Clinical trial results:
Long-term effects of Aldara® 5% cream and Solaraze® 3% gel in the treatment of actinic keratoses on the face or scalp with respect to the risk of progression to in-situ and invasive squamous cell carcinoma (LEIDA 2)

Summary

EudraCT number	2010-022054-16
Trial protocol	DE AT
Global end of trial date	27 March 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2016
First version publication date	09 April 2016

Trial information

Trial identification

Sponsor protocol code	X-03016-3284

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01453179
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Meda Pharma GmbH & Co. KG
Sponsor organisation address	Benzstrasse 1, Bad Homburg, Germany, 61352
Public contact	Group leader study manager, Meda Pharma GmbH & Co. KG, 42b@medapharma.de
Scientific contact	Head of Corporate Clinical Affairs, Meda Pharma GmbH & Co. KG, 42b@medapharma.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2015
Global end of trial reached?	Yes
Global end of trial date	27 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the long-term outcome with respect to the risk of progression to SCC (in situ and/or invasive) of treatment with Aldara® 5% cream (IMIQ) and Solaraze® 3% gel (DIC) with increased precision (meta-analysis with study X-03016-3271).

Protection of trial subjects:

No specific additional measures to minimise pain and distress were required. The patients could withdraw from treatment at any time and for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2011
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	Austria: 16
Country: Number of subjects enrolled	Germany: 205
Worldwide total number of subjects	221
EEA total number of subjects	221

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)	39
From 65 to 84 years	170
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Immunocompetent patients with 5 to 10 visible lesions typical for actinic keratoses (AK) in one contiguous area of up to 50 cm² on the face or scalp (to be defined as STA) were enrolled. A positive histological finding for AK grade I or II was required for inclusion.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	IMIQ (Aldara)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Aldara® 5% cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use, Local use

Dosage and administration details:

1 or 2 course(s) of treatment (COTs) lasting 4 weeks each and separated by a 4-week treatment pause were possible. One course of treatment (COT) consisted of an overnight application of Aldara (1 sachet for up to 50 cm2), applied 3 nights per week (e.g. Monday, Wednesday, Friday) for 4 weeks. If the study treatment area (STA) was cleared 4 weeks after end of the first COT of a cycle, the patient received no further treatment for the next 12 weeks. If not cleared 4 weeks after end of the first COT of a cycle, the patient received a second COT lasting for 4 weeks. The total treatment cycle including 8 weeks treatment free follow-up lasted 20 weeks. If the STA was not completely cleared at a regular half-yearly follow-up visit (i.e. Month 6, 12, 18, 24, or 30), the patient had to receive an additional treatment cycle using study medication as randomised, starting at that visit.

Arm title	DIC (Solaraze)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Solaraze 3% gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use, Local use

Dosage and administration details:

Solaraze was applied locally to the skin 2 times daily and smoothed into the skin gently. The amount needed depended on the size of STA. Normally 0.5 g (the size of a pea) of the gel was used on a 25 cm2 of STA. Thus, the maximum total daily dose did not exceed 2 g of gel, equivalent to 60 mg diclofenac. The duration of therapy was 12 weeks. The total treatment cycle lasted 20 weeks (as for IMIQ). If the STA was not completely cleared at a regular half-yearly follow-up visit (i.e. Month 6, 12, 18, 24, or 30), the patient had to receive an additional treatment cycle using study medication as randomised, starting at that visit.

Number of subjects in period 1	IMIQ (Aldara)	DIC (Solaraze)
Started	110	111
Completed	92	92
Not completed	18	19
Adverse event, serious fatal	2	1
Adverse event, non-fatal	3	3
Any other reasons	13	15

Baseline characteristics

Reporting groups	
Reporting group title	IMIQ (Aldara)
Reporting group description: -	
Reporting group title	DIC (Solaraze)
Reporting group description: -	

Reporting group values	IMIQ (Aldara)	DIC (Solaraze)	Total
Number of subjects	110	111	221
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	71.36	70.75	
standard deviation	± 8.084	± 8.382	-
Gender categorical Units: Subjects			
Female	18	12	30
Male	92	99	191

End points

End points reporting groups

Reporting group title	IMIQ (Aldara)
Reporting group description: -	
Reporting group title	DIC (Solaraze)
Reporting group description: -	
Subject analysis set title	a) FAS IMIQ
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS) for IMIQ. Included all patients exposed to study medication and who had at least one follow-up information on efficacy. In the FAS, patients were analysed according to the study treatment to which they were randomised (ITT principle) and not as-treated.	
Subject analysis set title	b) FAS DIC
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS) for DIC. Included all patients exposed to study medication and who had at least one follow-up information on efficacy. In the FAS, patients were analysed according to the study treatment to which they were randomised (ITT principle) and not as-treated.	

Primary: Histological progression in patients under follow-up

End point title	Histological progression in patients under follow-up
End point description:	
End point type	Primary
End point timeframe:	
Day 1 treatment until withdrawal from follow-up.	

End point values	a) FAS IMIQ	b) FAS DIC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	110		
Units: patients				
Yes	3	13		
No	106	97		

Statistical analyses

Statistical analysis title	Newcombe-Wilson Confidence Interval
Comparison groups	a) FAS IMIQ v b) FAS DIC
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Risk difference (RD)
Point estimate	-9.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	-2.1

Notes:

[1] - Explorative.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Entire study duration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Safety set - IMIQ
Reporting group description: Safety set for IMIQ.	
Reporting group title	Safety set - DIC
Reporting group description: Safety set for the DIC treatment.	

Serious adverse events	Safety set - IMIQ	Safety set - DIC	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 110 (25.45%)	31 / 111 (27.93%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 110 (0.91%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			

subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 110 (0.91%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 110 (0.91%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 110 (0.91%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery occlusion			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preventive surgery			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prosthesis implantation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Application site dermatitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device dislocation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	2 / 110 (1.82%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural swelling			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural headache			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	2 / 110 (1.82%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	0 / 110 (0.00%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 110 (0.91%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 110 (1.82%)	4 / 111 (3.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 110 (0.91%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 110 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			

subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw cyst			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 110 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 110 (0.91%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety set - IMIQ	Safety set - DIC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 110 (77.27%)	84 / 111 (75.68%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	13 / 110 (11.82%)	17 / 111 (15.32%)	
occurrences (all)	20	21	
Seborrhoeic keratosis			
subjects affected / exposed	6 / 110 (5.45%)	4 / 111 (3.60%)	
occurrences (all)	6	4	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 110 (6.36%)	2 / 111 (1.80%)	
occurrences (all)	10	3	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	34 / 110 (30.91%)	40 / 111 (36.04%)	
occurrences (all)	117	104	
Eczema			
subjects affected / exposed	8 / 110 (7.27%)	3 / 111 (2.70%)	
occurrences (all)	8	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 110 (10.91%)	10 / 111 (9.01%)	
occurrences (all)	16	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2012	Summary of Product Characteristics (SmPC) of Solaraze had been modified by the comparator's Marketing Authorisation Holder and this had to be announced to investigators and patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported