



Clinical trial results:

Risk of Squamous Cell Carcinoma on Skin Areas Treated with Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-003112-31 |
| Trial protocol | GB DE FR |
| Global end of trial date | 11 July 2019 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 06 August 2020 |
| First version publication date | 06 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | LP0041-63 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01926496 |
| 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 Disclosure, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com |
| Scientific contact | Clinical Disclosure, LEO Pharma A/S, +45 44945888, 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 October 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 July 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 July 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the cumulative incidence of squamous cell carcinoma (SCC) after treatment with ingenol mebutate gel and imiquimod cream.

Protection of trial subjects:

This 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 or their legally acceptable representative received written and verbal information concerning the clinical trial. Subjects or their legally acceptable representative were asked to consent that their personal data were recorded, collected, processed and could be transferred to EU and non-EU countries in accordance with any national legislation regulating privacy and data protection

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 03 June 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 | United Kingdom: 162 |
| Country: Number of subjects enrolled | France: 123 |
| Country: Number of subjects enrolled | Germany: 200 |
| Worldwide total number of subjects | 485 |
| EEA total number of subjects | 485 |

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) | 76 |

| | |
|---------------------|-----|
| From 65 to 84 years | 390 |
| 85 years and over | 19 |

Subject disposition

Recruitment

Recruitment details:

The clinical trial was performed at 44 sites in 3 countries: France, 11 sites; Germany, 15 sites; and United Kingdom, 18 sites

Pre-assignment

Screening details:

A total number of 578 male or female subjects aged 18–94 years with actinic keratosis in face or scalp were screened. Of these were 68 screening failures and 25 were not assigned to treatment. In total, 485 subjects were randomized 1:1 to treatment.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Open-label (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, 0.015% |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Ingenol mebutate gel, 0.015% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cutaneous solution |
| Routes of administration | Cutaneous use |

Dosage and administration details:

Topical application; 0.015% gel was applied to the selected treatment area (actinic keratosis lesions within a contiguous 25 cm² treatment area on the face or the scalp) once-daily for 3 consecutive days followed by 8 weeks of rest. Retreatment was done if the treatment fields were not completely cleared of AK.

| | |
|--|---------------------|
| Arm title | Imiquimod cream, 5% |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Imiquimod cream, 5% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Cutaneous use |

Dosage and administration details:

Topical application; 5% cream was applied to the selected treatment area (actinic keratosis lesions within a contiguous 25 cm² treatment area on the face or the scalp) once-daily for 3 days per week (e.g. Monday, Wednesday, and Friday) for 4 weeks followed by 4 weeks of rest. Retreatment was done if the treatment fields were not completely cleared of AK.

| Number of subjects in period 1^[1] | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% |
|---|------------------------------|---------------------|
| Started | 240 | 244 |
| Completed | 203 | 197 |
| Not completed | 37 | 47 |
| Adverse event, serious fatal | 8 | 5 |
| Consent withdrawn by subject | 14 | 15 |
| Exclusion criteria emerging | - | 2 |
| Adverse event, non-fatal | 3 | 4 |
| Not known | 2 | 7 |
| Unacceptable LSR | - | 3 |
| Lost to follow-up | 10 | 11 |

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: In total, 485 subjects were randomised (full analysis set), but 1 subject (randomised in United Kingdom) was not treated. To support the primary safety endpoints, all baseline and safety results are based on the 484 subjects. Efficacy analysis are based on all 485 randomized subjects due to the intention-to-treat principle.

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------------------------|
| Reporting group title | Ingenol mebutate gel, 0.015% |
| Reporting group description: - | |
| Reporting group title | Imiquimod cream, 5% |
| Reporting group description: - | |

| Reporting group values | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% | Total |
|---|------------------------------|---------------------|-------|
| Number of subjects | 240 | 244 | 484 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 34 | 42 | 76 |
| >=65 | 206 | 202 | 408 |
| <=18 | 0 | 0 | 0 |
| Gender categorical Units: Subjects | | | |
| Female | 10 | 15 | 25 |
| Male | 230 | 229 | 459 |
| Ethnicity Units: Subjects | | | |
| Unknown or Not Reported | 0 | 0 | 0 |
| Hispanic or Latino | 226 | 232 | 458 |
| Not Hispanic or Latino | 14 | 12 | 26 |
| Region of Enrollment Units: Subjects | | | |
| United Kingdom | 80 | 81 | 161 |
| Germany | 100 | 100 | 200 |
| France | 60 | 63 | 123 |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

In total, 485 subjects were randomised (full analysis set), but 1 subject (randomised in United Kingdom) was not treated. To support the primary safety endpoints, all baseline and safety results are based on the 484 subjects. Efficacy analysis are based on all 485 randomized subjects due to the intention-to-treat principle. 240 subjects were randomized to ingenol mebutate, and 245 were randomized to imiquimod.

| Reporting group values | Full analysis set | | |
|------------------------------------|-------------------|--|--|
| Number of subjects | 485 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 76 | | |
| >=65 | 408 | | |
| <=18 | 0 | | |

| | | | |
|-------------------------|-----|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | | |
| Male | 459 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Unknown or Not Reported | 0 | | |
| Hispanic or Latino | 26 | | |
| Not Hispanic or Latino | 458 | | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| United Kingdom | 161 | | |
| Germany | 200 | | |
| France | 123 | | |

End points

End points reporting groups

| | |
|--------------------------------|------------------------------|
| Reporting group title | Ingenol mebutate gel, 0.015% |
| Reporting group description: - | |
| Reporting group title | Imiquimod cream, 5% |
| Reporting group description: - | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

In total, 485 subjects were randomised (full analysis set), but 1 subject (randomised in United Kingdom) was not treated. To support the primary safety endpoints, all baseline and safety results are based on the 484 subjects. Efficacy analysis are based on all 485 randomized subjects due to the intention-to-treat principle. 240 subjects were randomized to ingenol mebutate, and 245 were randomized to imiquimod.

Primary: Incidence of SCC

| | |
|------------------------|---|
| End point title | Incidence of SCC ^[1] |
| End point description: | Cumulative incidence of SCC after treatment with ingenol mebutate gel and imiquimod cream. The primary response criterion is diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in the treatment field across the 3-year trial period. Kaplan-Meier estimate based on time to SCC or censoring. |
| End point type | Primary |
| End point timeframe: | 3 years |

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: The primary response criterion is diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in the treatment field across the 3-year trial period. Kaplan-Meier estimate based on time to SCC or censoring.

No comparison between treatment groups was made.

| End point values | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% | | |
|----------------------------------|------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 244 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 3.1 (1.4 to 6.0) | 0.4 (0.0 to 2.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of SCC and Other Neoplasia

| | |
|------------------------|---|
| End point title | Incidence of SCC and Other Neoplasia |
| End point description: | Cumulative incidence of SCC and other neoplasia after treatment with ingenol mebutate gel and imiquimod cream. The secondary response criterion is diagnosis of SCC and other |

neoplasia in the treatment field across the 3-year trial period.
Kaplan-Meier estimate based on time to SCC and other neoplasia, or censoring.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

| End point values | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% | | |
|----------------------------------|------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 244 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 6.2 (3.5 to 9.8) | 2.3 (0.9 to 4.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Clearance of AK Lesions After Last Treatment

| | |
|---|---|
| End point title | Complete Clearance of AK Lesions After Last Treatment |
| End point description: | |
| To compare the complete clearance of AK lesions in the selected treatment area after the last treatment cycle (at Week 8 or 16) | |
| End point type | Secondary |
| End point timeframe: | |
| 8-16 weeks | |

| End point values | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% | | |
|------------------------------|------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 244 ^[2] | | |
| Units: Count of Participants | 168 | 192 | | |

Notes:

[2] - One additional subject was analyzed (N=245). See description under the 'Full analysis set'

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | Comparison of relative risk |
| Statistical analysis description: | |
| Cochran-Mantel-Haenszel relative risk (ingenol mebutate / imiquimod), stratified by country, anatomical location and history of squamous cell | |

carcinoma.

| | |
|---|--|
| Comparison groups | Imiquimod cream, 5% v Ingenol mebutate gel, 0.015% |
| Number of subjects included in analysis | 484 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 0.99 |

Secondary: Partial Clearance of AK Lesions

| | |
|---|---------------------------------|
| End point title | Partial Clearance of AK Lesions |
| End point description: | |
| To compare the partial (at least 75%) clearance of AK lesions in the selected treatment area after the last treatment cycle (at Week 8 or 16) | |
| End point type | Secondary |
| End point timeframe: | |
| 8-16 weeks | |

| End point values | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% | | |
|------------------------------|------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 244 ^[3] | | |
| Units: Count of Participants | 195 | 210 | | |

Notes:

[3] - One additional subject was analyzed (N=245). See description under the 'Full analysis set'

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Comparison of relative risk |
| Statistical analysis description: | |
| Cochran-Mantel-Haenszel relative risk (ingenol mebutate / imiquimod), stratified by country, anatomical location and history of squamous cell carcinoma. | |
| Comparison groups | Ingenol mebutate gel, 0.015% v Imiquimod cream, 5% |
| Number of subjects included in analysis | 484 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.18 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.95 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.03 |

Secondary: Complete Clearance of AK Lesions at 12 Months

| | |
|--|---|
| End point title | Complete Clearance of AK Lesions at 12 Months |
| End point description: | |
| To compare the complete clearance of AK lesions at 12 months, defined as no AK lesions in the selected treatment area at any time from the last treatment cycle at Week 8 or 16 through to Month 12. | |
| End point type | Secondary |
| End point timeframe: | |
| 1 year | |

| End point values | Ingenol mebutate gel, 0.015% | Imiquimod cream, 5% | | |
|------------------------------|------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 244 ^[4] | | |
| Units: Count of Participants | 70 | 108 | | |

Notes:

[4] - One additional subject was analyzed (N=245). See description under the 'Full analysis set'

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Comparison of relative risk |
| Statistical analysis description: | |
| Cochran-Mantel-Haenszel relative risk (ingenol mebutate / imiquimod), stratified by country, anatomical location and history of squamous cell carcinoma. | |
| Comparison groups | Ingenol mebutate gel, 0.015% v Imiquimod cream, 5% |
| Number of subjects included in analysis | 484 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.84 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported differently before and after Week 20. Before Week 20, all AEs and serious AEs were recorded; after Week 20, all AEs inside the treatment area but only BCC/SCC and related SAEs outside the treatment area, were recorded.

Adverse event reporting additional description:

Adverse events (AEs) were reported differently before and after Week 20. Before Week 20, all AEs and serious AEs were recorded; after Week 20, all AEs inside the treatment area but only BCC/SCC and related SAEs outside the treatment area, were recorded.

Week 20 is the first week of the follow-up period.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Imiquimod until week 20 |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|-------------------------|
| Reporting group title | Imiquimod after week 20 |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|--------------------------------|
| Reporting group title | Ingenol mebutate after week 20 |
|-----------------------|--------------------------------|

Reporting group description: -

| | |
|-----------------------|--------------------------------|
| Reporting group title | Ingenol mebutate until week 20 |
|-----------------------|--------------------------------|

Reporting group description: -

| Serious adverse events | Imiquimod until week 20 | Imiquimod after week 20 | Ingenol mebutate after week 20 |
|---|-------------------------|-------------------------|--------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 244 (5.74%) | 2 / 244 (0.82%) | 11 / 240 (4.58%) |
| number of deaths (all causes) | 1 | 5 | 8 |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign neoplasm of skin | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bowen's disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 244 (0.41%) | 2 / 244 (0.82%) | 3 / 240 (1.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-Hodgkin's lymphoma stage I | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 2 / 244 (0.82%) | 0 / 244 (0.00%) | 5 / 240 (2.08%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound complication | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Skin neoplasm excision | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reversible ischaemic neurological deficit | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal achalasia | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Alveolitis | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 244 (0.41%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Ingenol mebutate until week 20 | | |
|---|-----------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 240 (8.75%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Benign neoplasm of skin | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastatic squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-Hodgkin's lymphoma stage I | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 240 (1.67%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Skin neoplasm excision | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reversible ischaemic neurological deficit | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal wall haematoma | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea haemorrhagic | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulum | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal achalasia | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Alveolitis | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Imiquimod until week 20 | Imiquimod after week 20 | Ingenol mebutate after week 20 |
|---|-------------------------|-------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 70 / 244 (28.69%) | 50 / 244 (20.49%) | 51 / 240 (21.25%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 12 / 244 (4.92%) | 36 / 244 (14.75%) | 33 / 240 (13.75%) |
| occurrences (all) | 15 | 62 | 56 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 24 / 244 (9.84%) | 24 / 240 (10.00%) |
| occurrences (all) | 3 | 38 | 42 |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 13 / 244 (5.33%) 14 | 0 / 244 (0.00%) 0 | 0 / 240 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Application site pain | | | |
| subjects affected / exposed | 15 / 244 (6.15%) | 0 / 244 (0.00%) | 1 / 240 (0.42%) |
| occurrences (all) | 17 | 0 | 2 |
| Application site pruritus | | | |
| subjects affected / exposed | 13 / 244 (5.33%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 15 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 8 / 244 (3.28%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 16 / 244 (6.56%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 19 | 0 | 0 |
| Eye disorders | | | |
| Eye swelling | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 244 (2.05%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |

| | | | |
|-----------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed | 11 / 244 (4.51%) | 0 / 244 (0.00%) | 0 / 240 (0.00%) |
| occurrences (all) | 11 | 0 | 0 |

| | | | |
|---|-----------------------------------|--|--|
| Non-serious adverse events | Ingenol mebutate until week 20 | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 67 / 240 (27.92%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 6 / 240 (2.50%) | | |
| occurrences (all) | 8 | | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 4 / 240 (1.67%) | | |
| occurrences (all) | 4 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 10 / 240 (4.17%) | | |
| occurrences (all) | 12 | | |
| General disorders and administration site conditions | | | |
| Application site pain | | | |
| subjects affected / exposed | 22 / 240 (9.17%) | | |
| occurrences (all) | 28 | | |
| Application site pruritus | | | |
| subjects affected / exposed | 14 / 240 (5.83%) | | |
| occurrences (all) | 15 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 240 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 240 (0.42%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Eye swelling | | | |
| subjects affected / exposed | 6 / 240 (2.50%) | | |
| occurrences (all) | 6 | | |
| Eyelid oedema | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 8 / 240 (3.33%) 9 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 3 / 240 (1.25%) 3 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 5 / 240 (2.08%) 5 6 / 240 (2.50%) 6 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 11 / 240 (4.58%) 12 | | |

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