



## Clinical trial results:

**Efficacy and safety of ingenol mebutate gel 0.015% compared to diclofenac sodium gel 3% in subjects with actinic keratoses on the face or scalp.**

### Summary

EudraCT number	2014-003218-98
Trial protocol	DE GB ES
Global end of trial date	10 June 2016

### Results information

Result version number	v1 (current)
This version publication date	25 June 2017
First version publication date	25 June 2017

### Trial information

#### Trial identification

Sponsor protocol code	LP0041-1120
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02406014
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark, 2750
Public contact	Clinical Trial Disclosure Specialist, LEO Pharma A/S, +45 4494 5888, disclosure@leo-pharma.com
Scientific contact	Clinical Trial Disclosure Specialist, LEO Pharma A/S, +45 4494 5888, 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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	15 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2016
Global end of trial reached?	Yes
Global end of trial date	10 June 2016
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To compare the efficacy of daily application for 3 consecutive days of ingenol mebutate gel 0.015% with the efficacy of diclofenac sodium gel 3% for 90 days in subjects with AK on the face or scalp.

Protection of trial subjects:

The clinical trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Association General Assembly, 1964, and subsequent amendments.

All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the clinical trial was voluntary and that the subject could withdraw from the clinical trial at any time and for any reason. All subjects were given an opportunity to ask questions and were given sufficient time to consider before consenting.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Spain: 100
Country: Number of subjects enrolled	United Kingdom: 150
Country: Number of subjects enrolled	Germany: 252
Worldwide total number of subjects	502
EEA total number of subjects	502

Notes:

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**Subjects enrolled per age group**

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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)	57
From 65 to 84 years	409
85 years and over	36

## Subject disposition

### Recruitment

Recruitment details:

A total of 511 subjects were enrolled, of which 502 subjects were randomised (255 subjects to ingenol mebutate and 247 subjects to diclofenac sodium). The subjects were enrolled in a total of 33 sites in 3 countries Germany (14 sites), Spain (7 sites) and the United Kingdom (12 sites).

### Pre-assignment

Screening details:

Inclusion criteria: Subjects with 4 to 8 clinically typical, visible and discrete AKs within a contiguous 25 cm<sup>2</sup> treatment area on the face or scalp.

### Period 1

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

Blinding implementation details:

Not applicable as this is an open-label trial.

The (sub) investigators were blinded at the time the aktinic keratosis (AK) assessments and count were performed.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	ingenol mebutate 0.015%
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Picato®
Investigational medicinal product code	
Other name	ingenol mebutate gel 0.015%
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

At Day 1 selected treatment areas (STA) were identified and marked by the investigator.

At Week 8 for the ingenol mebutate group, subjects who presented existing AKs or newly emergent AKs in the STA started a second treatment course with ingenol mebutate gel 0.015% (treatment area already marked).

The subjects were instructed to apply the IMPs according to the respective SmPCs.

<b>Arm title</b>	diclofenac sodium 3%
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Solaraze®
Investigational medicinal product code	
Other name	diclofenac sodium gel 3%
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

The subjects were instructed to apply the IMPs according to the respective SmPCs.

<b>Number of subjects in period 1</b>	ingenol mebutate 0.015%	diclofenac sodium 3%
Started	255	247
Completed	233	211
Not completed	22	36
Consent withdrawn by subject	11	11
Adverse event, non-fatal	7	15
Death	-	2
Other	-	2
Investigator decision	-	1
Lost to follow-up	2	3
Protocol deviation	2	2

## Baseline characteristics

### Reporting groups

Reporting group title	ingenol mebutate 0.015%
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Reporting group description: -
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Reporting group title	diclofenac sodium 3%
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Reporting group description: -
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Reporting group values	ingenol mebutate 0.015%	diclofenac sodium 3%	Total
Number of subjects	255	247	502
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)	32	25	57
From 65-84 years	202	207	409
85 years and over	21	15	36
Age continuous Units: years			
arithmetic mean	74.1	73.6	
standard deviation	± 8.2	± 8.4	-
Gender categorical Units: Subjects			
Female	39	35	74
Male	216	212	428

## End points

### End points reporting groups

Reporting group title	ingenol mebutate 0.015%
Reporting group description:	-
Reporting group title	diclofenac sodium 3%
Reporting group description:	-

### Primary: Complete clearance at Week 8 (ingenol mebutate) versus Week 17 (diclofenac sodium)

End point title	Complete clearance at Week 8 (ingenol mebutate) versus Week 17 (diclofenac sodium)
End point description:	
End point type	Primary
End point timeframe:	
Day 1 to Week 8 (ingenol mebutate)	
Day 1 to Week 17 (diclofenac sodium)	

End point values	ingenol mebutate 0.015%	diclofenac sodium 3%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	247		
Units: Subjects				
Cleared	88	58		
Not cleared	167	189		

### Statistical analyses

Statistical analysis title	Complete clearance
Comparison groups	ingenol mebutate 0.015% v diclofenac sodium 3%
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 <sup>[1]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	2.71

Notes:

[1] - Logistic regression with factors treatment and anatomical location and site as random effect.

## Secondary: Complete clearance after last treatment course

End point title	Complete clearance after last treatment course
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End point description:

Last treatment course is defined as:

Ingenol mebutate arm: subjects receiving only one treatment course evaluated at Week 8, subjects receiving two treatment courses evaluated at Week 17.

End point type	Secondary
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End point timeframe:

Day 1 to Week 8 or Week 17 (ingenol mebutate)

Day 1 to Week 17 (diclofenac sodium)

End point values	ingenol mebutate 0.015%	diclofenac sodium 3%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	247		
Units: Subjects				
Cleared	136	58		
Not cleared	119	189		

## Statistical analyses

Statistical analysis title	Complete clearance after last treatment course
Comparison groups	ingenol mebutate 0.015% v diclofenac sodium 3%
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.86
upper limit	6.64

Notes:

[2] - Odds of complete clearance (Ingenol mebutate relative to Diclofenac sodium), logistic regression with factors treatment and anatomical location and site as random effect

## Secondary: Complete clearance at Week 17

End point title	Complete clearance at Week 17
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End point description:

The complete clearance at Week 17 for ingenol mebutate and diclofenac sodium.

End point type	Secondary
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End point timeframe:

Day 1 to Week 17

End point values	ingenol mebutate 0.015%	diclofenac sodium 3%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	247		
Units: Subjects				
Cleared	115	58		
Not cleared	140	189		

### Statistical analyses

Statistical analysis title	Complete clearance at Week 17
Comparison groups	ingenol mebutate 0.015% v diclofenac sodium 3%
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4.62

Notes:

[3] - Odds of complete clearance (Ingenol mebutate relative to Diclofenac sodium), logistic regression with factors treatment and anatomical location and site as random effect.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of Informed Consent Form til End of Trial.

Adverse event reporting additional description:

The reported adverse events include events reported both inside and outside of treatment area.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Picato®
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Reporting group description: -

Reporting group title	Solaraze®
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Reporting group description: -

Serious adverse events	Picato®	Solaraze®	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 247 (3.64%)	10 / 234 (4.27%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 247 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			

subjects affected / exposed	0 / 247 (0.00%)	1 / 234 (0.43%)	
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 / 247 (0.40%)	0 / 234 (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			
Spinal fracture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Granulomatosis with polyangiitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Orthostatic hypotension			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 247 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 247 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Coronary artery stenosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (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			
Cholecystectomy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (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			
Carotid artery stenosis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (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			
Glomerulonephritis membranous			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (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			
Diverticulitis			

subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 234 (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 / 247 (0.40%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 247 (0.00%)	1 / 234 (0.43%)	
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: 2 %

<b>Non-serious adverse events</b>	Picato®	Solaraze®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 247 (47.77%)	90 / 234 (38.46%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	7 / 247 (2.83%)	3 / 234 (1.28%)	
occurrences (all)	8	3	
Squamous cell carcinoma of skin			
subjects affected / exposed	5 / 247 (2.02%)	0 / 234 (0.00%)	
occurrences (all)	5	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 247 (2.43%)	2 / 234 (0.85%)	
occurrences (all)	7	2	
General disorders and administration site conditions			

Application site erythema subjects affected / exposed occurrences (all)	47 / 247 (19.03%) 55	27 / 234 (11.54%) 29	
Application site scab subjects affected / exposed occurrences (all)	20 / 247 (8.10%) 21	6 / 234 (2.56%) 7	
Application site pain subjects affected / exposed occurrences (all)	16 / 247 (6.48%) 16	8 / 234 (3.42%) 9	
Application site vesicles subjects affected / exposed occurrences (all)	11 / 247 (4.45%) 13	3 / 234 (1.28%) 3	
Application site pruritus subjects affected / exposed occurrences (all)	5 / 247 (2.02%) 7	11 / 234 (4.70%) 12	
Application site exfoliation subjects affected / exposed occurrences (all)	6 / 247 (2.43%) 6	11 / 234 (4.70%) 12	
Application site oedema subjects affected / exposed occurrences (all)	7 / 247 (2.83%) 7	4 / 234 (1.71%) 4	
Application site dermatitis subjects affected / exposed occurrences (all)	0 / 247 (0.00%) 0	5 / 234 (2.14%) 5	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 247 (2.02%) 5	1 / 234 (0.43%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported