Clinical trial results:
Multicentre, randomized, parallel, double-blind, vehicle controlled study to evaluate the efficacy and safety of Actikerall® solution in the field-directed treatment of actinic keratoses grade I to II (field cancerization)

Summary

EudraCT number	2014-001171-31
Trial protocol	DE GB
Global end of trial date	10 August 2015

Results information

Result version number	v1 (current)
This version publication date	24 August 2016
First version publication date	24 August 2016

Trial information

Trial identification

Sponsor protocol code	98605101-1401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ADP18998: Project Code, ALM014: CRO Trial Code (TFS)

Notes:

Sponsors

Sponsor organisation name	Almirall Hermal GmbH
Sponsor organisation address	Scholtzstraße 3, Reinbek, Germany, 21465
Public contact	Disclosure Central Team, ALMIRALL S.A, R&D@almirall.com
Scientific contact	Disclosure Central Team, ALMIRALL S.A, R&D@almirall.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	10 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 August 2015
Global end of trial reached?	Yes
Global end of trial date	10 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and safety of Actikerall® solution in the field-directed treatment of actinic keratosis grade I to II (field cancerization)

Protection of trial subjects:

This trial was conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly of Helsinki (1964), revised at Tokyo (1975), Venice (1983), Hong-Kong (1989), Somerset West (1996) and Edinburgh (2000), including the Notes of clarification made by the World Medical Assembly of Washington (2002) and Tokyo (2004), and 59th WMA General Assembly, Seoul (2008) as well as in compliance with Good Clinical Practice (ICH GCP guidelines) and local regulations

Each Investigator was responsible for conducting the trial in accordance with the procedures described in the Protocol. All personnel involved in the clinical trial were fully informed about the drug and the nature of the trial and were subject to protocol procedures concerning their duties in the trial

The Investigator, Clinical Research Organisation, and the Sponsor ensured that all work and services described herein, or incidental to those described herein, were conducted in accordance to the standards of Good Clinical Practice (ICH GCP guidelines), local regulations and European Directive 2001/20/EC and 2005/28/EC as well as local transpositions of such Directives, as applicable

At the completion of treatment (or premature discontinuation) subjects were instructed to resume the medication they were taking before starting the clinical trial, or any other as deemed appropriate by the Investigator. Medical care after discharge from the study was provided by the subject's family practitioner or specialist that usually treated his/her condition

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 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	United Kingdom: 32
Country: Number of subjects enrolled	Germany: 134
Worldwide total number of subjects	166
EEA total number of subjects	166

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)	22
From 65 to 84 years	141
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 14 sites from two countries in Europe (10 in Germany and 4 in the UK)

First patient visit was October 2014 and final patient visit was August 2015

Pre-assignment

Screening details:

Screening took place up to 2 weeks prior to treatment. A total of 175 subjects were screened and 166 were randomised into the study; 3 patients were excluded from efficacy/ safety analysis

Nine subjects were not randomised (1 did not meet inclusion/exclusion criteria; 8 declined)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Actikerall

Arm description:

5-fluorouracil/salicylic acid administered daily

Arm type	Experimental
Investigational medicinal product name	Actikerall
Investigational medicinal product code	
Other name	5-fluorouracil 0.5%, salicylic acid 10.0%
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use, Topical use

Dosage and administration details:

Actikerall® solution and its corresponding vehicle formulation was applied once daily (preferably always at the same time) in a total area of skin of 25 cm² with 4-10 clinical lesions located on the subject's face/forehead or bald scalp and, additionally, at least 3 sub-clinical lesions for the subjects participating in the sub-study

The dose regimen could be decreased by the physician from 7 doses/week to 3 doses/week (i.e. Monday, Wednesday and Friday) in case of severe local skin reactions on the test area due to the study drug

Arm title	Vehicle

Arm description:

Administered once daily

Arm type	Placebo
Investigational medicinal product name	Product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use , Cutaneous use

Dosage and administration details:

Actikerall® solution and its corresponding vehicle formulation was applied once daily (preferably always at the same time) in a total area of skin of 25 cm² with 4-10 clinical lesions located on the subject's face/forehead or bald scalp and, additionally, at least 3 sub-clinical lesions for the subjects participating in the sub-study

The dose regimen could be decreased by the physician from 7 doses/week to 3 doses/week (i.e. Monday, Wednesday and Friday) in case of severe local skin reactions on the test area due to the study drug

Number of subjects in period 1[1]	Actikerall	Vehicle
Started	108	55
Completed	93	50
Not completed	15	5
Consent withdrawn by subject	12	2
Adverse event, non-fatal	2	2
Protocol deviation	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 3 patients were excluded from efficacy/ safety analysis

Baseline characteristics

Reporting groups	
Reporting group title	Actikerall
Reporting group description:	
5-fluorouracil/salicylic acid administered daily	
Reporting group title	Vehicle
Reporting group description:	
Administered once daily	

Reporting group values	Actikerall	Vehicle	Total
Number of subjects	108	55	163
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	5	22
From 65-84 years	89	49	138
85 years and over	2	1	3
Age continuous			
Units: years			
arithmetic mean	71.8	72.8	
standard deviation	± 7.3	± 6.9	-
Gender categorical			
Units: Subjects			
Female	16	4	20
Male	92	51	143

End points

End points reporting groups

Reporting group title	Actikerall
Reporting group description: 5-fluorouracil/salicylic acid administered daily	
Reporting group title	Vehicle
Reporting group description: Administered once daily	
Subject analysis set title	Actikerall RCM substudy
Subject analysis set type	Sub-group analysis
Subject analysis set description: Reflectance confocal microscopy (RCM) was conducted in a subset of subjects to evaluate efficacy in subclinical actinic keratosis lesions	
Subject analysis set title	Vehicle RCM substudy
Subject analysis set type	Sub-group analysis
Subject analysis set description: Reflectance confocal microscopy (RCM) was conducted in a subset of subjects to evaluate efficacy in subclinical actinic keratosis lesions	

Primary: Percentage of subjects with complete clinical clearance of AK lesions in the treatment field at 8 weeks post last treatment

End point title	Percentage of subjects with complete clinical clearance of AK lesions in the treatment field at 8 weeks post last treatment
End point description: Complete Clinical Clearance was considered when the clearance rate was 100% at the end of study; that is, all the lesions counted at baseline were cleared	
End point type	Primary
End point timeframe: Week 8 post last treatment	

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	55		
Units: Percentage				
number (confidence interval 95%)	49.52 (39.62 to 59.45)	18.18 (9.08 to 30.9)		

Statistical analyses

Statistical analysis title	Actikerall vs vehicle
Comparison groups	Vehicle v Actikerall

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.892
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.745
upper limit	8.679

Secondary: Percentage of subjects with complete clinical clearance of AK lesions in the treatment field at each treatment visit

End point title	Percentage of subjects with complete clinical clearance of AK lesions in the treatment field at each treatment visit

End point description:

End point type	Secondary

End point timeframe:

Up to Week 12 of treament

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Percentage				
number (not applicable)				
Week 2	1.01	0		
Week 4	4	1.85		
Week 6	8	9.26		
Week 12	23.76	22.22		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with partial clearance of AK lesions in the treatment field at each treatment visit and at 8 weeks post last treatment

End point title	Percentage of subjects with partial clearance of AK lesions in the treatment field at each treatment visit and at 8 weeks post last treatment

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Percentage				
number (not applicable)				
Week 2	1.01	0		
Week 4	5	7.41		
Week 6	15	11.11		
Week 12	40.59	31.48		
Week 8 post last treatment	69.52	34.55		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in the total number of AK lesion count at each treatment visit and at 8 weeks post last treatment

End point title	Percentage change from baseline in the total number of AK lesion count at each treatment visit and at 8 weeks post last treatment

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks post treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[1]	55[2]		
Units: percent				
arithmetic mean (standard deviation)				
Baseline	5.61 (± 1.35)	5.62 (± 1.46)		
Week 2	-5.1 (± 14.85)	-6.36 (± 14.3)		
Week 4	-14.46 (± 27.19)	-16.41 (± 27.02)		
Week 6	-28.19 (± 33.61)	-26.26 (± 34.22)		
Week 12	-52.16 (± 39.07)	-44.67 (± 40.68)		
Week 8 post last treatment	-78.42 (± 29.42)	-47.4 (± 38.61)		

Notes:

[1] - n=99 at Week 2; n=100 at Week 4 and 6; n=101 at Week 12; n=105 at Week 8 post last treatment
[2] - n=54 at Week 2, Week 4, Week 6 and Week 12

Statistical analyses

No statistical analyses for this end point

Secondary: Number of lesions by AK grade severity according to Olsen et al. (0, I, II or III) at baseline and at 8 weeks post-treatment

End point title	Number of lesions by AK grade severity according to Olsen et al. (0, I, II or III) at baseline and at 8 weeks post-treatment

End point description:

0: No AK lesion present, neither visible nor palpable
I: Flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, with AK felt better than seen
II: Pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick AK that are easily seen and felt
III: Very thick and / or obvious AK

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Number of lesion				
Grade 0 (Baseline)	0	0		
Grade I (Baseline)	340	178		
Grade II (Baseline)	266	131		
Grade III (Baseline)	0	0		
Grade 0 (Week 8 post last treatment)	470	147		
Grade I (Week 8 post last treatment)	84	103		
Grade II (Week 8 post last treatment)	21	38		
Grade III (Week 8 post last treatment)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of efficacy by the physician (PGA, Physician Global Assessment) at each treatment visit and at 8 weeks post last treatment (Week 2 and 4)

End point title	Global assessment of efficacy by the physician (PGA, Physician Global Assessment) at each treatment visit and at 8 weeks post last treatment (Week 2 and 4)

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks post treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Number of patients				
Very good (Week 2)	1	0		
Good (Week 2)	46	33		
Moderate (Week 2)	41	6		
Minimal (Week 2)	13	9		
None (Week 2)	3	6		
Very good (Week 4)	4	1		
Good (Week 4)	48	37		
Moderate (Week 4)	36	4		
Minimal (Week 4)	5	7		
None (Week 4)	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of efficacy by the physician (PGA, Physician Global Assessment) at each treatment visit and at 8 weeks post last treatment (Week 6 and 12)

End point title	Global assessment of efficacy by the physician (PGA, Physician Global Assessment) at each treatment visit and at 8 weeks post last treatment (Week 6 and 12)

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Number of patients				
Very good (Week 6)	6	3		
Good (Week 6)	55	32		
Moderate (Week 6)	29	8		
Minimal (Week 6)	4	3		
None (Week 6)	1	4		
Very good (Week 12)	21	11		
Good (Week 12)	47	26		
Moderate (Week 12)	22	6		
Minimal (Week 12)	3	3		
None (Week 12)	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of efficacy by the physician (PGA, Physician Global Assessment) at each treatment visit and at 8 weeks post last treatment (Week 8 post last treatment)

End point title	Global assessment of efficacy by the physician (PGA, Physician Global Assessment) at each treatment visit and at 8 weeks post last treatment (Week 8 post last treatment)

End point description:

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Number of patients				
Very good (Week 8 post last treatment)	46	8		
Good (Week 8 post last treatment)	46	32		
Moderate (Week 8 post last treatment)	6	8		
Minimal (Week 8 post last treatment)	2	1		
None (Week 8 post last treatment)	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total score and individual domains of the DLQI questionnaire after 12 weeks of treatment and at 8 weeks post last treatment (Daily Activities, Leisure, Personal Relationships)

End point title	Change from baseline in total score and individual domains of the DLQI questionnaire after 12 weeks of treatment and at 8 weeks post last treatment (Daily Activities, Leisure, Personal Relationships)

End point description:

The DLQI consists of ten items and covers six domains including 'symptoms and feelings', 'daily activities', 'leisure', 'work and school', 'personal relationships' and 'treatment'. Responses are 'not at all', 'a little', 'a lot', and 'very much', with corresponding scores of 0, 1, 2, and 3, respectively. A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. Higher scores indicate more impairment

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Score				
arithmetic mean (standard deviation)				
Daily activities (baseline)	0.21 (± 0.74)	0.16 (± 0.54)		
Daily activities (Week 12)	0.12 (± 0.61)	-0.04 (± 0.34)		
Daily activities (Week 8 post last treatment)	-0.05 (± 0.59)	0.17 (± 0.77)		
Leisure (baseline)	0.15 (± 0.47)	0.27 (± 0.87)		
Leisure (Week 12)	0.15 (± 0.65)	-0.12 (± 0.82)		
Leisure (Week 8 post last treatment)	-0.01 (± 0.48)	-0.06 (± 0.56)		
Personal relationships (baseline)	0.14 (± 0.46)	0.11 (± 0.46)		
Personal relationships (Week 12)	0.01 (± 0.48)	-0.08 (± 0.39)		
Personal relationships (Wk 8 post last treatment)	-0.08 (± 0.39)	0 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total score and individual domains of the DLQI questionnaire after 12 weeks of treatment and at 8 weeks post last treatment (Symptoms and Feelings, Treatment, Work and School)

End point title	Change from baseline in total score and individual domains of the DLQI questionnaire after 12 weeks of treatment and at 8 weeks post last treatment (Symptoms and Feelings, Treatment, Work and School)

End point description:

The DLQI consists of ten items and covers six domains including 'symptoms and feelings', 'daily activities', 'leisure', 'work and school', 'personal relationships' and 'treatment'. Responses are 'not at all',

'a little', 'a lot', and 'very much', with corresponding scores of 0, 1, 2, and 3, respectively. A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. Higher scores indicate more impairment

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Score				
arithmetic mean (standard deviation)				
Symptoms and feelings (baseline)	0.92 (± 0.91)	1.11 (± 1.18)		
Symptoms and feelings (Week 12)	0.25 (± 1.33)	-0.31 (± 0.86)		
Symptoms and feelings (Week 8 post last treatment)	-0.44 (± 1.15)	-0.44 (± 1.02)		
Treatment (baseline)	0.06 (± 0.25)	0.07 (± 0.33)		
Treatment (Week 12)	0.09 (± 0.38)	0.16 (± 0.5)		
Treatment (Week 8 post last treatment)	0 (± 0.42)	-0.02 (± 0.24)		
Work and school (baseline)	0.04 (± 0.3)	0.04 (± 0.19)		
Work and school (Week 12)	0 (± 0.15)	-0.02 (± 0.25)		
Work and school (Week 8 post last treatment)	-0.03 (± 0.33)	0.08 (± 0.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total score and individual domains of the DLQI questionnaire after 12 weeks of treatment and at 8 weeks post last treatment (Total Score)

End point title	Change from baseline in total score and individual domains of the DLQI questionnaire after 12 weeks of treatment and at 8 weeks post last treatment (Total Score)

End point description:

The DLQI consists of ten items and covers six domains including 'symptoms and feelings', 'daily activities', 'leisure', 'work and school', 'personal relationships' and 'treatment'. Responses are 'not at all', 'a little', 'a lot', and 'very much', with corresponding scores of 0, 1, 2, and 3, respectively. A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. Higher scores indicate more impairment

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	55		
Units: Score				
arithmetic mean (standard deviation)				
Baseline	1.52 (± 2.08)	1.76 (± 2.93)		
Week 12	0.62 (± 2.23)	-0.41 (± 1.76)		
Week 8 post last treatment	-0.61 (± 2.05)	-0.26 (± 1.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in the selected subclinical AK lesions counts after 4, 6 and 12 weeks of treatment and 8 weeks post last treatment

End point title	Percentage change from baseline in the selected subclinical AK lesions counts after 4, 6 and 12 weeks of treatment and 8 weeks post last treatment

End point description:

Subclinical lesions were assessed with reflectance confocal microscopy (RCM)

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall RCM substudy	Vehicle RCM substudy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	10		
Units: Number of lesions				
arithmetic mean (standard deviation)				
Baseline	3 (± 0)	3 (± 0)		
Week 4	-10.42 (± 20.07)	-3.7 (± 11.11)		
Week 6	-22.92 (± 37.94)	-18.52 (± 37.68)		
Week 12	-66.67 (± 43.89)	-40.74 (± 49.38)		
Week 8 post last treatment	-89.58 (± 15.96)	-46.67 (± 50.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Individual domains (effectiveness, side effects, convenience and overall satisfaction) of the TSQM at 8 weeks post last treatment

End point title	Individual domains (effectiveness, side effects, convenience and overall satisfaction) of the TSQM at 8 weeks post last treatment

End point description:

Treatment Satisfaction Questionnaire for Medication (version 1.4) consists of 14 items divided in three specific scales (Effectiveness, Side effects and Convenience) and one global satisfaction scale (Global)

TSQM Scale scores range from 0 to 100

End point type	Secondary

End point timeframe:

Up to 8 weeks post treatment

End point values	Actikerall	Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[3]	53[4]		
Units: Score				
arithmetic mean (standard deviation)				
TSQM Convenience	70.93 (± 20.96)	71.58 (± 21.29)		
TSQM Effectiveness	70.93 (± 22.88)	59.43 (± 27.55)		
TSQM Side Effects	92.31 (± 15.54)	96.23 (± 11.39)		
TSQM Overall Satisfaction	69.11 (± 23.05)	56.03 (± 26.62)		

Notes:

[3] - n=99 for TSQM Effectiveness and n=100 for TSQM Side Effects

[4] - n=52 for TSQM Convenience

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects for which the clearance of one pre-defined representative actinic keratosis clinical lesion is confirmed by means of RCM 8 weeks post-treatment.

End point title	Percentage of subjects for which the clearance of one pre-defined representative actinic keratosis clinical lesion is confirmed by means of RCM 8 weeks post-treatment.

End point description:

Subclinical lesions were assessed with reflectance confocal microscopy (RCM)

End point type	Secondary

End point timeframe:

Up to 8 weeks post treatment

End point values	Actikerall RCM substudy	Vehicle RCM substudy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	10		
Units: Percentage of patients				
number (not applicable)				
Week 4	0	0		
Week 6	12.5	11.11		
Week 12	56.25	33.33		
Week 8 post last treatment	68.75	40		

Statistical analyses

No statistical analyses for this end point

Secondary: AK lesions assessments by RCM at baseline (only one clinical preselected lesion)

End point title	AK lesions assessments by RCM at baseline (only one clinical preselected lesion)

End point description:

Subclinical lesions were assessed with reflectance confocal microscopy (RCM)

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall RCM substudy	Vehicle RCM substudy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	10		
Units: Percentage of patients				
number (not applicable)				
Architectural disarray	100	100		
Keratinocyte atypia	100	100		
Parakeratosis	100	100		
Pleomorphism	100	100		
Single detached keratinocytes	64.7	60		
Solar elastosis	58.8	50		
Superficial scale	64.7	10		

Statistical analyses

No statistical analyses for this end point

Secondary: AK lesions assessments by RCM at Week 8 post last treatment (only one clinical preselected lesion)

End point title	AK lesions assessments by RCM at Week 8 post last treatment (only one clinical preselected lesion)

End point description:

Subclinical lesions were assessed with reflectance confocal microscopy (RCM)

End point type	Secondary

End point timeframe:

Up to 8 weeks post last treatment

End point values	Actikerall RCM substudy	Vehicle RCM substudy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	10		
Units: Percentage of patients				
number (not applicable)				
Architectural disarray	12.5	55.6		
Keratinocyte atypia	25	66.7		
Parakeratosis	12.5	77.8		
Pleomorphism	31.3	66.7		
Single detached keratinocytes	12.5	66.7		
Solar elastosis	37.5	55.6		
Superficial scale	12.5	55.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Day 140 ±5 (Week 20 or Week 8 post-treatment)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Actikerall
Reporting group description: -	
Reporting group title	Vehicle
Reporting group description: -	

Serious adverse events	Actikerall	Vehicle	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 108 (5.56%)	3 / 55 (5.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 108 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			

subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Polypectomy			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (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			
Spinal osteoarthritis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis bacterial			

subjects affected / exposed	0 / 108 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Actikerall	Vehicle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 108 (97.22%)	42 / 55 (76.36%)	
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	96 / 108 (88.89%)	29 / 55 (52.73%)	
occurrences (all)	103	35	
Application site pain			
subjects affected / exposed	75 / 108 (69.44%)	23 / 55 (41.82%)	
occurrences (all)	102	31	
Application site irritation			
subjects affected / exposed	64 / 108 (59.26%)	15 / 55 (27.27%)	
occurrences (all)	70	19	
Application site scab			
subjects affected / exposed	63 / 108 (58.33%)	12 / 55 (21.82%)	
occurrences (all)	69	15	
Application site inflammation			
subjects affected / exposed	60 / 108 (55.56%)	15 / 55 (27.27%)	
occurrences (all)	67	15	
Application site erosion			
subjects affected / exposed	46 / 108 (42.59%)	6 / 55 (10.91%)	
occurrences (all)	55	7	
Application site pruritus			
subjects affected / exposed	36 / 108 (33.33%)	16 / 55 (29.09%)	
occurrences (all)	39	17	
Application site dermatitis			
subjects affected / exposed	34 / 108 (31.48%)	3 / 55 (5.45%)	
occurrences (all)	38	4	
Application site haemorrhage			

subjects affected / exposed	26 / 108 (24.07%)	3 / 55 (5.45%)	
occurrences (all)	30	4	
Application site oedema			
subjects affected / exposed	17 / 108 (15.74%)	0 / 55 (0.00%)	
occurrences (all)	18	0	
Application site exfoliation			
subjects affected / exposed	6 / 108 (5.56%)	3 / 55 (5.45%)	
occurrences (all)	6	4	
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	12 / 108 (11.11%)	2 / 55 (3.64%)	
occurrences (all)	12	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 108 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2014	Per the MHRA's request, the following modifications were made: the study drug should be discontinued in case withdrawal criteria were met brivudine, sorivudine and analogues had to be explicitly mentioned as prohibited medication in the Protocol since, according to the approved SmPC, Actikerall must not have been used in conjunction with these agents highly effective methods of birth control were to be used not only two months before the Screening visit but also throughout the trial During the local implementation of the substantial amendment in Germany (2nd October 2014), the text of exclusion criteria #12 was modified to clarify that the "8 weeks prior to Visit 1" referred to the last study drug application that happened in the previous trial regardless of the duration of the follow-up period. This modification was consistent with the exclusion criteria requiring the wash-out specified for investigational drugs was 8 weeks

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported