-0,

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	18 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2015
Global end of trial reached?	Yes
Global end of trial date	25 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy and safety of a new diclofenac 3% gel formulation vs. the originator Solaraze (licensed) vs. vehicle in patients with actinic keratosis.

Protection of trial subjects:

There were no specific measures necessary.

Background therapy:

There was no background therapy.

Evidence for comparator:

The trial aimed to show non-inferiority with regard to the comparator in order to obtain a generic marketing authorization for the test product.

Actual start date of recruitment	23 September 2014
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: 439
Worldwide total number of subjects	439
EEA total number of subjects	439

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)	66
From 65 to 84 years	355
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

all study centers in Germany; first patient first visit: 25 September 2014; last patient last visit: 25 June 2015

Pre-assignment

Screening details:

Main criteria for inclusion:
Immunocompetent women and men ≥ 18 years of age; Diagnosis of "actinic keratosis"; treatment area of approximately 50 cm² on the face or the scalp; at least 7 delimitable target lesions with the following properties: mild to moderate clinical severity, diameter ≥ 4 mm, not hypertrophic, not massively hyperkeratotic

Period 1

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

Blinding implementation details:

All study preparations were indistinguishable in terms of appearance and were filled in white tubes of identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	DicloGel

Arm description:

Treatment arm with test product

Arm type	Experimental
Investigational medicinal product name	Diclofenac 3% gel
Investigational medicinal product code	D11AX18
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

To be rubbed in slightly on the observation area twice daily (in the morning, in the evening)

Arm title	Solaraze

Arm description:

Treatment arm with reference product

Arm type	Active comparator
Investigational medicinal product name	Solaraze
Investigational medicinal product code	D11AX18
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

To be rubbed in slightly on the observation area twice daily (in the morning, in the evening)

Arm title	Vehicle

Arm description:

Treatment arm with vehicle to test product

Arm type	Placebo

Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

To be rubbed in slightly on the observation area twice daily (in the morning, in the evening)

Number of subjects in period 1	DicloGel	Solaraze	Vehicle
Started	146	147	146
Completed	141	133	143
Not completed	5	14	3
Adverse event, serious fatal	-	4	-
Consent withdrawn by subject	2	2	-
Physician decision	-	1	-
Adverse event, non-fatal	3	5	2
Technical-logistic reasons	-	1	1
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Observation Period

Reporting group description: -

Reporting group values	Observation Period	Total	
Number of subjects	439	439	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	66	66	
From 65-84 years	355	355	
85 years and over	18	18	
Gender categorical Units: Subjects			
Female	68	68	
Male	371	371	

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

includes all patients of the safety data set who comply with the study diagnosis (according to the associated inclusion criteria) and provide the baseline value and at least one post baseline value under treatment

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

includes all patients of the ITT data set who do not exhibit any major protocol violations

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

comprises all patients who had administered the study medication at least once

Reporting group values	ITT	PP	Safety
Number of subjects	433	349	439
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	65	61	66
From 65-84 years	351	276	355
85 years and over	17	12	18
Gender categorical Units: Subjects			
Female	67	56	68
Male	366	293	371

End points

End points reporting groups

Reporting group title	DicloGel
Reporting group description: Treatment arm with test product	
Reporting group title	Solaraze
Reporting group description: Treatment arm with reference product	
Reporting group title	Vehicle
Reporting group description: Treatment arm with vehicle to test product	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: includes all patients of the safety data set who comply with the study diagnosis (according to the associated inclusion criteria) and provide the baseline value and at least one post baseline value under treatment	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: includes all patients of the ITT data set who do not exhibit any major protocol violations	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: comprises all patients who had administered the study medication at least once	

Primary: Treatment effect

End point title	Treatment effect[1]
End point description: Number (percentage) of patients with "clinical success" according to predefined criteria at end of observation period	
End point type	Primary
End point timeframe: Inclusion visit (= start of treatment) and main visit (= 30 days after end of treatment)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary goal of this trial was to show therapeutic equivalence of test to reference product. The vehicle arm served as verification of the assay sensitivity. The three end point tests had to be done separately in order to avoid the otherwise necessary adjustment of the significance levels.

End point values	DicloGel	Solaraze	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	112	111	223	
Units: Number	72	75	147	

Statistical analyses

Statistical analysis title	Analysis of efficacy
Statistical analysis description:	
equivalence test (two-sided) with 95% CI and a pre-defined equivalence interval [-0.20; 0.20]	
Comparison groups	DicloGel v Solaraze
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-0.0328
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1661
upper limit	0.1005

Other pre-specified: Superiority of Test over Vehicle

End point title	Superiority of Test over Vehicle[2]
End point description:	
Number (percentage) of patients with "clinical success" according to predefined criteria at end of observation period	
End point type	Other pre-specified
End point timeframe:	
Inclusion visit (= start of treatment) and main visit (= 30 days after end of treatment)	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis for this end point served as verification of the assay sensitivity and had to be done individually for each active preparation in accordance with CPMP/EWP/908/99.

End point values	DicloGel	Vehicle	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	141	143	284	
Units: Number	83	43	126	

Statistical analyses

Statistical analysis title	Superiority Test - Placebo
Comparison groups	DicloGel v Vehicle
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Other pre-specified: Superiority of Reference over Vehicle

End point title	Superiority of Reference over Vehicle[3]

End point description:

Number (percentage) of patients with "clinical success" according to predefined criteria at end of observation period

End point type	Other pre-specified

End point timeframe:

Inclusion visit (= start of treatment) and main visit (= 30 days after end of treatment)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis for this end point served as verification of the assay sensitivity and had to be done individually for each active preparation in accordance with CPMP/EWP/908/99.

End point values	Solaraze	Vehicle	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	133	143	276	
Units: Number	83	43	126	

Statistical analyses

Statistical analysis title	Superiority Comparator - Placebo
Comparison groups	Solaraze v Vehicle
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Inclusion visit (start of treatment) to main visit (= 30 days after end of treatment; end of observation period)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	DicloGel
Reporting group description: treatment arm with test product	
Reporting group title	Solaraze
Reporting group description: treatment arm with reference product	
Reporting group title	Vehicle
Reporting group description: treatment arm with vehicle (to test product)	

Serious adverse events	DicloGel	Solaraze	Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 146 (3.42%)	5 / 147 (3.40%)	3 / 146 (2.05%)
number of deaths (all causes)	0	4	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Colon cancer			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (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
Road traffic accident			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (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			
Aortic aneurysm			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (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
Coronary artery disease			
subjects affected / exposed	2 / 146 (1.37%)	0 / 147 (0.00%)	0 / 146 (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
Myocardial infarction			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 146 (1.37%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	DicloGel	Solaraze	Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 146 (36.99%)	52 / 147 (35.37%)	37 / 146 (25.34%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 146 (1.37%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	2	0	0
Squamous cell carcinoma of the skin			

subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	1 / 146 (0.68%)
occurrences (all)	0	1	1
Bowen's disease			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Basal cell carcinoma			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Keratoacanthoma			
subjects affected / exposed	0 / 146 (0.00%)	2 / 147 (1.36%)	0 / 146 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Varicose vein			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Lymphoedema			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	6 / 146 (4.11%)	6 / 147 (4.08%)	6 / 146 (4.11%)
occurrences (all)	6	6	6
Application site erythema			
subjects affected / exposed	13 / 146 (8.90%)	15 / 147 (10.20%)	5 / 146 (3.42%)
occurrences (all)	13	15	5
Application site eczema			
subjects affected / exposed	3 / 146 (2.05%)	3 / 147 (2.04%)	1 / 146 (0.68%)
occurrences (all)	3	3	1
Application site exfoliation			
subjects affected / exposed	7 / 146 (4.79%)	10 / 147 (6.80%)	4 / 146 (2.74%)
occurrences (all)	7	10	4
Application site pruritus			
subjects affected / exposed	5 / 146 (3.42%)	7 / 147 (4.76%)	4 / 146 (2.74%)
occurrences (all)	5	7	4
Application site haemorrhage			

subjects affected / exposed	2 / 146 (1.37%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	2	0	0
Application site erosion			
subjects affected / exposed	2 / 146 (1.37%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	2	1	0
Application site scab			
subjects affected / exposed	1 / 146 (0.68%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Application site pustules			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Application site inflammation			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Application site discomfort			
subjects affected / exposed	2 / 146 (1.37%)	1 / 147 (0.68%)	2 / 146 (1.37%)
occurrences (all)	2	1	2
Application site dysaesthesia			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Atopy			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 146 (0.68%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Prostatitis			

subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 146 (0.68%)	2 / 147 (1.36%)	0 / 146 (0.00%)
occurrences (all)	1	2	0
Pulmonary oedema			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 146 (1.37%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	2	1	0
Asthma			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Investigations			
Traumatic haematoma			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Tendon rupture			

subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Skin wound			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 146 (0.68%)	2 / 147 (1.36%)	1 / 146 (0.68%)
occurrences (all)	1	2	1
Carpal tunnel syndrome			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Eye swelling			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Eye irritation			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0

Keratitis			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Eyelid erosion			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 146 (0.68%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Actinic keratosis	Additional description: not in the treatment/ observation area		
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	6 / 146 (4.11%)	4 / 147 (2.72%)	4 / 146 (2.74%)
occurrences (all)	6	4	4
Androgenetic alopecia			
subjects affected / exposed	3 / 146 (2.05%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	3	0	1
Unguis incarnatus			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed	3 / 146 (2.05%)	2 / 147 (1.36%)	1 / 146 (0.68%)
occurrences (all)	3	2	1
Erythema			
subjects affected / exposed	3 / 146 (2.05%)	3 / 147 (2.04%)	0 / 146 (0.00%)
occurrences (all)	3	3	0
Skin irritation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Stasis dermatitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	1 / 146 (0.68%)	3 / 147 (2.04%)	1 / 146 (0.68%)
occurrences (all)	1	3	1
Rosacea			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	1 / 146 (0.68%)
occurrences (all)	0	1	1
Eczema nummular			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Hand dermatitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Intertrigo			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Renal and urinary disorders			

Urge incontinence			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	1 / 146 (0.68%)
occurrences (all)	0	1	1
Synovial cyst			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Invertebral disc disorder			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Onychomycosis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 146 (3.42%)	6 / 147 (4.08%)	3 / 146 (2.05%)
occurrences (all)	5	6	3
Eczema infected			
subjects affected / exposed	2 / 146 (1.37%)	1 / 147 (0.68%)	2 / 146 (1.37%)
occurrences (all)	2	1	2
Nasopharyngitis			
subjects affected / exposed	6 / 146 (4.11%)	5 / 147 (3.40%)	3 / 146 (2.05%)
occurrences (all)	6	5	3
Bronchitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	1	0	1
Pyoderma			
subjects affected / exposed	1 / 146 (0.68%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	1	1	0
Folliculitis			

subjects affected / exposed	1 / 146 (0.68%)	1 / 147 (0.68%)	1 / 146 (0.68%)
occurrences (all)	1	1	1
Fungal skin infection			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Urethritis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Oesophageal candidiasis			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	1 / 146 (0.68%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 146 (0.00%)	2 / 147 (1.36%)	0 / 146 (0.00%)
occurrences (all)	0	2	0
Paronychia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Pulpitis dental			
subjects affected / exposed	0 / 146 (0.00%)	0 / 147 (0.00%)	2 / 146 (1.37%)
occurrences (all)	0	0	3
Epididymitis ureaplasmal			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Spinal cord abscess			
subjects affected / exposed	0 / 146 (0.00%)	1 / 147 (0.68%)	0 / 146 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0

Hyperuricaemia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	0 / 146 (0.00%)
occurrences (all)	1	0	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 147 (0.00%)	2 / 146 (1.37%)
occurrences (all)	1	0	2

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