Clinical trial results:
A Simultaneous Treatment Regimen Compared to a Sequential Treatment Regimen with Ingenol Mebutate Gel 0.015% and 0.05% of Two Areas with Actinic Keratosis on Face/Scalp and Trunk/Extremities

Summary

EudraCT number	2012-002863-88
Trial protocol	ES IT
Global end of trial date	22 January 2014

Results information

Result version number	v1 (current)
This version publication date	19 February 2016
First version publication date	17 July 2015

Trial information

Trial identification

Sponsor protocol code	LP0041-64

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01787383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark,
Public contact	Clinical trial Disclosure Manager , LEO Pharma A/S, + 45 44945888, ctr.disclosure@leo-pharma.com
Scientific contact	Clinical trial Disclosure Manager , LEO Pharma A/S, + 45 44945888, ctr.disclosure@leo-pharma.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	22 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2014
Global end of trial reached?	Yes
Global end of trial date	22 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of a simultaneous treatment regimen compared to a sequential treatment regimen when two separate areas with AKs (one located on face or scalp and the other located on trunk or extremities) are treated with ingenol mebutate gel.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2013
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	Italy: 124
Country: Number of subjects enrolled	Spain: 75
Worldwide total number of subjects	199
EEA total number of subjects	199

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)	21
From 65 to 84 years	155
85 years and over	23

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In the clinical study protocol 200 subjects were planned to be enrolled and 199 subjects were acutally enrolled and randomised.

Pre-assignment period milestones

Number of subjects started	199
Number of subjects completed	199

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	Ingenol Mebutate Gel Simultaneous Treatment

Arm description:

Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied simultaneously: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.

Arm type	Experimental
Investigational medicinal product name	Ingenol mebutate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.

Arm title	Ingenol Mebutate Gel Sequential Treatment

Arm description:

Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied sequentially: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.

Arm type	Experimental
Investigational medicinal product name	Ingenol mebutate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied sequentially: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.

Number of subjects in period 1	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment
Started	101	98
Completed	92	76
Not completed	9	22
Voluntary	-	8
Afraid skin reactions	-	2
More than 8 AK	-	1
Adverse event, non-fatal	2	1
Personal reason	-	1
Treatment area over 25 square centimeters	2	1
Wrong kit number used	2	5
Treatment area under 25 square centimeters	2	-
Lost to follow-up	-	3
Wrong study treatment used	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ingenol Mebutate Gel Simultaneous Treatment
Reporting group description:	
Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied simultaneously: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.	
Reporting group title	Ingenol Mebutate Gel Sequential Treatment
Reporting group description:	
Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied sequentially: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.	

Reporting group values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment	Total
Number of subjects	101	98	199
Age categorical Units: Subjects			
Adults (18-64 years)	12	9	21
From 65-84 years	78	77	155
85 years and over	11	12	23
Age continuous Units: years			
arithmetic mean	74.4	74.5	
full range (min-max)	43 to 94	48 to 92	-
Gender categorical Units: Subjects			
Female	13	18	31
Male	88	80	168

End points

End points reporting groups

Reporting group title	Ingenol Mebutate Gel Simultaneous Treatment
Reporting group description:	
Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied simultaneously: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.	
Reporting group title	Ingenol Mebutate Gel Sequential Treatment
Reporting group description:	
Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied sequentially: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.	

Primary: Composite Local Skin Reaction (LSR) Score 3 Days After Treatment of Each Selected Treatment Area

End point title	Composite Local Skin Reaction (LSR) Score 3 Days After Treatment of Each Selected Treatment Area
End point description:	
Composite Local Skin Reaction (LSR) score 3 days after treatment of each selected treatment area in both treatment groups (simultaneous or sequential). The composite LSR score (0 to 24), reflecting the sum of individual LSR grades (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, grade 0 to 4), was calculated for each selected treatment area at each visit.	
End point type	Primary
End point timeframe:	
3 days after each treatment of each selected treatement area	

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	98		
Units: Local Skin Reaction (LSR) Score				
arithmetic mean (standard deviation)	10.4 (± 5.1)	9.7 (± 4.5)		

Statistical analyses

Statistical analysis title	Comparison groups
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment

Number of subjects included in analysis	199
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.13
Method	Wilcoxon (Mann-Whitney)

Secondary: Complete Clearance of AKs in Each Separate Treatment Area 8 Weeks After Treatment

End point title	Complete Clearance of AKs in Each Separate Treatment Area 8 Weeks After Treatment

End point description:

Complete clearance of Aktinic Keratosis lesions (AKs) analysed in each separate treatment area and presented by treatment regimen

End point type	Secondary

End point timeframe:

8 weeks after treatment

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	98		
Units: Complete clearance				
number (not applicable)	52.7	46.9		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.34
Method	Regression, Logistic

Secondary: Partial Clearance of AKs in Each Separate Treatment Area 8 Weeks After Treatment

End point title	Partial Clearance of AKs in Each Separate Treatment Area 8 Weeks After Treatment

End point description:

Partial clearance of Actinic Keratosis lesions (AKs) in each separate treatement area defined as 75% or greater reduction in Actinic Keratosis lesions (AKs) from start of treatment to 8 weeks after treatment,

was analysed in each separate treatment area and presented by treatment regimen

End point type	Secondary

End point timeframe:

8 weeks after treatment

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	98		
Units: Partial Clearance of AKs				
number (not applicable)	76.6	68.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.088
Method	Regression, Logistic

Secondary: Percent Reduction in Number of AKs in Each Separate Treatment Area 8 Weeks After Treatment

End point title	Percent Reduction in Number of AKs in Each Separate Treatment Area 8 Weeks After Treatment

End point description:

Percent reduction in number of Actinic Keratosis lesions (AKs) in each separate treatment area, analysed in each separate treatment area and presented by treatment regimen

End point type	Secondary

End point timeframe:

8 weeks after treatment

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	98		
Units: Percent Reduction in Number of AKs				

arithmetic mean (standard deviation)	83.4 (± 22)	79.1 (± 26.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment
Number of subjects included in analysis	199
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Secondary: Effectiveness Satisfaction Questionniarre for Medication (TSQM)

End point title	Effectiveness Satisfaction Questionniarre for Medication (TSQM)
End point description:	
Effectiveness of TSQM After a Treatment Cycle of 8 Weeks. Measurement of the perceived effectiveness of medication, ranging from 0 (worst possible outcome) to 100 (best possible outcome)	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	73		
Units: Units on a scale				
arithmetic mean (standard deviation)	63.1 (± 23.4)	66.4 (± 21.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment

Number of subjects included in analysis	163
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.38
Method	Wilcoxon (Mann-Whitney)

Secondary: Side Effects of TSQM

End point title	Side Effects of TSQM

End point description:

Side Effects of TSQM After a Treatment Cycle of 8 Weeks. Measurement of the perceived side effects of medication, ranging from 0 (worst possible outcome) to 100 (best possible outcome).

End point type	Secondary

End point timeframe:

8 weeks

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	73		
Units: Units on a scale				
arithmetic mean (standard deviation)	93.1 (± 18.4)	96.1 (± 16.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment
Number of subjects included in analysis	163
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.033
Method	Wilcoxon (Mann-Whitney)

Secondary: Global Satisfaction TSQM

End point title	Global Satisfaction TSQM

End point description:

Global Satisfaction TSQM After a Treatment Cycle of 8 weeks. Measurement of the perceived overall satisfaction with medication, ranging from 0 (worst possible outcome) to 100 (best possible outcome).

End point type	Secondary

End point timeframe:

8 weeks

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	72		
Units: Units on a scale				
arithmetic mean (standard deviation)	64.6 (± 19)	67.4 (± 20.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ingenol Mebutate Gel Sequential Treatment v Ingenol Mebutate Gel Simultaneous Treatment
Number of subjects included in analysis	154
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.37
Method	Wilcoxon (Mann-Whitney)

Secondary: Convenience of TSQM

End point title	Convenience of TSQM

End point description:

Convenience TSQM After a Treatment Cycle of 8 Weeks. Measurement of the perceived convenience with medication, ranging from 0 (worst possible outcome) to 100 (best possible outcome).

End point type	Secondary

End point timeframe:

8 weeks

End point values	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	73		
Units: Units on a scale				
arithmetic mean (standard deviation)	73.7 (± 14.6)	74.7 (± 18.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ingenol Mebutate Gel Simultaneous Treatment v Ingenol Mebutate Gel Sequential Treatment
Number of subjects included in analysis	156
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.66
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

8 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Ingenol Mebutate Gel Simultaneous Treatment

Reporting group description:

Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied simultaneously: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.

Reporting group title	Ingenol Mebutate Gel Sequential Treatment

Reporting group description:

Ingenol mebutate gel in 2 doses (0.015 %: and 0.05 %) were applied sequentially: ingenol mebutate gel 0.015% (Picato®) was applied once daily for 3 consecutive days on face/scalp and ingenol mebutate gel 0.05% (Picato®) was applied once daily for 2 consecutive days on trunk/extremities.

Serious adverse events	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 101 (2.97%)	4 / 98 (4.08%)	
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)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
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: 0 %

Non-serious adverse events	Ingenol Mebutate Gel Simultaneous Treatment	Ingenol Mebutate Gel Sequential Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 101 (20.79%)	19 / 98 (19.39%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: non-serious as occured outside the treatment area		
subjects affected / exposed	3 / 101 (2.97%)	3 / 98 (3.06%)	
occurrences (all)	3	3	
Squamous cell carcinoma of skin	Additional description: non-serious as occured outside the treatment area		

subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences (all)	2	2	
Malignant melanoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Application site burn			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Fall			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 101 (4.95%)	2 / 98 (2.04%)	
occurrences (all)	5	3	
Loss of consciousness			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	8 / 101 (7.92%)	1 / 98 (1.02%)	
occurrences (all)	9	1	
Application site pain			
subjects affected / exposed	5 / 101 (4.95%)	1 / 98 (1.02%)	
occurrences (all)	6	1	
Feeling cold			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Scotoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Subcutaneous nodule			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	1 / 98 (1.02%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2013	One protocol amendment (see Appendix 1.1) was issued 5-Jun-2013, mainly issuing changes in trial administrative structure. In addition, the protocol appendix named "Treatment Satisfaction Questionnaire for Medication" (English version – version 1.4) used in the LP0041-64 clinical study protocol version 1 (dated 15-Oct-2012) was not complete and was thus updated to contain all questionnaire questions required.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported