Clinical trial results:
A multi-center, randomized study on oral 8-methoxypsoralen plus UVA with or without maintenance therapy in mycosis fungoides EORTC/ISCL stage Ia to IIb.

Summary

EudraCT number	2012-000212-28
Trial protocol	AT
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	M-PUVA2012

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Graz
Sponsor organisation address	Auenbruggerplatz 8, Graz, Austria,
Public contact	Information Klinische Studie, Medical University of Graz, 43 316385 12538, dermatologie@medunigraz.at
Scientific contact	Information Klinische Studie, Medical University of Graz, 43 316385 12538, dermatologie@medunigraz.at

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2018
Global end of trial reached?	Yes
Global end of trial date	02 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether PUVA maintenance therapy does prolong disease free survival after initial complete response.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2012
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	Austria: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started in April 2012. The last patient was enrolled in March 2016.
Enrollment was closed in August 2016.

Pre-assignment

Screening details:

28 patients were assessed for eligibility. 1 patient was excluded due to an unconfirmed histologic diagnosis. 27 patients received induction treatment. Of these, 19..... patients reached complete remission and were randomised.

Period 1

Period 1 title	Enrolment to randomisation
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Initial treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Oxsoralen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Initial treatment with a maximum duration of 24 weeks, depending on whether complete remission occurred

Number of subjects in period 1	Initial treatment
Started	28
Randomisation	19
Completed	19
Not completed	9
Screening failure	1
Adverse event, non-fatal	1
Non achievement of complete remission	7

Period 2

Period 2 title	Randomisation to complete follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance group

Arm description:

Maintenance treatment was given once a week for one month (4 weeks), every 2 weeks for 2 months (8 weeks) and after three months once a month over 6 months. After 9 (10, 11, or 12) months of maintenance therapy (14 treatments) patients discontinued therapy. If PUVA treatment did lead to erythema during maintenance therapy, the dose for the next treatment was reduced by up to 30%.

Arm type	Experimental
Investigational medicinal product name	Oxsoralen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Maintenance treatment was given once a week for one month (4 weeks), every 2 weeks for 2 months (8 weeks) and after three months once a month over 6 months. After 9 (10, 11, or 12) months of maintenance therapy (14 treatments) patients discontinued therapy. If PUVA treatment didlead to erythema during maintenance therapy, the dose for the next treatment was reduced by up to 30%.

Arm title	Control

Arm description:

Patients received no therapy. Patients were followed up at the same intervals like patients in study arm A (maintenance).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Maintenance group	Control
Started	11	8
Completed	11	8

Baseline characteristics

Reporting groups	
Reporting group title	Enrolment to randomisation

Reporting group description: -

Reporting group values	Enrolment to randomisation	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	0	0	
85 years and over	0	0	
65-85 years	10	10	
Gender categorical Units: Subjects			
Female	6	6	
Male	22	22	

End points

End points reporting groups

Reporting group title	Initial treatment
Reporting group description: -	
Reporting group title	Maintenance group
Reporting group description:	
Maintenance treatment was given once a week for one month (4 weeks), every 2 weeks for 2 months (8 weeks) and after three months once a month over 6 months. After 9 (10, 11, or 12) months of maintenance therapy (14 treatments) patients discontinued therapy. If PUVA treatment did lead to erythema during maintenance therapy, the dose for the next treatment was reduced by up to 30%.	
Reporting group title	Control
Reporting group description:	
Patients received no therapy. Patients were followed up at the same intervals like patients in study arm A (maintenance).	
Subject analysis set title	Mainentance group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Maintenance treatment was given once a week for one month (4 weeks), every 2 weeks for 2 months (8 weeks) and after three months once a month over 6 months. After 9 (10, 11, or 12) months of maintenance therapy (14 treatments) patients discontinued therapy.	
Subject analysis set title	Control group
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients received no therapy	

Primary: median time to recurrence after complete remission

End point title	median time to recurrence after complete remission
End point description:	
The median duration of disease-free rremission was 15 months in patients with maintenance therapy compared with 4 months in those without it (p: 0.02)	
End point type	Primary
End point timeframe:	
max. 12 months	

End point values	Mainentance group	Control group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	8		
Units: days	10	8		

Statistical analyses

Statistical analysis title	Median duration of disease-free remission
Comparison groups	Mainentance group v Control group

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Secondary: Expression of Treg-related molecules in lesional tissue

End point title	Expression of Treg-related molecules in lesional tissue

End point description:

Expression of CD3 and CD4 mRNA was significantly lower than at baseline.

The expression of CTLA-4, Foxp3, GITR and TGF-ß was quantified to characterize Tregs in skin and their change throughout treatment.
In general, the expression of each of these markers was higher in lesional skin at baseline than in normal skin from donors. After 12 to 24 weeks, PUVA treatment significantly reduced the expression of these markers.

End point type	Secondary

End point timeframe:

after 12 to 24 weeks of PUVA treatment

End point values	Initial treatment			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Relative units	28			

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell proliferative capacity

End point title	T-cell proliferative capacity

End point description:

Analysis of T-cell proliferative capacity in cells from blood at baseline and throughout treatment showed that PUVA therapy reduced the response to CD3/CD28 stimulation, reaching statistical significance after 12 to 24 weeks of treatment.

End point type	Secondary

End point timeframe:

Start of induction phase until end of induction phase (12 to 24 weeks)

End point values	Initial treatment			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Treg index	28			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From time of informed consent to end of follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Enrolled patients

Reporting group description: -

Serious adverse events	Enrolled patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Melanoma	Additional description: Melanoma in situ		
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Enrolled patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 28 (82.14%)		
General disorders and administration site conditions			
Nausea			

subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	7		
Vertigo			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cephalalgia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Burning sensation skin			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Application site itching			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Urticaria			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Administration site erythema			
subjects affected / exposed	12 / 28 (42.86%)		
occurrences (all)	13		
Skin lesion			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Increased serum creatinine			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2013	Addition of two study sites
03 May 2013	Change of one principal investigator
05 August 2013	Change of one principal investigator
10 March 2014	Change of one principal investigator
05 June 2014	Possible prolongation of initial treatment phase from 3 to max. 6 months Change of one exclusion criterion Addition of the observatory arm for patients who did not response completely after initial therapy after the maximum treatment period Change of time period for taking of biopsies Additional amount of blood taken

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported