



## Clinical trial results:

### Primary Imiquimod Treatment versus Surgery for Vulvar Intraepithelial Neoplasia:

### A Prospective Randomized Controlled Trial

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-002052-17   |
| Trial protocol           | AT               |
| Global end of trial date | 11 February 2021 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 02 June 2022 |
| First version publication date | 02 June 2022 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | PITVIN |
|-----------------------|--------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Medizinische Universität Graz   |
| Sponsor organisation address | Auenbruggerplatz 14, Graz, Austria, 8036  |
| Public contact               | Univ.- Frauenklinik Graz, Medizinische Universität Graz, 43 316385 12150, kks@medunigraz.at |
| Scientific contact           | Univ.- Frauenklinik Graz, Medizinische Universität Graz, 43 316385 12150, kks@medunigraz.at |

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                       | 04 October 2021  |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 11 February 2021 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The present study aims to compare primary imiquimod treatment with the standard treatment (surgery) for treatment of VIN (complete clinical response).

Protection of trial subjects:

Trial subjects will be invited for a clinical follow-up (medical history and clinical examination)

Subjects will be identified with Study IDs.

Background therapy: -

Evidence for comparator: -

|   |                                       |
|---|---------------------------------------|
| Actual start date of recruitment                          | 01 May 2013                           |
| Long term follow-up planned                               | Yes                                   |
| Long term follow-up rationale                             | Safety, 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 | Austria: 110 |
| Worldwide total number of subjects   | 110          |
| EEA total number of subjects         | 110          |

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)                      | 88 |
| From 65 to 84 years                       | 22 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

146 patients assessed for eligibility

36 excluded (16 did not meet inclusion criteria, 20 declined to participate)

110 enrolled and randomly assigned

### Pre-assignment

Screening details:

Patients with histologically confirmed vulvar HSIL

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

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

Arm description:

Topical treatment with Imiquimod

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Imiquimod     |
| Investigational medicinal product code |               |
| Other name                             | Aldara        |
| Pharmaceutical forms                   | Cream         |
| Routes of administration               | Cutaneous use |

Dosage and administration details:

Treatment with imiquimod was self-administered for a period of 4 months with possible extension to 6 months. Patients were handed a package of 5% imiquimod cream (Aldara®, Mylan) and received comprehensive oral and written instructions for usage. They were instructed to apply a thin layer of cream on the affected area remaining overnight without a cover in a slowly escalating dosage scheme: once a week for two weeks, twice a week the following two weeks, and if tolerated, 3 times a week for the last weeks

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

Arm description:

Patients allocated to surgical treatment were informed about the surgical procedure at the study center, and written informed consent was obtained. The type of surgery, i.e. excision or ablation, was based on clinical findings and the surgeon's judgement and was performed according to the standard procedures of the clinical trial site.

|          |         |
|----------|---------|
| Arm type | Surgery |
|----------|---------|

No investigational medicinal product assigned in this arm

| <b>Number of subjects in period 1</b> | Imiquimod | Surgery |
|---------------------------------------|-----------|---------|
| Started                               | 56        | 54      |
| Completed                             | 54        | 53      |
| Not completed                         | 2         | 1       |
| Consent withdrawn by subject          | -         | 1       |
| Lost to follow-up                     | 2         | -       |

## Baseline characteristics

### Reporting groups

|   |           |
|---|-----------|
| Reporting group title   | Imiquimod |
| Reporting group description:  |           |
| Topical treatment with Imiquimod  |           |
| Reporting group title   | Surgery   |
| Reporting group description:  |           |
| Patients allocated to surgical treatment were informed about the surgical procedure at the study center, and written informed consent was obtained. The type of surgery, i.e. excision or ablation, was based on clinical findings and the surgeon`s judgement and was performed according to the standard procedures of the clinical trial site. |           |

| Reporting group values                             | Imiquimod    | Surgery      | Total |
|--|--------------|--------------|-------|
| Number of subjects                                 | 56           | 54           | 110   |
| Age categorical                                    |              |              |       |
| Units: Subjects                                    |              |              |       |
| In utero   |              |              | 0     |
| Preterm newborn infants (gestational age < 37 wks) |              |              | 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)                               |              |              | 0     |
| From 65-84 years                                   |              |              | 0     |
| 85 years and over                                  |              |              | 0     |
| Age continuous                                     |              |              |       |
| Units: years                                       |              |              |       |
| median   | 54.0         | 49.0         |       |
| inter-quartile range (Q1-Q3)                       | 44.0 to 67.0 | 43.0 to 60.0 | -     |
| Gender categorical                                 |              |              |       |
| only female patients were included                 |              |              |       |
| Units: Subjects                                    |              |              |       |
| Female   | 56           | 54           | 110   |
| Male   | 0            | 0            | 0     |

### Subject analysis sets

|  |                               |
|--|-------------------------------|
| Subject analysis set title   | Intention-to-treat population |
| Subject analysis set type  | Intention-to-treat            |
| Subject analysis set description:  |                               |
| ITT analysis was performed in 107 patients (54 imiquimod, 53 surgery)      |                               |
| Subject analysis set title   | Per-protocol population       |
| Subject analysis set type  | Per protocol                  |
| Subject analysis set description:  |                               |
| 98 patients completed the study per-protocol (46 imiquimod and 52 surgery) |                               |

| <b>Reporting group values</b>   | Intention-to-treat<br>population | Per-protocol<br>population |  |
|---|----------------------------------|----------------------------|--|
| Number of subjects  | 107                              | 98                         |  |
| Age categorical   |                                  |                            |  |
| Units: Subjects   |                                  |                            |  |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>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  |                                  |                            |  |
| Units: years  |                                  |                            |  |
| median  | 51.0                             | 51.5                       |  |
| inter-quartile range (Q1-Q3)  | 43.0 to 62.0                     | 44.0 to 62.0               |  |
| Gender categorical  |                                  |                            |  |
| only female patients were included  |                                  |                            |  |
| Units: Subjects   |                                  |                            |  |
| Female  | 107                              |                            |  |
| Male  | 0                                |                            |  |

## End points

### End points reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | Imiquimod                     |
| Reporting group description:<br>Topical treatment with Imiquimod  |                               |
| Reporting group title   | Surgery                       |
| Reporting group description:<br>Patients allocated to surgical treatment were informed about the surgical procedure at the study center, and written informed consent was obtained. The type of surgery, i.e. excision or ablation, was based on clinical findings and the surgeon's judgement and was performed according to the standard procedures of the clinical trial site. |                               |
| Subject analysis set title  | Intention-to-treat population |
| Subject analysis set type   | Intention-to-treat            |
| Subject analysis set description:<br>ITT analysis was performed in 107 patients (54 imiquimod, 53 surgery)  |                               |
| Subject analysis set title  | Per-protocoll population      |
| Subject analysis set type   | Per protocol                  |
| Subject analysis set description:<br>98 patients completed the study per-protocol (46 imiquimod and 52 surgery)   |                               |

### Primary: Complete clinical response

|  |                            |
|--|----------------------------|
| End point title  | Complete clinical response |
| End point description:<br>Complete clinical response (CCR) was defined as no clinical evidence of vulvar lesion, meaning 100% reduction of primary lesion size after primary allocated study treatment (one surgical intervention or local imiquimod treatment up to 6 months). Clinical response was determined by clinical assessment and confirmed by control biopsy. In case of discrepancy between clinical evaluation and histology, the endpoint was adjusted according to the histological result. |                            |
| End point type   | Primary                    |
| End point timeframe:<br>The primary endpoint was clinical response at 6 months.  |                            |

| End point values            | Imiquimod       | Surgery         | Per-protocoll population |  |
|-----------------------------|-----------------|-----------------|--------------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set     |  |
| Number of subjects analysed | 46              | 52              | 98                       |  |
| Units: Number of patients   | 37              | 41              | 98                       |  |

### Statistical analyses

|  |                 |
|--|-----------------|
| Statistical analysis title   | Primary outcome |
| Statistical analysis description:<br>To evaluate the non-inferiority of imiquimod to surgical treatment, |                 |

the difference in CCR proportions (surgical vs imiquimod) at 6 months and the corresponding 95% CIs were estimated with the Farrington-Manning method. Imiquimod was regarded as non-inferior if the upper bound of the CI did not exceed 20%. As a sensitivity analysis of the primary endpoint, we used the Cochran-Mantel-Haenszel method to adjust the proportion difference regarding the stratum used for randomisation.

|   |                          |
|---|--------------------------|
| Comparison groups                       | Imiquimod v Surgery      |
| Number of subjects included in analysis | 98                       |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | non-inferiority          |
| P-value                                 | = 0.0056                 |
| Method                                  | Farrington-Manning Test  |
| Parameter estimate                      | difference in proportion |
| Point estimate                          | 0.016                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.015                    |
| upper limit                             | 0.018                    |
| Variability estimate                    | Standard deviation       |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 months

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Imiquimod |
|-----------------------|-----------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Surgery |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | Imiquimod      | Surgery         |  |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events |                |                 |  |
| subjects affected / exposed                       | 4 / 56 (7.14%) | 9 / 52 (17.31%) |  |
| number of deaths (all causes)                     | 1              | 0               |  |
| number of deaths resulting from adverse events    | 0              | 0               |  |
| Surgical and medical procedures                   |                |                 |  |
| Hospitalisation                                   |                |                 |  |
| subjects affected / exposed                       | 3 / 56 (5.36%) | 9 / 52 (17.31%) |  |
| occurrences causally related to treatment / all   | 1 / 6          | 4 / 14          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0           |  |
| Pregnancy   |                |                 |  |
| subjects affected / exposed                       | 1 / 56 (1.79%) | 0 / 52 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0           |  |

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

| Non-serious adverse events                            | Imiquimod         | Surgery           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 56 / 56 (100.00%) | 52 / 52 (100.00%) |  |
| Surgical and medical procedures                       |                   |                   |  |
| Headache  |                   |                   |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 28 / 56 (50.00%) | 12 / 52 (23.08%) |  |
| occurrences (all)           | 28               | 12               |  |
| Fatigue                     |                  |                  |  |
| subjects affected / exposed | 30 / 56 (53.57%) | 15 / 52 (28.85%) |  |
| occurrences (all)           | 30               | 15               |  |
| Muscle discomfort           |                  |                  |  |
| subjects affected / exposed | 16 / 56 (28.57%) | 8 / 52 (15.38%)  |  |
| occurrences (all)           | 16               | 8                |  |
| Vulvar erosion              |                  |                  |  |
| subjects affected / exposed | 17 / 56 (30.36%) | 14 / 52 (26.92%) |  |
| occurrences (all)           | 17               | 14               |  |
| Genital erythema            |                  |                  |  |
| subjects affected / exposed | 30 / 56 (53.57%) | 24 / 52 (46.15%) |  |
| occurrences (all)           | 30               | 24               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

selection bias: only patients compliant with the study medication were included in the per-protocol analysis.

Measurement bias: patients receiving imiquimod had on average more assessments

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35483400>