

**Clinical trial results:****RANDOMISED PILOT STUDY TO ASSESS THE CLINICAL EFFICACY OF DAYLIGHT PHOTODYNAMIC THERAPY WITH METHYL AMINOLEVULINATE CREAM (METVIX?), (MAL-PDT), IN THE PREVENTION OF ACTINIC KERATOSIS AND NON MELANOMA SKIN CANCER IN TRANSPLANT PATIENTS****Summary**

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-002663-42 |
| Trial protocol | ES |
| Global end of trial date | 25 October 2018 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 20 October 2021 |
| First version publication date | 20 October 2021 |
| Summary attachment (see zip file) | Final report summary (INFORME FINAL 17-06-2019. FIRMADO.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | TFDTRASP |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Clínica Universidad de Navarra |
| Sponsor organisation address | Avda. Pío XII, 36, Pamplona, Spain, 31008 |
| Public contact | UCEC, Clínica Universidad de Navarra, 34 9482554002725, ucicec@unav.es |
| Scientific contact | UCEC, Clínica Universidad de Navarra, 34 9482554002725, ucicec@unav.es |

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 | 02 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Assess if there are less appearance of AK in the side treated with repeated treatments of daylight photodynamic therapy compared with the side treated with cryotherapy, in transplant patients, at 21 months from treatment initiation.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 March 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 21 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 24 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 24 |

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) | 4 |
| From 65 to 84 years | 20 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 24 patients were included. Three patients were lost. One after the first intervention and two after the 3-month visit. All treatment and follow-up visits were completed by 21 patients. All patients were male and Caucasian.

Pre-assignment

Screening details:

Recruitment started in April 2016 and ended in February 2017.

25 patients were selected, of which 24 were included. One patient was not finally included because he did not meet the inclusion criteria.

Period 1

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

Blinding implementation details:

Blind for evaluator and not blind for the patient and the doctor.

Arms

| | |
|-----------|-----------|
| Arm title | Treatment |
|-----------|-----------|

Arm description:

This study has an intra-individual comparison design, in which a half-face was treated with MAL-PDT in daylight and the contralateral side was the control in each patient. The control side was treated with cryotherapy, which is the best treatment option for now, and is what is commonly used to treat actinic keratoses in these types of patients. This design, therefore, is not a crossover design since each treatment was applied to a different area at the same time. It is a design commonly used in dermatology for the comparison of topical treatments.

The sides of the face and / or the scalp were randomly assigned to the interventions based on a computer generated sequence. Each patient was assigned an order number.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | metil-aminolevulinato (MAL) in combination with Photodynamic therapy (PDT) |
| Investigational medicinal product code | |
| Other name | Metvix |
| Pharmaceutical forms | Cream |
| Routes of administration | Cutaneous use |

Dosage and administration details:

1st Treatment at most 3 weeks after inclusion: TFD-MAL with daylight of a half face and Cryotherapy (2 freezing cycles) on the contralateral side on the day of initiation of treatment.

2nd Treatment carried out 3 months after the first treatment: TFD-MAL with daylight of a half face and Cryotherapy (2 freezing cycles) on the contralateral side on the day of initiation of treatment.

3rd Treatment: carried out 9 months after the first treatment: TFD-MAL with daylight of a half face and Cryotherapy (2 freezing cycles) on the contralateral side on the day of initiation of treatment.

| Number of subjects in period 1 | Treatment |
|---------------------------------------|-----------|
| Started | 24 |
| Completed | 21 |
| Not completed | 3 |
| Consent withdrawn by subject | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description: -

| Reporting group values | Treatment | Total | |
|------------------------|-----------|-------|--|
| Number of subjects | 24 | 24 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 4 | 4 | |
| From 65-84 years | 20 | 20 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 24 | 24 | |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description:

This study has an intra-individual comparison design, in which a half-face was treated with MAL-PDT in daylight and the contralateral side was the control in each patient. The control side was treated with cryotherapy, which is the best treatment option for now, and is what is commonly used to treat actinic keratoses in these types of patients. This design, therefore, is not a crossover design since each treatment was applied to a different area at the same time. It is a design commonly used in dermatology for the comparison of topical treatments.

The sides of the face and / or the scalp were randomly assigned to the interventions based on a computer generated sequence. Each patient was assigned an order number.

Primary: Difference in the number of total lesions between the two treatment areas at the final visit

| | |
|-----------------|---|
| End point title | Difference in the number of total lesions between the two treatment areas at the final visit ^[1] |
|-----------------|---|

End point description:

Difference in the number of total lesions between the two treatment areas at the final visit, V21, observed in the physical examination performed at that visit, compared to the pretreatment physical examination.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

21 months

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: No statistical analyses have been specified for this primary end point because there is only one group treatment and the end point is measure of the difference number of lesions before and after the clinical trial.

All the variables were analyzed using the Student's t test for paired data or the Wilcoxon test of signed ranks for paired data. The cut-off point for establishing statistical significance was 0.05. All analyses were performed using Stata 14 (StataCorp. 2015).

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Treatment | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: number | 21 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

21 months

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

Dictionary used

| | |
|-----------------|----|
| Dictionary name | NA |
|-----------------|----|

| | |
|--------------------|----|
| Dictionary version | NA |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events | Treatment | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 24 (41.67%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| cellulitis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Fever | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Dyspnea and edema in the legs | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| unstable angina | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|--|--|--|
| Decompensated heart failure subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Diffuse B lymphoma in jejunum subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Herpes zoster | Additional description: Herpes zoster | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Social circumstances | | | |
| Cognitive deterioration | Additional description: Subacute cognitive deterioration detected in visit on August 8, 2016 | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| acute diverticulitis subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudoaneurysm bleeding subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| | | | |
|--|-------------------|--|--|
| Non-serious adverse events | Treatment | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 24 (100.00%) | | |

| | | | |
|---|--|--|--|
| Cardiac disorders coronary stent placement subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | | |
| General disorders and administration site conditions Headache subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) heatstroke subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 3 / 24 (12.50%) 3 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1 | | |
| Social circumstances Accidental fall subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | | |
| Eye disorders Cataract surgery subjects affected / exposed occurrences (all) vitreous hemorrhage subjects affected / exposed occurrences (all) Loss of sight subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1 | | |
| Gastrointestinal disorders Diarrhoea | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| bronchitis | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| itchiness | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 6 | | |
| blisters | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Scabs | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| desquamation | | | |
| subjects affected / exposed | 6 / 24 (25.00%) | | |
| occurrences (all) | 6 | | |
| Erythema | | | |
| subjects affected / exposed | 12 / 24 (50.00%) | | |
| occurrences (all) | 12 | | |
| Stinging | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| Squamous cell carcinoma removal | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| impetiginization | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Hip arthrosis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Edema | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Gout | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Hernia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Inflammation | | | |
| subjects affected / exposed | 4 / 24 (16.67%) | | |
| occurrences (all) | 4 | | |
| laminectomy | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Thrombosed fistula removal | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Common cold | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Flu | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| Herpes dermatitis | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 24 (16.67%) | | |
| occurrences (all) | 4 | | |
| Sialadenitis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 20 September 2016 | modificate some aspects about the recruitmen, inclusion criteria and withdrawal |
| 16 January 2018 | Include a partial statistical analysis |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported