Clinical trial results:
Double-blind, randomised clinical study comparing efficacy and safety of Imiquimod 5% Cream (Test) vs. Aldara® 5% Cream (Reference) vs. Vehicle in patients with actinic keratosis

Summary

EudraCT number	2016-000712-15
Trial protocol	DE
Global end of trial date	18 January 2019

Results information

Result version number	v1 (current)
This version publication date	06 April 2022
First version publication date	06 April 2022

Trial information

Trial identification

Sponsor protocol code	16-04/Imi-C

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	Clinical Research Department, Dermapharm AG, +49 89641860, Clinicaltrials.Dermapharm@dermapharm.com
Scientific contact	Clinical Research Department, Dermapharm AG, +49 89641860, Clinicaltrials.Dermapharm@dermapharm.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	13 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2019
Global end of trial reached?	Yes
Global end of trial date	18 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of efficacy and safety of a new cream with imiquimod 5% in comparison with the approved preparation Aldara® 5% Cream and the underlying 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 comparable efficacy and safety to the comparator in order to obtain a generic marketing authorization for the test product.

Actual start date of recruitment	03 April 2017
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: 431
Worldwide total number of subjects	431
EEA total number of subjects	431

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)	47
From 65 to 84 years	355
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

15 study centers in Germany; first patient first visit: 07 April 2017; last patient last visit: 18 January 2019

Pre-assignment

Screening details:

Main criteria for inclusion:
Women and men ≥ 18 years of age; Diagnosis of actinic keratosis according to generally accepted criteria; Presence of a (connected) area of approximately 25 cm² on either the face or balding scalp that requires medical treatment; Identification of 5 to 10 delimitable target lesions in the treatment area

Period 1

Period 1 title	Treatment 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:

The sachets containing the study medications were masked with a neutral white cover. The attached labels were identical for all three preparations. All three study medications were indistinguishable in terms of appearance. The random code was transferred to the data base not before the following actions were completed: data base closure, finalisation of the SAP, and a Blind Data Review Meeting and Report.

Arms

Are arms mutually exclusive?	Yes
Arm title	Imiquimod Cream

Arm description:

Test product

Arm type	Experimental
Investigational medicinal product name	Imiquimod 5% Cream
Investigational medicinal product code	D06BB10
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Three sachets per week in a treatment cycle of 4 weeks; Application in the evening prior to normal sleeping hours and remaining on the skin for approximately 8 hours

Arm title	Aldara

Arm description:

Reference Product

Arm type	Active comparator
Investigational medicinal product name	Aldara 5% Cream
Investigational medicinal product code	D06BB10
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Three sachets per week in a treatment cycle of 4 weeks; Application in the evening prior to normal sleeping hours and remaining on the skin for approximately 8 hours

Arm title	Vehicle

Arm description:	
Vehicle of test product	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Three sachets per week in a treatment cycle of 4 weeks; Application in the evening prior to normal sleeping hours and remaining on the skin for approximately 8 hours

Number of subjects in period 1	Imiquimod Cream	Aldara	Vehicle
Started	146	143	142
Completed	115	117	101
Not completed	31	26	41
Consent withdrawn by subject	4	3	2
Adverse event, non-fatal	12	7	2
Technical-logistic reasons	2	7	7
Poor tolerability	2	1	-
Lost to follow-up	2	-	-
Lack of efficacy	9	8	30

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	431	431	
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)	47	47	
From 65-84 years	355	355	
85 years and over	29	29	
Gender categorical Units: Subjects			
Female	38	38	
Male	393	393	

Subject analysis sets

Subject analysis set title	Safety data set
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes all randomised patients who had administered the study medication at least once and who provided at least one safety related outcome.

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 complied with the study diagnosis (according to the associated inclusion criteria) and for whom a value of the primary efficacy variable could be derived.

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 violation.

Reporting group values	Safety data set	ITT	PP
Number of subjects	431	431	364
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)	47	47	42
From 65-84 years	355	355	300
85 years and over	29	29	22
Gender categorical Units: Subjects			
Female	38	38	31
Male	393	393	333

End points

End points reporting groups

Reporting group title	Imiquimod Cream
Reporting group description:	
Test product	
Reporting group title	Aldara
Reporting group description:	
Reference Product	
Reporting group title	Vehicle
Reporting group description:	
Vehicle of test product	
Subject analysis set title	Safety data set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes all randomised patients who had administered the study medication at least once and who provided at least one safety related outcome.	
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 complied with the study diagnosis (according to the associated inclusion criteria) and for whom a value of the primary efficacy variable could be derived.	
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 violation.	

Primary: Treatment effect

End point title	Treatment effect
End point description:	
The primary efficacy variable is clinical success (yes, no) at the main examination visit (LOCF). Clinical success is defined as decrease of the target lesions of at least 75% between treatment start (Visit 1) and main examination (4 weeks post (final) treatment).	
End point type	Primary
End point timeframe:	
Start of treatment (visit 1) to main examination (4 weeks post (final) treatment): either one cycle of 4 weeks treatment or two cycles of 4 weeks treatment with one period of 4 weeks non-treatment in between.	

End point values	Imiquimod Cream	Aldara	Vehicle	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	118	116	142	431
Units: Percentage				
number (not applicable)	77	75	40	221

End point values	PP			

Subject group type	Subject analysis set			
Number of subjects analysed	364			
Units: Percentage				
number (not applicable)	188			

Statistical analyses

Statistical analysis title	Analysis of efficacy

Statistical analysis description:

The primary objective of this study was to show equivalence of Imiquimod Cream in comparison to Aldara with respect to the primary efficacy variable. Equivalence was statistically proven if the two-sided 95% confidence interval for the mean difference in proportions between Test and Reference was completely contained within [-20; 20].

Comparison groups	Imiquimod Cream v Aldara
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.5
upper limit	13.7

Statistical analysis title	Superiority of Test over Vehicle

Statistical analysis description:

In order to verify assay sensitivity of the study design, superiority of the two active preparations over vehicle was tested by means of two-sided significance tests with α = 0.05. The primary test of superiority was carried out for the ITT data set.

Comparison groups	Imiquimod Cream v Vehicle v ITT
Number of subjects included in analysis	691
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Statistical analysis title	Superiority of Reference over Vehicle

Statistical analysis description:

In order to verify assay sensitivity of the study design, superiority of the two active preparations over vehicle was tested by means of two-sided significance tests with α = 0.05. The primary test of superiority was carried out for the ITT data set.

Comparison groups	Aldara v Vehicle v ITT

Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the inclusion visit (visit 0) to the final visit (main visit).	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Imiquimod Cream
Reporting group description: Test product	
Reporting group title	Aldara
Reporting group description: Reference Product	
Reporting group title	Vehicle
Reporting group description: Vehicle of test product	

Serious adverse events	Imiquimod Cream	Aldara	Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 146 (4.11%)	5 / 143 (3.50%)	4 / 142 (2.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (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			
Fall			

subjects affected / exposed	2 / 146 (1.37%)	0 / 143 (0.00%)	0 / 142 (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
Lower limb fracture			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (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
Postoperative wound complication			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (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
Tendon rupture			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Wound			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
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			
Hypertension			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Venous thrombosis limb			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (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			
Angina pectoris			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (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
Atrial flutter			

subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
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			
Syncope			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (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			
Duodenitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Jaundice			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord leukoplakia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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			
Pneumonia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (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

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

Non-serious adverse events	Imiquimod Cream	Aldara	Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 146 (74.66%)	103 / 143 (72.03%)	62 / 142 (43.66%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acanthoma			
subjects affected / exposed	0 / 146 (0.00%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	0	2	0
Fibrous histiocytoma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Basal cell carcinoma			
subjects affected / exposed	3 / 146 (2.05%)	2 / 143 (1.40%)	4 / 142 (2.82%)
occurrences (all)	3	2	4
Malignant neoplasm of eyelid			

subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Melanocytic naevus			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
squamous cell carcinoma of skin			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	1	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Varicose ulceration			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Application site dermatitis			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	1	1	1
Application site dysaesthesia			
subjects affected / exposed	4 / 146 (2.74%)	4 / 143 (2.80%)	2 / 142 (1.41%)
occurrences (all)	4	4	2
Application site eczema			
subjects affected / exposed	4 / 146 (2.74%)	7 / 143 (4.90%)	1 / 142 (0.70%)
occurrences (all)	4	7	1
Application site erosion			
subjects affected / exposed	6 / 146 (4.11%)	4 / 143 (2.80%)	1 / 142 (0.70%)
occurrences (all)	6	4	1
Application site erythema			

subjects affected / exposed	69 / 146 (47.26%)	58 / 143 (40.56%)	7 / 142 (4.93%)
occurrences (all)	69	58	7
Application site exfoliation			
subjects affected / exposed	12 / 146 (8.22%)	6 / 143 (4.20%)	1 / 142 (0.70%)
occurrences (all)	12	6	1
Application site haematoma			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Application site haemorrhage			
subjects affected / exposed	2 / 146 (1.37%)	4 / 143 (2.80%)	0 / 142 (0.00%)
occurrences (all)	2	4	0
Application site hypoaesthesia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Application site inflammation			
subjects affected / exposed	22 / 146 (15.07%)	17 / 143 (11.89%)	0 / 142 (0.00%)
occurrences (all)	22	17	0
Application site irritation			
subjects affected / exposed	13 / 146 (8.90%)	13 / 143 (9.09%)	3 / 142 (2.11%)
occurrences (all)	13	13	3
Application site oedema			
subjects affected / exposed	2 / 146 (1.37%)	6 / 143 (4.20%)	0 / 142 (0.00%)
occurrences (all)	2	6	0
Application site pain			
subjects affected / exposed	20 / 146 (13.70%)	23 / 143 (16.08%)	3 / 142 (2.11%)
occurrences (all)	20	23	3
Application site papules			
subjects affected / exposed	2 / 146 (1.37%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	2	0	0
Application site paraesthesia			
subjects affected / exposed	4 / 146 (2.74%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	4	2	0
Application site pruritus			
subjects affected / exposed	34 / 146 (23.29%)	29 / 143 (20.28%)	4 / 142 (2.82%)
occurrences (all)	34	29	4
Application site reaction			

subjects affected / exposed	16 / 146 (10.96%)	14 / 143 (9.79%)	0 / 142 (0.00%)
occurrences (all)	16	14	0
Application site scab			
subjects affected / exposed	48 / 146 (32.88%)	50 / 143 (34.97%)	1 / 142 (0.70%)
occurrences (all)	48	50	1
Application site swelling			
subjects affected / exposed	10 / 146 (6.85%)	11 / 143 (7.69%)	0 / 142 (0.00%)
occurrences (all)	10	11	0
Application site ulcer			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Application site vesicles			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Application site warmth			
subjects affected / exposed	2 / 146 (1.37%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	2	1	0
Application site wound			
subjects affected / exposed	2 / 146 (1.37%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	2	2	0
Asthenia			
subjects affected / exposed	1 / 146 (0.68%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	1	2	0
Chills			
subjects affected / exposed	1 / 146 (0.68%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	1	2	0
Fatigue			
subjects affected / exposed	4 / 146 (2.74%)	4 / 143 (2.80%)	0 / 142 (0.00%)
occurrences (all)	4	4	0
Influenza like illness			
subjects affected / exposed	7 / 146 (4.79%)	3 / 143 (2.10%)	4 / 142 (2.82%)
occurrences (all)	7	3	4
Malaise			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	1	1	1
Peripheral swelling			

subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Sensation of foreign body			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 146 (1.37%)	1 / 143 (0.70%)	2 / 142 (1.41%)
occurrences (all)	2	1	2
Dyspnoea			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	2 / 142 (1.41%)
occurrences (all)	0	0	2
Psychiatric disorders			
Apathy			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0

Insomnia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Middle insomnia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatine decreased			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	2 / 146 (1.37%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	2	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
General physical health deterioration			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Eschar			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	2 / 142 (1.41%)
occurrences (all)	1	0	2
Overdose			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Retinal injury			

subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Wound			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	4 / 146 (2.74%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	4	1	1
Dysgeusia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Head discomfort			
subjects affected / exposed	1 / 146 (0.68%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	6 / 146 (4.11%)	7 / 143 (4.90%)	5 / 142 (3.52%)
occurrences (all)	6	7	5
Hypogeusia			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	2 / 146 (1.37%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	2	0	0
Sciatica			

subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Corneal opacity			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Erythema of eyelid			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Eye oedema			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Eye swelling			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	1	1	0
Eyelid oedema			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Eyelids pruritus			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Photopsia			

subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 146 (1.37%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 146 (1.37%)	2 / 143 (1.40%)	3 / 142 (2.11%)
occurrences (all)	2	2	3
Nausea			
subjects affected / exposed	2 / 146 (1.37%)	4 / 143 (2.80%)	1 / 142 (0.70%)
occurrences (all)	2	4	1
Oral discomfort			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Retching			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Tooth disorder			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	0	1	1

Hepatobiliary disorders			
Perihepatic discomfort			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	1	0	1
Alopecia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Blister			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Dermal cyst			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	3 / 146 (2.05%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	3	0	0
Dermatitis bullous			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Diffuse alopecia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	2 / 146 (1.37%)	3 / 143 (2.10%)	3 / 142 (2.11%)
occurrences (all)	2	3	3
Erythema			
subjects affected / exposed	3 / 146 (2.05%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	3	1	0
Hyperkeratosis			
subjects affected / exposed	0 / 146 (0.00%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	0	2	0
Pain of skin			

subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	1	1	0
Photosensitivity reaction			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Precancerous skin lesion			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	5 / 146 (3.42%)	3 / 143 (2.10%)	0 / 142 (0.00%)
occurrences (all)	5	3	0
Rosacea			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	0	1	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Skin erosion			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	1	1	0
Skin irritation			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Skin tightness			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Solar dermatitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Stasis dermatitis			

subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	4 / 142 (2.82%)
occurrences (all)	0	1	4
Back pain			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	3 / 142 (2.11%)
occurrences (all)	1	0	3
Intervertebral disc protrusion			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	1 / 142 (0.70%)
occurrences (all)	0	1	1
Joint swelling			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	5 / 142 (3.52%)
occurrences (all)	0	0	5
Myalgia			
subjects affected / exposed	1 / 146 (0.68%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences (all)	1	2	0
Pain in extremity			

subjects affected / exposed	3 / 146 (2.05%)	2 / 143 (1.40%)	1 / 142 (0.70%)
occurrences (all)	3	2	1
Plantar fasciitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic keratosis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	3 / 142 (2.11%)
occurrences (all)	1	0	3
Infections and infestations			
Application site folliculitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Application site infection			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Application site pustules			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	2 / 142 (1.41%)
occurrences (all)	0	1	2
Conjunctivitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Dermatitis infected			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Herpes ophthalmic			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0

Herpes zoster			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	1	1	0
Infected bite			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 146 (0.68%)	3 / 143 (2.10%)	11 / 142 (7.75%)
occurrences (all)	1	3	11
Onychomycosis			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Pulpitis dental			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	1	0	1
Pyoderma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	2 / 142 (1.41%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 146 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences (all)	0	0	1

Wound infection			
subjects affected / exposed	1 / 146 (0.68%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	1	1	0
Injury			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	2 / 142 (1.41%)
occurrences (all)	1	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	1 / 146 (0.68%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences (all)	1	0	0
Polydipsia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 143 (0.70%)	0 / 142 (0.00%)
occurrences (all)	0	1	0

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: