



Clinical trial results: Squamous cell carcinoma prevention in organ transplant recipients using topical treatments: a feasibility study (SPOT)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-000893-32 |
| Trial protocol | GB |
| Global end of trial date | 03 July 2018 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 |
| This version publication date | 04 September 2019 |
| First version publication date | 04 September 2019 |
| Summary attachment (see zip file) | SPOT Public Summary for lay readers (SPOT Public Summary 15-Aug-2019.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 008171BLT |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------------|
| ISRCTN number | ISRCTN26398197 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CRCTU Number: SK2007 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Queen Mary University of London |
| Sponsor organisation address | Lower Ground Floor, 5 Walden Street, London, United Kingdom, E1 2EF |
| Public contact | Mrs Yolande Jefferson-Hulme, Cancer Research UK Clinical Trials Unit (CRCTU), 44 0121 4143792, SPOT@trials.bham.ac.uk |
| Scientific contact | Mrs Yolande Jefferson-Hulme, Cancer Research UK Clinical Trials Unit (CRCTU), 44 0121 4143792, SPOT@trials.bham.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 15 August 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Cutaneous squamous cell carcinoma (cSCC) is economically a major burden to the NHS. The incidence is approximately 30,000 new cases per year in the UK. Immunosuppressed organ transplant recipients (OTR) have a more than 100-fold increased risk and an accelerated carcinogenic process, making them an ideal population in which to test interventions aimed at preventing cSCC. Premalignant lesions, termed actinic keratoses (AK), are present on sun-damaged skin and effective topical agents are available to treat them. The close relationship between AK and cSCC means that such topical treatment of a field bearing multiple AK should significantly reduce subsequent risk of developing cSCC, but this assumption has never been proven. The main objective of the trial is to determine the feasibility of performing a phase III RCT for either of the two interventions, whilst also assessing their activity.

Protection of trial subjects:

The trial has been performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (see Appendix 5).

The trial was conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments, the Data Protection Act 1998 and Human Tissue Act 2008) and the International Conference on Harmonisation Guidelines for GCP (ICH GCP). This trial was carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol was submitted to, and approved by, the REC prior to circulation.

Before any patients were enrolled into the trial, the Principal Investigator at each site was required to obtain local R&D approval. Sites were not permitted to enrol patients until written confirmation of R&D approval was received by the SPOT Trial Office.

It was the responsibility of the Principal Investigator to ensure that all subsequent amendments gained the necessary local approval. This was all done to protect the health and interest of individual patients.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

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) | 18 |
| From 65 to 84 years | 22 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first site was activated in December 2014 and the first patient was recruited on 10-Dec-2014. The last patient was recruited on 07-Sep-2016. The trial was closed to recruitment later that day. Recruitment to the ICP Arm closed in September 2015, with a total of 61 patients. Recruitment to the OTR arm reached 40 patients.

Pre-assignment

Screening details:

Screening procedures were undertaken for OTR who would potentially participate in the randomised trial and were performed 4-5 weeks before the treatment phase commenced. These included:

Medical history

Skin Exam

Details of immunosuppressive treatment and previous treatment for AK

Clinical assessment

Punch Biopsy

Vitamin D

hCG

Renal Function

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | OTR : 5-Fluorouracil (with discretionary sunscreen) |

Arm description:

Treatment Cycle 1

5-fluorouracil 1-2x/day for 4 wks

Four Weeks Rest

Treatment Cycle 2

5-fluorouracil 1-2x/day for 4 wks

Sunscreen as required throughout

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | Marketing Authorisation: PL 46302/0128 |
| Other name | Efudix 5% cream. |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Treatment Cycle 1

5-fluorouracil 1-2x/day for 4 weeks (elf-administered)

Four Weeks Rest

Treatment Cycle 2

5-fluorouracil 1-2x/day for 4 weeks (elf-administered)

Sunscreen as required throughout

| | |
|------------------|--|
| Arm title | OTR: 5% Imiquimod (with discretionary sunscreen) |
|------------------|--|

Arm description:

Treatment Cycle 1

Imiquimod 3-5x/wk for 4 wks

Four Weeks Rest

Treatment Cycle 2

Imiquimod 3-5x/wk for 4 wks

Sunscreen as required throughout

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | 5% Imiquimod |
| Investigational medicinal product code | Marketing Authorisation: EU/1/98/080/001-002 |
| Other name | ALDARA 5% cream |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Treatment Cycle 1
Imiquimod 3-5x/wk for 4 wks
Four Weeks Rest
Treatment Cycle 2
Imiquimod 3-5x/wk for 4 wks
Sunscreen as required throughout

| | |
|------------------|---|
| Arm title | OTR: Standard Care (discretionary sunscreen only) |
|------------------|---|

Arm description:

Sunscreen as required throughout

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Discretionary Sunscreen (Mixed Brands) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Cutaneous use |

Dosage and administration details:

Sunscreen as required throughout

| Number of subjects in period 1 | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) |
|---------------------------------------|---|--|---|
| Started | 13 | 14 | 13 |
| Completed | 13 | 14 | 13 |

Baseline characteristics

Reporting groups

| | |
|-----------------------------------|---|
| Reporting group title | OTR : 5-Fluorouracil (with discretionary sunscreen) |
| Reporting group description: | |
| Treatment Cycle 1 | |
| 5-fluorouracil 1-2x/day for 4 wks | |
| Four Weeks Rest | |
| Treatment Cycle 2 | |
| 5-fluorouracil 1-2x/day for 4 wks | |
| Sunscreen as required throughout | |
| Reporting group title | OTR: 5% Imiquimod (with discretionary sunscreen) |
| Reporting group description: | |
| Treatment Cycle 1 | |
| Imiquimod 3-5x/wk for 4 wks | |
| Four Weeks Rest | |
| Treatment Cycle 2 | |
| Imiquimod 3-5x/wk for 4 wks | |
| Sunscreen as required throughout | |
| Reporting group title | OTR: Standard Care (discretionary sunscreen only) |
| Reporting group description: | |
| Sunscreen as required throughout | |

| Reporting group values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) |
|---|---|--|---|
| Number of subjects | 13 | 14 | 13 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| median | 64.82 | 66.36 | 65.59 |
| inter-quartile range (Q1-Q3) | 61.85 to 68.76 | 57.27 to 68.92 | 62.1 to 69.13 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2 | 4 | 3 |
| Male | 11 | 10 | 10 |
| Gender | | | |
| Units: Subjects | | | |
| Male | 11 | 10 | 10 |
| Female | 2 | 4 | 3 |
| Stratification factor: Treatment zone | | | |

| | | | |
|--|----------------|----------------|----------------|
| Units: Subjects | | | |
| Head and neck | 7 | 7 | 6 |
| Acral | 6 | 7 | 7 |
| Patient currently taking Acitretin? | | | |
| Units: Subjects | | | |
| No | 7 | 12 | 12 |
| Yes | 6 | 2 | 1 |
| Previously diagnosed with skin cancer? | | | |
| Units: Subjects | | | |
| No | 2 | 4 | 3 |
| Yes | 11 | 9 | 10 |
| Not Supplied | 0 | 1 | 0 |
| Age (years) | | | |
| Units: -- | | | |
| median | 64.82 | 66.36 | 65.59 |
| inter-quartile range (Q1-Q3) | 61.85 to 68.76 | 57.27 to 68.92 | 62.10 to 69.13 |
| Vitamin D (nmol/L) | | | |
| Units: -- | | | |
| median | 48.00 | 60.50 | 49.00 |
| inter-quartile range (Q1-Q3) | 35.10 to 65.00 | 55.00 to 75.60 | 36.00 to 80.20 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 40 | | |
| 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 | | | |
| inter-quartile range (Q1-Q3) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | | |
| Male | 31 | | |
| Gender | | | |
| Units: Subjects | | | |
| Male | 31 | | |
| Female | 9 | | |
| Stratification factor: Treatment zone | | | |
| Units: Subjects | | | |
| Head and neck | 20 | | |
| Acral | 20 | | |

| | | | |
|---|----|--|--|
| Patient currently taking Acitretin? Units: Subjects | | | |
| No | 31 | | |
| Yes | 9 | | |
| Previously diagnosed with skin cancer? Units: Subjects | | | |
| No | 9 | | |
| Yes | 30 | | |
| Not Supplied | 1 | | |
| Age (years) Units: -- median inter-quartile range (Q1-Q3) | - | | |
| Vitamin D (nmol/L) Units: -- median inter-quartile range (Q1-Q3) | - | | |

Subject analysis sets

| | |
|--|---------------|
| Subject analysis set title | Full analysis |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Total number of patients randomised in the trial | |

| Reporting group values | Full analysis | | |
|--|-------------------------|--|--|
| Number of subjects | 40 | | |
| Age categorical Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous Units: years median inter-quartile range (Q1-Q3) | 65.39 58.52 to 69.02 | | |
| Gender categorical Units: Subjects | | | |
| Female | 9 | | |
| Male | 31 | | |
| Gender Units: Subjects | | | |
| Male | 31 | | |
| Female | 9 | | |

| | | | |
|---|-------------------------|--|--|
| Stratification factor: Treatment zone Units: Subjects | | | |
| Head and neck | 20 | | |
| Acral | 20 | | |
| Patient currently taking Acitretin? Units: Subjects | | | |
| No | 31 | | |
| Yes | 9 | | |
| Previously diagnosed with skin cancer? Units: Subjects | | | |
| No | 9 | | |
| Yes | 30 | | |
| Not Supplied | 1 | | |
| Age (years) Units: -- median inter-quartile range (Q1-Q3) | 65.39 58.52 to 69.02 | | |
| Vitamin D (nmol/L) Units: -- median inter-quartile range (Q1-Q3) | 55.00 39.00 to 75.60 | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | OTR : 5-Fluorouracil (with discretionary sunscreen) |
| Reporting group description: | |
| Treatment Cycle 1 | |
| 5-fluorouracil 1-2x/day for 4 wks | |
| Four Weeks Rest | |
| Treatment Cycle 2 | |
| 5-fluorouracil 1-2x/day for 4 wks | |
| Sunscreen as required throughout | |
| Reporting group title | OTR: 5% Imiquimod (with discretionary sunscreen) |
| Reporting group description: | |
| Treatment Cycle 1 | |
| Imiquimod 3-5x/wk for 4 wks | |
| Four Weeks Rest | |
| Treatment Cycle 2 | |
| Imiquimod 3-5x/wk for 4 wks | |
| Sunscreen as required throughout | |
| Reporting group title | OTR: Standard Care (discretionary sunscreen only) |
| Reporting group description: | |
| Sunscreen as required throughout | |
| Subject analysis set title | Full analysis |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Total number of patients randomised in the trial | |

Primary: The proportion of eligible patients willing to be randomised into the trial

| | |
|---|--|
| End point title | The proportion of eligible patients willing to be randomised into the trial ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Screening | |
| 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 statistical analysis is the proportion along with its 95% confidence interval, which has been presented. | |

| End point values | Full analysis | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 67 (55 to 77) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: The proportion of patients who complete treatment Cycle 1, for each active treatment arm

| | |
|-----------------|---|
| End point title | The proportion of patients who complete treatment Cycle 1, for each active treatment arm ^[2] |
|-----------------|---|

End point description:

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

End point timeframe:

Cycle 1

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis is the proportion along with its 95% confidence interval, which has been presented.

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | |
|----------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 13 | 14 | 0 ^[3] | |
| Units: percent | | | | |
| number (confidence interval 95%) | 85 (55 to 98) | 93 (66 to 100) | (to) | |

Notes:

[3] - This arm did not have treatment cycles and therefore cannot be included in this analysis

Statistical analyses

No statistical analyses for this end point

Primary: The proportion of patients who require treatment Cycle 2 and complete it, for each active treatment arm

| | |
|-----------------|--|
| End point title | The proportion of patients who require treatment Cycle 2 and complete it, for each active treatment arm ^[4] |
|-----------------|--|

End point description:

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

End point timeframe:

Cycle 2

Notes:

[4] - 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 statistical analysis is the proportion along with its 95% confidence interval, which has been presented.

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | |
|----------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 12 | 14 | 0 ^[5] | |
| Units: percent | | | | |
| number (confidence interval 95%) | 83 (52 to 98) | 93 (66 to 100) | (to) | |

Notes:

[5] - This arm did not have treatment cycles and therefore cannot be included in this analysis

Statistical analyses

No statistical analyses for this end point

Primary: The proportion of patients who would be willing to use the treatment again

| | |
|-----------------|---|
| End point title | The proportion of patients who would be willing to use the treatment again ^[6] |
|-----------------|---|

End point description:

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

End point timeframe:

End of trial

Notes:

[6] - 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 statistical analysis is the proportion along with its 95% confidence interval, which has been presented.

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | Full analysis |
|----------------------------------|---|--|---|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 11 | 11 | 9 | 31 |
| Units: percent | | | | |
| number (confidence interval 95%) | 73 (39 to 94) | 82 (48 to 98) | 89 (52 to 100) | 81 (63 to 93) |

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance of AK trial treatment field(s): defined as the proportion of patients which have had AKs identified at baseline that are no longer detectable at 4 weeks post treatment

| | |
|-----------------|---|
| End point title | Clearance of AK trial treatment field(s): defined as the proportion of patients which have had AKs identified at baseline that are no longer detectable at 4 weeks post treatment |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

4 weeks post treatment

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | Full analysis |
|----------------------------------|---|--|---|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 13 | 14 | 13 | 40 |
| Units: percent | | | | |
| number (confidence interval 95%) | 23 (5 to 54) | 14 (2 to 43) | 23 (5 to 54) | 20 (9 to 36) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | 5-Fluorouracil vs. Standard Care Risk Difference |
| Comparison groups | OTR : 5-Fluorouracil (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.32 |

| | |
|---|--|
| Statistical analysis title | 5% Imiquimod vs. Standard Care Risk Difference |
| Comparison groups | OTR: Standard Care (discretionary sunscreen only) v OTR: 5% Imiquimod (with discretionary sunscreen) |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.648 |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | 0.21 |

Secondary: Clearance of AK trial treatment field(s): defined as the proportion of patients which have had AKs identified at baseline that are no longer detectable at 8 weeks post treatment

| | |
|-----------------|---|
| End point title | Clearance of AK trial treatment field(s): defined as the proportion of patients which have had AKs identified at baseline that are no longer detectable at 8 weeks post treatment |
|-----------------|---|

End point description:

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 8 weeks post treatment | |

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | Full analysis |
|----------------------------------|---|--|---|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 13 | 14 | 13 | 40 |
| Units: percent | | | | |
| number (confidence interval 95%) | 46 (19 to 75) | 14 (2 to 43) | 0 (0 to 25) | 20 (9 to 36) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | 5-Fluorouracil vs. Standard Care Risk Difference |
| Comparison groups | OTR : 5-Fluorouracil (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.015 |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.19 |
| upper limit | 0.73 |

| | |
|-----------------------------------|--|
| Statistical analysis title | 5% Imiquimod vs. Standard Care Risk Difference |
| Comparison groups | OTR: Standard Care (discretionary sunscreen only) v OTR: 5% Imiquimod (with discretionary sunscreen) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.481 |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.33 |

Secondary: Persistence of AK clearance trial treatment field: defined as the proportion of patients with AKs which were cleared at 4 weeks post treatment which remain undetectable at the completion of the 12 month follow-up period

| | |
|--|---|
| End point title | Persistence of AK clearance trial treatment field: defined as the proportion of patients with AKs which were cleared at 4 weeks post treatment which remain undetectable at the completion of the 12 month follow-up period |
| End point description: It is not possible to present 5% Imiquimod (with discretionary sunscreen) (0/2) vs. Standard Care (discretionary sunscreen only) (0/3) due to both groups have 0 as the numerator. | |
| End point type | Secondary |
| End point timeframe: 12 month follow-up period | |

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | Full analysis |
|----------------------------------|---|--|---|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 3 | 2 | 3 | 8 |
| Units: percent | | | | |
| number (confidence interval 95%) | 33 (1 to 91) | 0 (0 to 84) | 0 (0 to 71) | 13 (0 to 53) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | 5-Fluorouracil vs. Standard Care Risk Difference |
| Comparison groups | OTR : 5-Fluorouracil (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 6 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.87 |

Secondary: Persistence of AK clearance trial treatment field: defined as the proportion of patients with AKs which were cleared at 8 weeks post treatment which remain undetectable at the completion of the 12 month follow-up period

| | |
|--|---|
| End point title | Persistence of AK clearance trial treatment field: defined as the proportion of patients with AKs which were cleared at 8 weeks post treatment which remain undetectable at the completion of the 12 month follow-up period |
| End point description: | |
| Risk difference was not calculable due to Standard Care (discretionary sunscreen only) having 0 patients who cleared at week 8, thus the proportion was 0/0. | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months follow-up | |

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | Full analysis |
|----------------------------------|---|--|---|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 6 | 2 | 0 ^[7] | 8 |
| Units: percent | | | | |
| number (confidence interval 95%) | 50 (12 to 88) | 50 (1 to 99) | (to) | 50 (16 to 84) |

Notes:

[7] - The proportion for this arm is 0/0

Statistical analyses

No statistical analyses for this end point

Secondary: Development of cSCC at 12 months post treatment

| | |
|---|---|
| End point title | Development of cSCC at 12 months post treatment |
| End point description: | |
| The 1 year event rates are presented here | |
| End point type | Secondary |

End point timeframe:

Trial entry until 12 months follow-up

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | Full analysis |
|----------------------------------|---|--|---|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 13 | 14 | 13 | 40 |
| Units: percent | | | | |
| number (confidence interval 95%) | 47 (25 to 77) | 50 (28 to 77) | 31 (13 to 63) | 37 (25 to 54) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | 5-Fluorouracil vs.Standard Care |
| Comparison groups | OTR: Standard Care (discretionary sunscreen only) v OTR : 5-Fluorouracil (with discretionary sunscreen) |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.52 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.43 |
| upper limit | 5.39 |

| | |
|---|--|
| Statistical analysis title | 5% Imiquimod vs. Standard Care |
| Comparison groups | OTR: 5% Imiquimod (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.32 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 6.58 |

Secondary: EQ5D Quality of Life

| | |
|-----------------|----------------------|
| End point title | EQ5D Quality of Life |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to end of trial follow-up

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 12 | |
| Units: mean | 11 | 12 | 12 | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | 5-Fluorouracil vs. Standard Care |
|-----------------------------------|----------------------------------|

Statistical analysis description:

This is the model output for treatment from a multilevel mixed-effects model for EQ5D

| | |
|-------------------|---|
| Comparison groups | OTR : 5-Fluorouracil (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
|-------------------|---|

| | |
|---|----|
| Number of subjects included in analysis | 23 |
|---|----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------|
| Analysis type | other |
|---------------|-------|

| | |
|---------|---------|
| P-value | = 0.196 |
|---------|---------|

| | |
|--------|-----------------------|
| Method | Mixed models analysis |
|--------|-----------------------|

| | |
|--------------------|--------------------------------|
| Parameter estimate | Mean difference (final values) |
|--------------------|--------------------------------|

| | |
|----------------|-------|
| Point estimate | 0.046 |
|----------------|-------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|--------|
| lower limit | -0.024 |
|-------------|--------|

| | |
|-------------|-------|
| upper limit | 0.116 |
|-------------|-------|

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | 5% Imiquimod vs. Standard Care |
|-----------------------------------|--------------------------------|

Statistical analysis description:

This is the model output for treatment from a multilevel mixed-effects model for EQ5D

| | |
|-------------------|--|
| Comparison groups | OTR: Standard Care (discretionary sunscreen only) v OTR: 5% Imiquimod (with discretionary sunscreen) |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.988 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.072 |
| upper limit | 0.073 |

Secondary: DLQI Quality of Life

| | |
|------------------------------------|----------------------|
| End point title | DLQI Quality of Life |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to end of trial follow-up | |

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 12 | |
| Units: Mean | 11 | 12 | 12 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | 5-Fluorouracil vs. Standard Care |
| Comparison groups | OTR : 5-Fluorouracil (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
| Number of subjects included in analysis | 23 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.437 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.695 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.449 |
| upper limit | 1.059 |

| | |
|---|--|
| Statistical analysis title | 5% Imiquimod vs. Standard Care |
| Comparison groups | OTR: 5% Imiquimod (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.236 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.027 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.673 |
| upper limit | 2.728 |

Secondary: AK Index Quality of Life

| | |
|------------------------------------|--------------------------|
| End point title | AK Index Quality of Life |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to end of trial follow-up | |

| End point values | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: 5% Imiquimod (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 11 | |
| Units: Mean | 10 | 10 | 11 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | 5-Fluorouracil vs. Standard Care |
| Comparison groups | OTR : 5-Fluorouracil (with discretionary sunscreen) v OTR: Standard Care (discretionary sunscreen only) |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.091 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.938 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.786 |
| upper limit | 10.661 |

| | |
|---|--|
| Statistical analysis title | 5% Imiquimod vs. Standard Care |
| Comparison groups | OTR: Standard Care (discretionary sunscreen only) v OTR: 5% Imiquimod (with discretionary sunscreen) |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.354 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -2.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.445 |
| upper limit | 3.025 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting was from commencement of treatment to 30 days after completion of trial treatment.

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

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | 4.0 |

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | OTR : 5-Fluorouracil (with discretionary sunscreen) |
|-----------------------|---|

Reporting group description:

Treatment Cycle 1
5-fluorouracil 1-2x/day for 4 wks
Four Weeks Rest
Treatment Cycle 2
5-fluorouracil 1-2x/day for 4 wks
Sunscreen as required throughout

| | |
|-----------------------|---|
| Reporting group title | OTR: Standard Care (discretionary sunscreen only) |
|-----------------------|---|

Reporting group description:

Sunscreen as required throughout

| | |
|-----------------------|--|
| Reporting group title | OTR: 5% Imiquimod (with discretionary sunscreen) |
|-----------------------|--|

Reporting group description:

Treatment Cycle 1
Imiquimod 3-5x/wk for 4 wks
Four Weeks Rest
Treatment Cycle 2
Imiquimod 3-5x/wk for 4 wks
Sunscreen as required throughout

| Serious adverse events | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | OTR: 5% Imiquimod (with discretionary sunscreen) |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | 2 / 14 (14.29%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Neuropathic pain (R foot) | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | 0 / 14 (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 |
| Ear and labyrinth disorders | | | |
| Hearing impaired | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | OTR : 5-Fluorouracil (with discretionary sunscreen) | OTR: Standard Care (discretionary sunscreen only) | OTR: 5% Imiquimod (with discretionary sunscreen) |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 13 (61.54%) | 3 / 13 (23.08%) | 11 / 14 (78.57%) |
| Vascular disorders | | | |
| Bruising | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Chest pain - cardiac | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | 2 / 14 (14.29%) |
| occurrences (all) | 2 | 0 | 3 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 1 / 13 (7.69%) | 4 / 14 (28.57%) |
| occurrences (all) | 5 | 2 | 7 |
| Flu like symptoms | | | |

| | | | |
|---|-----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 13 (0.00%) 0 | 3 / 14 (21.43%) 4 |
| Malaise subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | 1 / 13 (7.69%) 1 | 2 / 14 (14.29%) 3 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 14 (0.00%) 0 |
| External ear inflammation subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 14 (0.00%) 0 |
| Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 13 (7.69%) 1 | 2 / 14 (14.29%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 13 (15.38%) 2 | 2 / 14 (14.29%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Skin and subcutaneous tissue disorders Photosensitivity subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 13 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 7 / 13 (53.85%) 11 | 1 / 13 (7.69%) 1 | 3 / 14 (21.43%) 4 |
| Skin hypopigmentation subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 13 (0.00%) 0 | 2 / 14 (14.29%) 2 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | 1 / 13 (7.69%) 2 | 2 / 14 (14.29%) 2 |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| Bone pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 13 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 2 | 0 | 1 |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Crystal arthropathy | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| R foot pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 19 December 2013 | Substantial amendment: Protocol Update -Addition of "or intolerance" to exclusion criteria regarding trial medication - Change to recruitment and follow up duration - Other minor amendments & corrections |
| 09 December 2016 | Substantial amendment: Protocol Update -Updated Section 6.1 randomisation method -Updated section 5.1.1: clarify that biopsies can be taken from inside or outside the treatment area -Updated section 7.6 to remove reference to Reference Safety Information (RSI) and replace with Summary of Product Characteristics (SPC). -Updated Section 7.3.4 to incorporate guidance from SPC relating to avoidance of exposure to UV radiation -Updated section 6.2, Section 7.5.2 to clarify that photocopies of the transparencies form part of the CRF -Updated Sponsor and Trial Staff contact details -Other minor amendments & corrections |

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/29782648>