Clinical trial results:
Safety and efficacy of repeat use of Picato® 0.05% in the treatment of anogenital warts

Summary

EudraCT number	2014-004465-24
Trial protocol	DK
Global end of trial date	26 November 2015

Results information

Result version number	v1 (current)
This version publication date	08 December 2016
First version publication date	08 December 2016

Trial information

Trial identification

Sponsor protocol code	EXP-1167

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02377999
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 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	15 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2015
Global end of trial reached?	Yes
Global end of trial date	26 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of single treatment with Picato® 0.05% repeated up to 2 times with two weeks intervals in subjects with anogenital warts.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2015
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	Denmark: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 41 subjects were enrolled in the trial, 1 subject was a screening failure, and 40 subjects were assigned treatment with ingenol mebutate gel 0.05%. All subjects were enrolled at a single site in Denmark.

Pre-assignment

Screening details:

A screening visit was conducted up to 7 days before start of treatment to screen for eligibility, to obtain informed consent, and collect demographic and baseline data.

Period 1

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

Arms

Arm title	All subjects

Arm description:

Of the 40 subjects assigned treatment, 22 subjects (55%) received 1 dose of ingenol mebutate gel 0.05%, 8 subjects (20%) received 2 doses and 10 subjects (25%) received 3 doses.

Arm type	Experimental
Investigational medicinal product name	ingenol mebutate gel 0.05%
Investigational medicinal product code	
Other name	Picato® gel 0.05%
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Ingenol mebutate gel 0.05% was applied to the genital wart on Day 1 and if complete clearance of the genital wart was not obtained on Day 15, ingenol mebutate gel 0.05% was to be applied again on Day 15 and Day 29, as applicable.
The applications were done at the trial site by the (sub)investigator.

Any hair on the treatment area was cut with scissors to a length of maximum 2-3 mm. Picato® gel was applied in a generous amount, covering the genital wart in a thick layer and also covering 1-2 mm of the normal skin surrounding the wart.

Number of subjects in period 1[1]	All subjects
Started	40
Completed	26
Not completed	14
Adverse event, non-fatal	5
Lost to follow-up	2
Unacceptable Local Skin Reaction (LSR)	5
Lack of efficacy	2

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: 1 enrolled subject was a screening failure and was not assigned to treatment.

Baseline characteristics

Reporting groups	
Reporting group title	All subjects
Reporting group description:	
Of the 40 subjects assigned treatment, 22 subjects (55%) received 1 dose of ingenol mebutate gel 0.05%, 8 subjects (20%) received 2 doses and 10 subjects (25%) received 3 doses.	

Reporting group values	All subjects	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	38	
From 65-84 years	2	2	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	7	7	
Male	33	33	

End points

End points reporting groups

Reporting group title	All subjects
Reporting group description: Of the 40 subjects assigned treatment, 22 subjects (55%) received 1 dose of ingenol mebutate gel 0.05%, 8 subjects (20%) received 2 doses and 10 subjects (25%) received 3 doses.	
Subject analysis set title	Subjects receiving 1 dose
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received 1 dose of IMP.	
Subject analysis set title	Subjects receiving 2 doses
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received 2 doses of IMP.	
Subject analysis set title	Subjects receiving 3 doses
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received 3 doses of IMP.	
Subject analysis set title	Day 15
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who were assessed on Day 15/Visit 4.	
Subject analysis set title	Day 29
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who were assessed on Day 29/Visit 5.	
Subject analysis set title	Day 43
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who were assessed on Day 43/Visit 6.	
Subject analysis set title	Follow-up
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who were assessed at follow-up visit - 12 weeks after Day 29 or Day 43.	

Primary: Safety and tolerability - Day of Maximum Composite Local Skin Reaction (LSR) score by number of doses

End point title	Safety and tolerability - Day of Maximum Composite Local Skin Reaction (LSR) score by number of doses[1]

End point description:

The primary endpoint of this trial was incidence and severity of LSRs and treatment related AEs, assessed by:
-Day of Maximum Composite LSR score by number of doses
-Maximum Composite LSR score across visits
-Maximum Composite LSR score across visits by treated area

LSRs were assessed for presence/absence and grade (0 to 3) of the following individual LSRs: erythema, edema, weeping/exudate, vesiculation/blistering, crusting/(scabbing), and erosion/ulceration. A composite LSR score (0 to 18), reflecting the sum of the individual LSR components, was calculated at each visit.

End point type	Primary

End point timeframe:

Day 1 to Day 43

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this was an exploratory trial, no statistical analysis was planned.

End point values	Subjects receiving 1 dose	Subjects receiving 2 doses	Subjects receiving 3 doses	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	8	10	
Units: Subjects				
Day 3/Visit 3	22	8	9	
Day 29/Visit 5	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability - Maximum Composite Local Skin Reaction (LSR) score across visits by number of doses

End point title	Safety and tolerability - Maximum Composite Local Skin Reaction (LSR) score across visits by number of doses[2]

End point description:

End point type	Primary

End point timeframe:

Day 1 to Day 43

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this was an exploratory trial, no statistical analysis was planned.

End point values	All subjects	Subjects receiving 1 dose	Subjects receiving 2 doses	Subjects receiving 3 doses
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	22	8	10
Units: NA				
arithmetic mean (standard deviation)				
Maximum Composite LSR score	8.2 (± 3.4)	8.5 (± 3.6)	9 (± 3.7)	7.1 (± 3)

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability - Maximum Composite Local Skin Reaction (LSR) score across visits by treated area

End point title	Safety and tolerability - Maximum Composite Local Skin Reaction (LSR) score across visits by treated area[3]

End point description:

End point type	Primary

End point timeframe:

Day 1 to Day 43

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this was an exploratory trial, no statistical analysis was planned.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	40[4]			
Units: NA				
arithmetic mean (standard deviation)				
Foreskin (n=11)	10.3 (± 3.2)			
Glans penis (n=2)	10 (± 2.8)			
Penis shaft (n=19)	7.4 (± 2.4)			
Perianal (n=7)	6.3 (± 1.3)			
Perineal (n=3)	9.3 (± 4.2)			
Scrotum (n=7)	9.3 (± 4.2)			
Vulva (n=4)	8.3 (± 5.7)			
Total (n=53)	8.4 (± 3.3)			

Notes:

[4] - 40 subjects with a total of 53 (n=53) treated areas

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Clearance of Anogenital Warts 14 Days after Last Treatment Application

End point title	Complete Clearance of Anogenital Warts 14 Days after Last Treatment Application

End point description:

Complete clearance of anogenital warts after end of trial (defined as 14 days after last treatment application) and by visits.

End point type	Secondary

End point timeframe:

14 Days after last treatment application

End point values	All subjects	Day 15	Day 29	Day 43
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[5]	38	33	17
Units: Subjects				
Subjects cleared	17	12	11	4
Subjects not cleared	22	26	22	13

Notes:
[5] - Assessment was missing for 1 subject withdrawn at visit 3

End point values	Follow-up			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: Subjects				
Subjects cleared	6			
Subjects not cleared	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Reduction in Anogenital Wart Count from Baseline to End of Trial

End point title	Percentage Reduction in Anogenital Wart Count from Baseline to End of Trial

End point description:

Percentage reduction in anogenital wart count from baseline to end of trial (defined as 14 days after last treatment application) and by visit.

'End of trial' measure was defined as occurring 14 days after last treatment application.

End point type	Secondary

End point timeframe:

Day 1 to End of Trial

End point values	All subjects	Day 15	Day 29	Day 43
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	38	33	17
Units: percent				
arithmetic mean (standard deviation)				
Subject level	80.7 (± 25.5)	71.4 (± 31)	69.4 (± 30.8)	66.5 (± 30.9)

End point values	Follow-up			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: percent				
arithmetic mean (standard deviation)				
Subject level	61.5 (± 48.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence Rate - subject level

End point title	Recurrence Rate - subject level

End point description:

Recurrence of genital warts was assessed 12 weeks after Day 29 or Day 43 for subjects with complete clearance at any previous visit.

Reporting group: 16 subjects had complete clearance at the last visit, but 2 subjects did not attend the follow-up visit and were not assessed for recurrence. 8 out of 14 subjects (57.1%) had recurrence.

End point type	Secondary

End point timeframe:

12 weeks after Day 29 or Day 43

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	16[6]			
Units: percent				
arithmetic mean (confidence interval 95%)				
Recurrence	57.1 (28.9 to 82.3)			

Notes:

[6] - 16 subjects subjects had complete clearance at the last visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to the end of follow-up after final treatment (12 weeks from Day 29 or Day 43)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 40 (95.00%)		
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	15		
Skin injury			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Tendon injury			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			

Phimosis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
General disorders and administration site conditions Application site pain subjects affected / exposed occurrences (all) Application site pruritus subjects affected / exposed occurrences (all) Application site reaction subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Application site discolouration subjects affected / exposed occurrences (all) Application site induration subjects affected / exposed occurrences (all) Hunger subjects affected / exposed occurrences (all) Inflammation subjects affected / exposed occurrences (all)	34 / 40 (85.00%) 39 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		

Nausea subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Application site infection subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4 3 / 40 (7.50%) 3 1 / 40 (2.50%) 2 1 / 40 (2.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported