Clinical trial results:
Prospective, randomized, controlled, multicenter, two-armed, study comparing daylight photodynamic therapy using MAL with cryosurgery for the treatment and prophylaxis of actinic keratoses in photodamaged skin of the face

Summary

EudraCT number	2014-005121-13
Trial protocol	DE
Global end of trial date	07 May 2018

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022
Summary attachment (see zip file)	Abstract (Abstract.docx)

Trial information

Trial identification

Sponsor protocol code	Daylight_01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02736760
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Regensburg
Sponsor organisation address	Franz-Josef-Strauss Allee 11, 93042 Regensburg , Germany, 93053
Public contact	Klinik für Dermatologie Regensburg , University Hospital Regensburg, 0049 9419449656, sigrid.karrer@ukr.de
Scientific contact	Klinik für Dermatologie Regensburg , University Hospital Regensburg, 0049 9419449656, sigrid.karrer@ukr.de

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 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2018
Global end of trial reached?	Yes
Global end of trial date	07 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the study is the evaluation of the efficacy of daylight- PDT with MAL in the treatment and prophylaxis of AKs in the face compared to cryosurgery

Protection of trial subjects:

There were no specific measures

Background therapy:

There was no background therapy

Evidence for comparator:

Cryosurgery was chosen as control instead of a placebo treatment because it would have been unethical to leave AKs untreated for the study duration of 2 years due to their precancerous potential. Since cryosurgery only targets single lesions, no preventive effect in field-cancerized areas can be expected.

Actual start date of recruitment	01 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	29
From 65 to 84 years	29

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient entered the study on 3 April 2016, and the last patient finished the study on 7 May 2018.

Pre-assignment

Screening details:

Consecutive patients who fullfilled inclusion criteria were screened (n=59), 58 patients were randomised. 29 for the intervention group, 29 for the control group. 6 patients withdrew consent during the study. At the end of the study the ITT analysis set was n=55 and the PP analysis set was n = 44 patients

Pre-assignment period milestones

Number of subjects started	58
Number of subjects completed	

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	daylight-PDT

Arm description:

MAL application followed by illumination with daylight (daylight-PDT)

Arm type	Experimental
Investigational medicinal product name	Metvix
Investigational medicinal product code	L01XD03 (ATC code)
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

10 g, cutaneous use

Arm title	Kryosurgery

Arm description:

cryosurgery

Arm type	Active comparator
Investigational medicinal product name	Metvix
Investigational medicinal product code	L01XD03 (ATC code)
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

10 g, cutaneous use

Number of subjects in period 1	daylight-PDT	Kryosurgery
Started	29	29
Completed	24	24
Not completed	5	5
Adverse event, serious fatal	2	-
Consent withdrawn by subject	2	4
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	daylight-PDT
Reporting group description:	
MAL application followed by illumination with daylight (daylight-PDT)	
Reporting group title	Kryosurgery
Reporting group description:	
cryosurgery	

Reporting group values	daylight-PDT	Kryosurgery	Total
Number of subjects	29	29	58
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	4	6
From 65-84 years	26	25	51
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	24	23	47
Male	5	6	11

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat (ITT) collective comprises all patients who were included in the study. According to the ITT principle, all patients are evaluated according to their randomly assigned treatment, regardless of whether they refused or discontinued treatment or whether other protocol violations occurred. Only patients in whom the number of newly occurring AKs was recorded at least once via visits 2 to 6 will be included in the ITT collective.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) collective includes all patients from the ITT collective without serious protocol violations.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety collective includes all patients who received at least one treatment and had at least one post-baseline safety assessment.	

Reporting group values	ITT	PP	Safety
Number of subjects	55	44	58
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	5	6
From 65-84 years	48	39	51
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	45	34	47
Male	10	10	11

End points

End points reporting groups

Reporting group title	daylight-PDT
Reporting group description:	
MAL application followed by illumination with daylight (daylight-PDT)	
Reporting group title	Kryosurgery
Reporting group description:	
cryosurgery	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat (ITT) collective comprises all patients who were included in the study. According to the ITT principle, all patients are evaluated according to their randomly assigned treatment, regardless of whether they refused or discontinued treatment or whether other protocol violations occurred. Only patients in whom the number of newly occurring AKs was recorded at least once via visits 2 to 6 will be included in the ITT collective.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) collective includes all patients from the ITT collective without serious protocol violations.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety collective includes all patients who received at least one treatment and had at least one post-baseline safety assessment.	

Primary: Cumulative number of observed AKs at time points 2 to 6

End point title	Cumulative number of observed AKs at time points 2 to 6
End point description:	
End point type	Primary
End point timeframe:	
Assessment of number of lesions: 3, 6, 12, 18, 24 months after baseline.	

End point values	daylight-PDT	Kryosurgery	ITT	PP
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	29	26	55	44
Units: AK lesions	29	26	55	44

Statistical analyses

Statistical analysis title	Analysis of primary endpoint
Comparison groups	daylight-PDT v Kryosurgery v ITT v PP

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.183 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.18
upper limit	1.21
Variability estimate	Standard deviation

Notes:

[1] - P-value of per protocol analysis set p = 0.542

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline, 3, 6, 12, 18, 24 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21
Reporting groups	
Reporting group title	Daylight-PDT
Reporting group description: MAL application followed by illumination with daylight (daylight-PDT)	
Reporting group title	Cryosurgery
Reporting group description: cryosurgery	

Serious adverse events	Daylight-PDT	Cryosurgery	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	1 / 29 (3.45%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Lacunar infarction			

subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Daylight-PDT	Cryosurgery	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 29 (37.93%)	13 / 29 (44.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acanthoma			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Acrochordon			

subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Basal cell carcinoma			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Malignant melanoma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Bowen's disease			
subjects affected / exposed	3 / 29 (10.34%)	1 / 29 (3.45%)	
occurrences (all)	3	1	
Dysplastic naevus			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Haemangioma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Keratoacanthoma			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Skin papilloma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Surgical and medical procedures			
Joint arthroplasty			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Ulcer			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Asthma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Intertrigo			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic dermatitis			

subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary hesitation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Synovial cyst			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Infected bite			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	

Postoperative wound infection			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Pulpitis dental			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Body tinea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Tinea pedis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2016	Change of PI and deputy.
06 December 2016	Change of PI-deputy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported