



## Clinical trial results:

### Topical Ingenol mebutate versus 5% 5-fluorouracil versus 5% Imiquimod versus photodynamic therapy in the treatment of actinic keratosis: a multi-center randomized efficacy and cost-effectiveness study

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003691-23 |
| Trial protocol           | NL             |
| Global end of trial date |                |

#### Results information

|                                   |                                                               |
|-----------------------------------|---------------------------------------------------------------|
| Result version number             | v1 (current)                                                  |
| This version publication date     | 13 December 2021                                              |
| First version publication date    | 13 December 2021                                              |
| Summary attachment (see zip file) | Results of the primary outcome in article (NEJMoa1811850.pdf) |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | 50621 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02281682 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Academisch ziekenhuis Maastricht (AzM)                                                    |
| Sponsor organisation address | P. Debyelaan 25 , Maastricht, Netherlands, 6229 HX                                        |
| Public contact               | Shima Ahmady, Maastricht University Medical Center, shima.ahmady@mumc.nl                  |
| Scientific contact           | Shima Ahmady, Maastricht University Medical Center, +31 0433877295 , shima.ahmady@mumc.nl |

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                                       | Interim      |
| Date of interim/final analysis                       | 19 July 2018 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | No           |

Notes:

## General information about the trial

Main objective of the trial:

Primary outcome measure: treatment success (i.e. the proportion of patients with  $\geq 75\%$  lesion reduction in the number of AK lesions counted at baseline in the treatment area) 12 months post treatment.

Objective long-term follow-up: Proportion of patients who develop a squamous cell carcinoma in the treatment area during study follow-up (12 months), and long-term follow-up.

Protection of trial subjects:

The rights and well-being of human subjects are protected

Background therapy: -

Evidence for comparator:

PDT involves the application of 5-aminolevulinic acid (5-ALA) or methyl aminolevulinate (MAL) to the affected skin (by means of a cream), which is converted within the cells into the photosensitizer protoporphyrin IX. Surface illumination with 585-720 nm is then used to trigger the photodynamic reaction causing destruction of tumour cells by both apoptosis and necrosis. MAL-PDT (Metvix®, Galderma) has been registered for treatment of AK in Europe.

Imiquimod (registered for treatment of AK) is based on an immunomodulating mechanism which enhances the production of cytokines and natural killer cells, the proliferation of B cells and the activation of Langerhans cells, thereby stimulating the immune response. This treatment causes inflammation due to stimulation of the immune response at the tumour site resulting in erythema, oedema, scaling and erosions.

5-FU cream (registered for treatment of AK) is a topically applied chemical ablative agent that inhibits DNA synthesis, prevents cell proliferation, and causes tumour necrosis. Similar side-effects as mentioned with Imiquimod occur during treatment with 5-FU.

IM gel is a novel topical product, which is approved by Medicines Evaluation Board (MEB) and reimbursed by the Dutch healthcare insurances (as well as the other products) by health care insurances since October 2013. IM is a pleiotropic effector inducing cell death and activates the immune response.

|                                                           |                               |
|-----------------------------------------------------------|-------------------------------|
| Actual start date of recruitment                          | 01 January 2015               |
| Long term follow-up planned                               | Yes                           |
| Long term follow-up rationale                             | Efficacy, Scientific research |
| Long term follow-up duration                              | 5 Years                       |
| Independent data monitoring committee (IDMC) involvement? | No                            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 624 |
| Worldwide total number of subjects   | 624              |
| EEA total number of subjects         | 624              |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 83  |
| From 65 to 84 years                       | 511 |
| 85 years and over                         | 30  |

## Subject disposition

### Recruitment

Recruitment details:

patients who visit the outpatient departments of one of the participating centres because of AK, can be recruited. The eligible patients will be informed about the study by their treating resident in dermatology or dermatologist. If the patient is interested he/she will receive detailed patient information, including the informed consent form.

### Pre-assignment

Screening details:

From November 2014 through March 2017, a total of 1174 patients were assessed for eligibility.

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 624 |
| Number of subjects completed |     |

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Overall (overall period)    |
| Is this the baseline period? | Yes                         |
| Allocation method            | Randomised - controlled     |
| Blinding used                | Single blind                |
| Roles blinded                | Investigator <sup>[1]</sup> |

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | 5-fluourouracil |

Arm description:

5% 5-fluourouracil cream twice daily for 4 weeks

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | 5-Fluorouracil    |
| Investigational medicinal product code |                   |
| Other name                             | Efudix            |
| Pharmaceutical forms                   | Cream             |
| Routes of administration               | Topical           |

Dosage and administration details:

5% 5-Fluorouracil cream (Efudix®, Meda Pharma B.V., Amstelveen, the Netherlands) was self-applied twice daily for 4 weeks. Each patient received one tube of 40 grams independent of the treatment area size.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | imiquimod |
|------------------|-----------|

Arm description:

5% imiquimod cream,

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | imiquimod         |
| Investigational medicinal product code |                   |
| Other name                             | Aldara            |
| Pharmaceutical forms                   | Cream             |
| Routes of administration               | Topical           |

Dosage and administration details:

The 5% imiquimod cream (Aldara®, Meda Pharma B.V., Solna, Sweden) was self-applied once daily, 3 days a week (Monday-Wednesday-Friday), for 4 consecutive weeks. Per area of 25 cm<sup>2</sup> one sachet of 250 mg was used per day.

|                                                                                      |                              |
|--------------------------------------------------------------------------------------|------------------------------|
| <b>Arm title</b>                                                                     | MAL-PDT                      |
| Arm description:<br>methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session |                              |
| Arm type                                                                             | Active comparator            |
| Investigational medicinal product name                                               | methyl aminolevulinate cream |
| Investigational medicinal product code                                               |                              |
| Other name                                                                           | MAL cream                    |
| Pharmaceutical forms                                                                 | Cream                        |
| Routes of administration                                                             | Topical                      |

**Dosage and administration details:**

PDT treatment was performed by trained nurses who applied a thin (1 mm) layer of MAL cream (Metvix®, Galderma SA, Penn Pharmaceutical Services, Gwent, UK) to the treatment area, followed by coverage with light blocking aluminum foil and occlusive dressing (Tegaderm®, 3M, Leiden, the Netherlands) for 3 hours. Consecutively, the area was illuminated with a light emitting diode (LED): Aktelite® (Galderma, SA, Lausanne, Switzerland) or Omnilux® (Waldmann phototherapeutics, London, UK) with an optimum wavelength of 635 ± 18 nm (fluence 37 J/cm<sup>2</sup> during 7.23 minutes). Directly after illumination the treatment area was covered up for 24 hours. Per 25 cm<sup>2</sup> of treatment area, 2 grams of MAL cream were used.

|                                                  |                   |
|--------------------------------------------------|-------------------|
| <b>Arm title</b>                                 | ingenol mebutate  |
| Arm description:<br>0.015% ingenol mebutate gel. |                   |
| Arm type                                         | Active comparator |
| Investigational medicinal product name           | Ingenol mebutate  |
| Investigational medicinal product code           |                   |
| Other name                                       | Picato            |
| Pharmaceutical forms                             | Gel               |
| Routes of administration                         | Topical           |

**Dosage and administration details:**

Ingenol mebutate 0.015% gel (Picato®, LEO Pharma A/S, Bellerup, Denmark) was applied by the patient once daily for 3 consecutive days. Per 25 cm<sup>2</sup> of treatment area, one tube (0.47 gram) per day was used.

**Notes:**

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The investigator was blinded. Patients could not be blinded due to the investigated treatment options

| <b>Number of subjects in period 1</b> | 5-fluourouracil | imiquimod | MAL-PDT |
|---------------------------------------|-----------------|-----------|---------|
| Started                               | 155             | 156       | 156     |
| Completed                             | 155             | 156       | 156     |

| <b>Number of subjects in period 1</b> | ingenol mebutate |
|---------------------------------------|------------------|
| Started                               | 157              |
| Completed                             | 157              |

## Baseline characteristics

### Reporting groups

|                                                                                                  |                  |
|--------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                            | 5-fluourouracil  |
| Reporting group description:<br>5% 5-fluourouracil cream twice daily for 4 weeks                 |                  |
| Reporting group title                                                                            | imiquimod        |
| Reporting group description:<br>5% imiquimod cream,                                              |                  |
| Reporting group title                                                                            | MAL-PDT          |
| Reporting group description:<br>methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session |                  |
| Reporting group title                                                                            | ingenol mebutate |
| Reporting group description:<br>0.015% ingenol mebutate gel.                                     |                  |

| Reporting group values                                                                                                                                                                                                                                    | 5-fluourouracil | imiquimod | MAL-PDT  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------|----------|
| Number of subjects                                                                                                                                                                                                                                        | 155             | 156       | 156      |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                 |           |          |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                 |           |          |
| Age continuous                                                                                                                                                                                                                                            |                 |           |          |
| 73 (48-94)                                                                                                                                                                                                                                                |                 |           |          |
| Units: years                                                                                                                                                                                                                                              |                 |           |          |
| median                                                                                                                                                                                                                                                    | 74              | 73        | 73       |
| full range (min-max)                                                                                                                                                                                                                                      | 48 to 90        | 59 to 89  | 55 to 90 |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |                 |           |          |
| Female                                                                                                                                                                                                                                                    | 19              | 13        | 16       |
| Male                                                                                                                                                                                                                                                      | 136             | 143       | 140      |

| Reporting group values                                                                 | ingenol mebutate | Total       |  |
|----------------------------------------------------------------------------------------|------------------|-------------|--|
| Number of subjects                                                                     | 157              | 624         |  |
| Age categorical<br>Units: Subjects                                                     |                  |             |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days) |                  | 0<br>0<br>0 |  |

|                                          |          |     |  |
|------------------------------------------|----------|-----|--|
| Infants and toddlers (28 days-23 months) |          | 0   |  |
| Children (2-11 years)                    |          | 0   |  |
| Adolescents (12-17 years)                |          | 0   |  |
| Adults (18-64 years)                     |          | 0   |  |
| From 65-84 years                         |          | 0   |  |
| 85 years and over                        |          | 0   |  |
| Age continuous                           |          |     |  |
| 73 (48-94)                               |          |     |  |
| Units: years                             |          |     |  |
| median                                   | 72       |     |  |
| full range (min-max)                     | 51 to 94 | -   |  |
| Gender categorical                       |          |     |  |
| Units: Subjects                          |          |     |  |
| Female                                   | 18       | 66  |  |
| Male                                     | 139      | 558 |  |

## End points

### End points reporting groups

|                                                                                                  |                  |
|--------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                            | 5-fluourouracil  |
| Reporting group description:<br>5% 5-fluourouracil cream twice daily for 4 weeks                 |                  |
| Reporting group title                                                                            | imiquimod        |
| Reporting group description:<br>5% imiquimod cream,                                              |                  |
| Reporting group title                                                                            | MAL-PDT          |
| Reporting group description:<br>methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session |                  |
| Reporting group title                                                                            | ingenol mebutate |
| Reporting group description:<br>0.015% ingenol mebutate gel.                                     |                  |

### Primary: Primary end-point: treatment success

|                                                                                                                                                                                                                                                                                                                                                   |                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                   | Primary end-point: treatment success |
| End point description:<br>Primary outcome measure is adequate treatment success, defined as the proportion of participants at 12 months post final treatment, with $\geq 75\%$ reduction in the number of AK lesions counted at baseline in the treatment area ( $\geq 75\%$ patient clearance at 12 m<br>Status: Not ready for collecting values |                                      |
| End point type                                                                                                                                                                                                                                                                                                                                    | Primary                              |
| End point timeframe:<br>3 and 12 months after end of treatment                                                                                                                                                                                                                                                                                    |                                      |

| End point values            | 5-fluourouracil | imiquimod       | MAL-PDT         | ingenol mebutate |
|-----------------------------|-----------------|-----------------|-----------------|------------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group  |
| Number of subjects analysed | 155             | 156             | 156             | 157              |
| Units: AK                   | 75              | 54              | 38              | 29               |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Intention to treat primary outcome                       |
| Statistical analysis description:<br>The primary outcome measure (treatment success) will be described as percentages (number of patients with $\geq 75\%$ lesion reduction from baseline (n) / number of patients randomized (N)). Other data will be described as mean (+/- standard deviation, range), median as appropriate. The primary outcome (i.e., the proportion of patients with $\geq 75\%$ lesion reduction within 12 months) will be compared between the treatment groups using an intention-to-treat analysis. |                                                          |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 5-fluourouracil v imiquimod v MAL-PDT v ingenol mebutate |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 624               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | $\leq 0.05$       |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

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

### Dictionary used

|                 |      |
|-----------------|------|
| Dictionary name | CCMO |
|-----------------|------|

|                    |            |
|--------------------|------------|
| Dictionary version | Art. 1 lid |
|--------------------|------------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | 5-fluourouracil |
|-----------------------|-----------------|

Reporting group description:

5% 5-fluourouracil cream twice daily for 4 weeks

|                       |           |
|-----------------------|-----------|
| Reporting group title | imiquimod |
|-----------------------|-----------|

Reporting group description:

5% imiquimod cream,

|                       |         |
|-----------------------|---------|
| Reporting group title | MAL-PDT |
|-----------------------|---------|

Reporting group description:

methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session

|                       |                  |
|-----------------------|------------------|
| Reporting group title | ingenol mebutate |
|-----------------------|------------------|

Reporting group description:

0.015% ingenol mebutate gel.

| Serious adverse events                            | 5-fluourouracil | imiquimod       | MAL-PDT         |
|---------------------------------------------------|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |                 |                 |                 |
| subjects affected / exposed                       | 0 / 151 (0.00%) | 0 / 153 (0.00%) | 0 / 155 (0.00%) |
| number of deaths (all causes)                     | 2               | 1               | 1               |
| number of deaths resulting from adverse events    | 0               | 0               | 0               |

| Serious adverse events                            | ingenol mebutate |  |  |
|---------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 0 / 151 (0.00%)  |  |  |
| number of deaths (all causes)                     | 1                |  |  |
| number of deaths resulting from adverse events    | 0                |  |  |

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

| <b>Non-serious adverse events</b>                     | 5-fluorouracil                                                                                                                                                                                                                                            | imiquimod          | MAL-PDT            |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                                                                                                                                                                                                                                                           |                    |                    |
| subjects affected / exposed                           | 125 / 151 (82.78%)                                                                                                                                                                                                                                        | 103 / 153 (67.32%) | 113 / 155 (72.90%) |
| Skin and subcutaneous tissue disorders                |                                                                                                                                                                                                                                                           |                    |                    |
| skin reaction due to treatment                        | Additional description: Patient reported adverse events such as erythema, swelling, erosion, crusting, appearing of vesicles/bullae, scaling and itching were obtained through the diary, using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). |                    |                    |
| subjects affected / exposed                           | 125 / 151 (82.78%)                                                                                                                                                                                                                                        | 103 / 153 (67.32%) | 113 / 155 (72.90%) |
| occurrences (all)                                     | 1                                                                                                                                                                                                                                                         | 1                  | 1                  |

| <b>Non-serious adverse events</b>                     | ingenol mebutate                                                                                                                                                                                                                                          |  |  |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                                                                                                                                                                                                                                           |  |  |
| subjects affected / exposed                           | 134 / 151 (88.74%)                                                                                                                                                                                                                                        |  |  |
| Skin and subcutaneous tissue disorders                |                                                                                                                                                                                                                                                           |  |  |
| skin reaction due to treatment                        | Additional description: Patient reported adverse events such as erythema, swelling, erosion, crusting, appearing of vesicles/bullae, scaling and itching were obtained through the diary, using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). |  |  |
| subjects affected / exposed                           | 134 / 151 (88.74%)                                                                                                                                                                                                                                        |  |  |
| occurrences (all)                                     | 1                                                                                                                                                                                                                                                         |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment                                                                                                                                                          |
|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 May 2019 | Extra long-term follow-up visit to assess the number of squamous cell carcinoma during 12 months after treatment and long-term (up to five years after treatment). |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30855743>