



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
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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)
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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)
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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	65.39		
inter-quartile range (Q1-Q3)	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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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
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End point description:

End point type	Secondary
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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
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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
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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
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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
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End point description:

The 1 year event rates are presented here

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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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)
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Number of subjects included in analysis	23
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Analysis specification	Pre-specified
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Analysis type	other
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P-value	= 0.196
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Method	Mixed models analysis
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Parameter estimate	Mean difference (final values)
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Point estimate	0.046
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-0.024
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upper limit	0.116
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Statistical analysis title	5% Imiquimod vs. Standard Care
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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)
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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
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

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

Sunscreen as required throughout

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