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

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Study protocol:

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1. Background and Introduction

Mycosis Fungoides (MF) represents the most common type of cutaneous T-cell lymphoma (CTCL), accounting for about two thirds of all CTCLs and for almost 50% of all primary cutaneous lymphomas [WILLEMZE]. It is characterized by the progressive evolution of erythematous patches, plaques and tumours over years.

1.1. Prognosis

Most prognostic factors in MF include type and extent of skin involvement and presence or absence of extracutaneous disease, which determine clinical stage (Appendix: Table 1). Recent findings suggest that patient's life expectancy is not adversely affected in stage I A (limited patch, papules and/or plaques covering <10% of the skin surface), while patients diagnosed with tumor disease or erythroderma (stages IIB-IVB) have a worse overall outcome, with median survival of 4 to 5 years [WILLEMZE].

1.2. Aetiology and Pathogenesis

Although the aetiology of MF is unknown, important insights have been gained in the pathogenesis and immunological perturbations that are associated with this disease. Whereas the disease is characterized by infiltration and proliferation of T helper lymphocytes (mainly CD4+) in the skin, CDla+ Langerhans cells are thought to be involved in its pathogenesis as well. Furthermore there is evidence, that an abnormal cytokine expression in MF might be responsible for tumor progression. Moreover, cytokine loops might explain phenomena like the epidermotropism of malignant cells and/or the depression of the anti-tumor immune response [HWANG].

1.3. Treatment

There is no curative therapy for MF and the aim of treatment is to induce complete remissions of disease and to prolong disease free and finally overall survival while maintaining the patient's quality of life. There have been a large number of uncontrolled studies in MF with response data but virtually no other controlled studies with data on disease free and overall survival. Most comparative studies in MF have been based on relatively small numbers of patients, which has also severely limited any statistical interpretation.

1.3.1. PUVA therapy

It is now commonly accepted that early-stage MF should be initially treated with skin-directed therapies. More aggressive treatments should be reserved for higher stages or progression [TRAUTINGER]. Skin directed therapies include topical corticosteroids, topical chemotherapy, topical bexarotene, radiotherapy and phototherapy. The first report of PUVA treatment [psoralen plus ultraviolet (UV) A] in MF was published in 1976 [GILCHREST]. Since then several groups have successfully used PUVA to treat MF [ROENIGK, HÖNIGSMANN, DIEDEREN]. Today PUVA therapy is a well-accepted first-line treatment option for skin-limited MF, because there is good evidence that it is effective in clearing of skin lesions in early stages of the disease. Long-term remissions can be achieved in a certain percentage of patients [TRAUTINGER]. However, MF lesions may reappear after a very variable time interval with median time to recurrence of 9 to 15 months [WACKERNAGEL].

The mechanism of action of PUVA in MF is not entirely understood. PUVA selectively eliminates T-lymphocyte populations by induction of apoptosis. It causes a functional impairment of CDla+ Langerhans cells, which are thought to be involved in the pathogenesis of MF by perpetuating the epidermal affinity of infiltrating T cells. It may also act by directly downregulating homing receptors on epidermotropic malignant T cells and by interfering with epidermal cytokine production [HÖNIGSMANN].

1.3.2. Rationale for proposed study

Maintenance PUVA-therapy might be beneficial in slowing relapse of MF after complete initial remission. However, controlled clinical trials concerning PUVA maintenance have not been performed so far [QUERFELD, SANCHEZ, POTHIAWALA]. Moreover, no evidence is available on the optimal frequency and length of maintenance therapy either [HÖNIGSMANN].

2. Objectives of the trial

2.1 General objectives:

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

3. End-points

3.1. Primary endpoint:

Comparison of median time to recurrence after complete remission between patients treated with maintenance therapy vs. patients without maintenance therapy.

3.2. Secondary endpoints

- Comparison of time from end of treatment to recurrence on condition that the patient is in complete remission at the end of treatment between patients treated with maintenance therapy vs. patients without maintenance therapy.
- Cytokine response in serum and tissue
- Quality of life
- HADS

4. Patient selection criteria

4.1. Inclusion Criteria:

- Histopathologically documented MF clinical stage IA-IIB (see Table1) confirmed by current or previous diagnostic lesion biopsy
- A Karnofsky performance score $\geq$ 60 (see Table 2)
- Age $\geq$ 18 years - $\leq$ 85
- Anti-ds-DNA (antinuclear antibodies) AND anti-Ro/La antibodies: negative
- Acceptable organ function defined as follows:

SGOT (AST) and SGPT (ALT) $\leq$ 2.5 times the upper limit of normal for the institution

- Creatinine $\leq$ 2 times the upper limit of normal for the institution
- No evidence of severe cardiac insufficiency (NYHA grade III-IV)
- Women of child bearing potential must have a negative serum or urine pregnancy test (ß-HCG) within seven (7) days prior to randomization
- Absence of any serious intercurrent illness or infection at time of entry into the study that could interfere with planned treatment
- Patients must be willing to accept limiting sun exposure on the day receiving PUVA treatment
- Written informed consent

4.2. Exclusion criteria:

- Pregnancy and Lactation
- Photosensitive diseases such as lupus erythematosus or basal cell nevus syndrome
- Skin cancer syndromes such as Xeroderma pigmentosum or basal cell nevus syndrome
- PUVA (oral or topical) treatment within the last 3 months

5. PUVA treatment and follow-up

Psoralens are photosensitising agents. Methoxsalen – the most commonly used drug is a psoralen derivative that is structurally and pharmacologically related to trioxsalen. For PUVA treatment 8-methoxypsoralen (8-MOP) will be used. Patients receive a liquid preparation of 8-MOP (10 mg) in soft gelatine capsules (Oxsoralen®; Gerot Pharmazeutika GmbH, Vienna, Austria, please refer to the Summary of Product Characteristics). The dose of 8-MOP is based on the patient's weight. The standard dose of approximately10 mg per 20 kg body weight will be given 1 h before UVA exposure, according to the following table:

Body weight (kg)	**8-MOP (Oxsoralen) dose (10mg = 1 Cps) mg = Cps**
< 30	10 = 1
30 - 50	20 = 2
51 - 65	30 = 3
66 - 80	40 = 4
81 - 90	50 = 5
91 - 115	60 = 6
> 115	70 = 7

The initial (starting) UVA dose after psoralen administration will be applied according to the results of skin phototoxicity dose testing. The minimal phototoxic dose (MPD) will be determined by irradiating several skin areas 2 cm in diameter using a Waldmann UVA 800 unit (or similar equipment) with varying light exposure doses and determining the exposure dose that produces slight homogenous erythema at 72 hours. The following dose series will be applied in MPD phototesting: The standard series is Series 1; only if there is no erythema detectable at 72h at any dose in series 1, a second MPD testing with series 2 will be performed and read again at 72h after test exposure:

UVA dose (J/cm^2) series

Series 1	**0,5**	**1**	**2**	**3**	**4**	**5**
Series 2	**1,5**	**2**	**3**	**5**	**7**	**9**

The response in MPD testing will be scored as follows:

Erythema:

-, no erythema; +/- non-homogenous erythema; +, homogenous light erythema; ++, dark erythema; +++, erythema and edema; ++++, blistering

Pigmentation:

-, none; +, slight; ++, moderate; +++, strong; ++++, maximum

The initial dose of UVA administered will be 0.5 (50%) of the MPD. The dose of UVA will be increased weekly by 0-30%, depending on the presence or absence of erythema. Each patient will be treated 2 times a week (treatment week days at least 2 days apart, e.g. Monday/Thursday or Tuesday/Friday). UVA radiation will be delivered using a Waldmann PUVA 7001 K box (Waldmann Medizintechnik, Villingen-Schwenningen, Germany) equipped with Waldmann F85/100 W-PUVA fluorescent bulbs or similar UVA irradiations systems.

Dose adjustments will be done at any treatment, according to the erythema response of the skin:

no erythema (-)	regular dose, as scheduled according to protocol (increased by 30% once weekly)
non-homogenous erythema (i.e. erythema at certain body sites) (-/+)	same dose, no dose increment
homogenous light erythema (+)	skip one exposure and reduce dose to previous dose that was well tolerated
dark erythema, edema or blister (++ to ++++)	stop of treatment until remission of skin alterations; reduce dose to previous dose that was well tolerated

In addition side effects including nausea and vomiting will be recorded on the Initial Therapy sheet and Maintenance Therapy sheet according to the following ratings:

Nausea:

none (-)	
mild (+)	loss of appetite without alteration in eating habits
moderate (++)	oral intake decreased without significant weight loss, dehydration or malnutrition
severe (+++)	inadequate oral caloric or fluid intake

Vomiting:

none (-)	
mild (+)	1 episode in 24 hours
moderate (++)	2-5 episodes in 24 hours
severe (+++)	$\geq$ 6 episodes in 24 hours

After 12 weeks of treatment or thereafter at week 16, 20 or 24 (after 24, 32, 40, or 48 PUVA treatments, respectively) patients with complete remission will be randomized by a computer generated list for treatment allocation into two arms (arm A and B, see below). Patients who haven't experienced complete remission after 24 weeks will discontinue active study participation and will enter an observatory study arm.

Patients with complete response will be randomized to receive either PUVA-maintenance therapy (arm A) or no maintenance therapy (arm B) (Figure 1)

Arm A: oral 8-MOP+UVA

Patients will be treated with PUVA maintenance therapy at constant single UVA doses (UVA-dose will be the same as given in the last treatment session in week 12, 16, 20 or 24 of PUVA therapy). Maintenance treatment will be 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 (Appendix: Figure 1). After 9 (10, 11, or 12) months of maintenance therapy (14 treatments) patients will discontinue therapy. If PUVA treatment does lead to erythema during maintenance therapy, the dose for the next treatment will be reduced by up to 30%.

Patients with recurrence during PUVA maintenance will discontinue the study. After the end of maintenance therapy the patients will be followed up every three months in the first year after treatment, every 6 months in the second year and once a year from year 3 to 5 or until recurrence of the disease.

Arm B: control arm – Patients will receive no therapy. Patients are followed up at the same intervals like patients in study arm A (Appendix: Table 4).

Observatory patient arm:
Patients who did not response completely to therapy after a maximum of 24 weeks or 48 PUVA treatments and patients with recurrent disease (see section 7) after complete response will enter an observatory arm. Treatment of these patients will be entirely in the discretion of the treating physician. These patients will have follow-up visit at month 12 after stop of PUVA treatment or at time point of recurrence to record patient history and clinical status.

6. Definition of response

The extent of the cutaneous involvement of the disease will be determined before start of PUVA treatment and monitored during and after treatment by assessing the modified severity-weighted assessment tool (mSWAT) [STEVENS]. mSWAT is an objective, quantitative, severity-weighted method to assess the extent of CTCL lesions (Appendix: Table 3).

Quantitative tool to assess disease burden in CTCL [STEVENS]:

The body is divided into 12 regions with preassigned %TBSA based on methodology used to assess burns. The extent of skin disease is assessed for each region and quantified by using the patient's palm as a "ruler" to measure the %TBSA involvement within each region:

- Patient's palm with 4 fingers, excluding the thumb and measured from wrist to fingertips, is 1% of TBSA.
- Patient's palm without fingers is 0.5% of TBSA.

*mSWAT Score calculation***:** Sum of %TBSA from all body regions affected by patches X severity-weighting factor of 1 + Sum of %TBSA from all body regions affected by plaques X severity-weighting factor of 2 + Sum of %TBSA from all body regions affected by tumors X severity-weighting factor of 4 (Appendix: Table 3).

Specific skin lesions will be differentiated in:
Patches: flat lesions with a diameter larger than 1cm
Plaques: elevated/palpable lesions with increased consistency with a diameter larger than 1cm
Tumors: nodular lesions with the longest diameter larger than 1 cm.

Response will be determined as follows:

- Complete clinical response: Complete clinical disappearance of all cutaneous MF lesions compared to baseline mSWAT. (Clinically evident postlesional erythema and/or pigmentation will not be considered as persistent disease. It will be recorded but will not affect mSWAT.) If there is clinical doubt of complete remission, a diagnostic biopsy should be performed.
- Partial response (PR): more or at least 50% reduction in mSWAT
- Stable disease (SD): less than 50 % reduction (from baseline) and less than 25 % increase of skin disease (compared with the smallest mSWAT since treatment started)
- Progressive disease (PD): more than 25 % increase in mSWAT compared with the smallest mSWAT since treatment started.

7. Definition of recurrence

Recurrence will be defined as re-occurrence of cutaneous disease, as determined by mSWAT at any time point (Complete remission = 100% clearing of skin disease (mSWAT of 0); recurrence is reappearance of skin lesions (mSWAT $\geq$ 1)) `[OLSEN (b)]:`. If there is clinical doubt of continuous remission, a biopsy should be performed.

8. Adverse Events

Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see note for guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Serious Adverse Event (SAE), Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

• results in death,

• is life-threatening,

• requires inpatient hospitalisation or prolongation of existing hospitalisation,

• results in persistent or significant disability/incapacity,

or

• is a congenital anomaly/birth defect

Suspected unexpected serious adverse drug reactions (SUSARs)

Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) are side effects (probably or definitely connected with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product contained in the SmPC (Summary of medicinal Product Characteristics) should be used to verify if the adverse reaction has been previously described.

Safety reporting

Investigator:

The investigator is responsible for reporting AEs, SAEs and SUSARs to the sponsor.
All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Summary of Product Characteristics) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports.
The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the ethics committee.
Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
For reported deaths, the investigator should supply the sponsor and the ethics committee with any additional requested information (e.g., autopsy reports and terminal medical reports).

Sponsor:

The sponsor should keep records of all AEs reported by the investigators. These records should be forwarded upon request to the competent authority of the region where the Clinical Trial is performed.
In case of death or immediate danger of life caused by a SUSAR the competent authorities and Ethics Committee(s) concerned should be informed by the sponsor within 7 days after the event becomes known to the sponsor. Additional information should be given within further 8 days.
All other SUSAR ("requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect) should be reported as soon as possible, at latest within 15 days after the event becomes known to the sponsor, to the competent authorities and Ethics Committee(s) concerned.
Information on SUSARs should be forwarded to all other investigators of the same clinical trial by the sponsor. Once yearly during the trial, a safety report and a listing of all SUSARs that occurred during the trial should be forwarded to the competent authorities and to the Ethics Committees concerned by the sponsor.

Known Side effects of PUVA-Therapy

8.1 Dermatologic Effects

Phototoxic reactions including severe edema, erythema, painful acral blistering, burning, and peeling of skin may occur with methoxsalen and conventional UV light. In addition, PUVA therapy has produced marked hyperpigmentation and, with high cumulative doses, photoageing of skin.

8.2 Phototoxic reactions to methoxsalen occur most commonly when the skin is overexposed to UV light or when dosage is excessive. Severe burns may occur if treated skin is accidentally exposed to additional UV light. Pruritus occurs in about 10% of patients treated with PUVA therapy utilizing methoxsalen.

8.3 Other adverse dermatologic effects associated with PUVA therapy include skin freckling, hypopigmentation, uneven or excessive tanning, dry skin, vesiculation and bullae formation, generalized exfoliation, nonspecific rash, urticaria, miliaria, folliculitis, acneiform eruption, aggravation or extension of disease, cutaneous tenderness, severe skin pain (lasting 1—2 months), onycholysis, pigmentation of the nails, and exacerbation of latent photosensitive dermatoses (e.g., lupus erythematosus).

8.4 Gastrointestinal (GI) Effects

Nausea is the most common adverse effect of oral methoxsalen, occurring in about 10% of patients. Nausea and other adverse GI effects may be minimized by administering 8-MOP with milk or food.

8.5 Central Nervous System (CNS) Effects

Dizziness and headache can occur with PUVA therapy utilizing methoxsalen.

8.6 Other Adverse Effects

PUVA therapy may also damage the eyes and may increase the risk of cataract. To reduce these side effects eye shields will be used during irradiation and UV protective glasses are required for 24 hours after ingestion of 8-MOP.

Cheilitis and transient loss of muscle coordination reportedly occurred in patients receiving oral methoxsalen.

Although abnormal liver function test results were reported in a few patients receiving oral methoxsalen, this observation has not been confirmed by others and a causal relationship has not been established. Edema, malaise, leg cramps, and hypotension occurred with PUVA therapy utilizing methoxsalen.

9. Premature Termination

9.1 Drop-out

Drop-out of single study participants may be due to

• withdrawal of informed consent
• intolerable adverse events
• violation of the study protocol
• emergence of an exclusion criterion
• emergence of concomitant disease
• pregnancy
• any other circumstance that would endanger health of the proband with continued study participation

9.2 Discontinuation of the study

The investigator may discontinue the study anytime in the interest of the probands if severe adverse events or other unforeseen problems occur.
Ethics Committees concerned and competent authorities should be informed about premature discontinuation and its reason within 15 days.

10. Monitoring

Monitoring will be performed according to the monitoring plan of this study. The investigator will cooperate with the monitor and provide unrestricted access to source data and all other study materials. The investigator will keep detailed records in the patient charts on study visits, distribution of study drugs, test results, concomitant diseases, and adverse events. The monitor will regularly verify entries on the CRFs with source data and check compliance with the study protocol and continuous data entry. The monitor will handle all data confidentially to ensure integrity and privacy of the study participants.

11. Data protection

Recording and analysis of personal data within this clinical trial will be performed according to applicable data protection laws, provided the study participant has consented to this prior to enrolment. Informed consent will include information on data protection as follows:

1. Data collected within this clinical trial will be recorded on case report forms, handled in a strictly confidential way.

2. If necessary for evaluation of the clinical trial, authorized personnel of the sponsor, of competent authorities and/or Ethics Committees may confidentially review personal data of the study participants at the trial site.

3. The study participant will be informed that participation in the clinical trial may be terminated at any time without giving a reason and without any consecutive disadvantage. However, due to legal requirements, inspection of personal data by authorized persons may be continued in a confidential manner.

12. Clinical evaluation and laboratory tests

Patients with histopathologically documented MF and clinical stage IA to II B, who have given informed consent and are willing to participate in the study should undergo the following testing and investigation:

12.1. Before treatment start - Pretreatment evaluation (see also Appendix: Table 4: Summary of visits and assessments) (Within 28 days before treatment start):

- Medical history and clinical examination (if clinically palpable lymph nodes: lymph nodes ultrasounds); in case of ultrasonic suspicion of disease-specific lymph node involvement a lymph node biopsy and/or excision will be done
- Determination of mSWAT
- Skin biopsies for diagnostic purposes and for determination of cytokine levels as well as T-cell receptor rearrangement (TCR-R)
    - All standard study biopsies should be taken from the site of the marker lesion (defined at baseline). Biopsies should only be taken from other parts of the body (outside the area of the marker lesion) if the response at that site is clinically ambiguous.
- Ophthalmologic examination
- Laboratory tests: Hematology (hemoglobin, WBC with differential and platelet counts), serum biochemistry: serum AST (SGOT), ALT (SGPT), alkaline phosphatase, urea, creatinine, and glucose
- Antinuclear antibodies (dsDNA, Ro/SSA, La/SSB)
- Blood draw for cytokine, TCR-R and FOXP3 mRNA analysis and Cell free DNA BCT for blood tumor cell analysis (see Appendix: Table 5)
- Pregnancy test (for women with childbearing potential) in blood or urine
- Photographic documentation
- DLQI (Dermatology Life Quality Index)
- HADS (Hospital Anxiety and Depression Scale)

12.2. During treatment and in the follow-up period:

Assessments will be done, as described in Appendix Table 4 at specific time points. A biopsy after the start of PUVA therapy (e.g. scheduled at week 6 with a gray period of 2 weeks) should be taken on a day of PUVA treatment before UVA exposure.

For control purposes blood samples from a maximum of 30 healthy control subjects and 30 samples of normal skin available from other studies will be analyzed, together with the samples of this study.

13. Statistics

Previous studies have shown that MF lesions reappear after a very variable time interval with median 9 to 15 months, depending on the study [WACKERNAGEL]. PUVA maintenance therapy intends to prolong this lesion-free interval and to reduce recurrence rate after discontinuation of the maintenance therapy.

Appendix Figure 2: Overview of treatment effects. All patients get standard PUVA therapy. After remission patients are assigned either to controls or to nine months of maintenance therapy. The treatment effect is the extension of the median time to recurrence (black double arrow). This comes along with lower risk of recurrence (Curve (1) is higher than curve (2)). Some patients suffer from recurrence during maintenance therapy, i.e., the tilt in the straight line segment of curve (1) from month 3 to month 12. The secondary end point refers to time to recurrence after finishing treatments successfully (dashed curves (3) and (4), dashed arrow). Curve (3) gives the survival function after maintenance treatment conditional on being free from lesions after therapy. Curve (4) is a shifted version of curve (1) in order to align the survival functions for comparison.

13.1. Study design

A randomized placebo controlled clinical trial with 3 to 6 months of PUVA therapy as control and 3 to 6 months PUVA plus 9 months of PUVA maintenance therapy as index therapy. In the Appendix Figure 1 the time-dependent probability of recurrence (“Survival function”) is given for 4 settings.

The primary endpoint of the study is the comparison of median time to recurrence after complete remission between study arm A and study arm B (comparison of curve (1) vs. curve (2), Appendix: Figure 2). A secondary endpoint is the comparison of time from end of treatment to recurrence on condition that the patient is in remission at the end of treatment comparing study arm A and B (end of treatment in study arm A, month 12 to 15; end of treatment in study arm B, month 3 to month 6). This amounts to the comparison between curve (3) and curve (4). After the accrual period patients are observed until the closing date of the study for the main statistical outcome analysis. Patients who have not experienced recurrence by the closing date are considered as censored. Treatment groups are compared by survival analysis (logrank test).

13. 2. Sample size calculations and study duration

Sample sizes were calculated with nQuery Advisor 4.0 software (www.statistical-solutions-software.com). The assumptions were alpha=0.05, power=0.8, one(two)-sided logrank test and an accrual time of 2 years.

According to an earlier study at the dermatologic clinic the median time to recurrence after PUVA therapy was 1 year. An exponential survival function with parameter λ_1=0.7 was chosen for controls, giving a median time to recurrence of 1 year.

The alternative hypothesis (i.e. the minimum clinically relevant treatment effect) was chosen to be exponential with λ_2=0.35 (relative hazard 2, median time to recurrence 2 years) for the primary treatment effect. The overall duration of the study (to enrol 55 patients assuming an accrual period of 2 years) until closing date for the main statistical outcome analysis was assumed to be four years (accrual phase, 24 months; initial PUVA treatment of last patient enrolled, 3 months; PUVA maintenance treatment in last patient enrolled, 9 months; minimum follow-up period, 12 months). Scenario D1 and D4 refer to these assumptions. Independent of the closing date for the main statistical outcome analysis the maximum follow-up in an individual patient will be 60 months.

	Primary endpoint				Secondary endpoint			
	D1	D2	D3	D4	D5	D6	D7	D8
Test significance level	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
1 or 2 sided test?	2	1	2	1	2	1	2	2
Length of accrual period	2	2	3	3	2	2	3	3
Maximum follow up	3.75	3.75	4.75	4.75	3	3	4	4
Control hazard λ_1	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Maintenance hazard $\lambda 2$	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Hazard ratio, h=λ_1 / λ_2	2	2	2	2	2	2	2	2
Power (%)	80	80	80	80	**72**	**73**	**74**	**76**
n per group	**47**	**37**	**44**	**35**	47	37	44	35
Acrual per year (2 Treatments)	48	38	32	26	48	38	32	26

For the secondary endpoint (recurrence after 9 months of maintenance therapy vs. recurrence after standard therapy only) essentially the same scenario was assumed: exponential survival, hazard ratio 2. Only the length of follow up war shortened by 0.75 years. In this regard not power but sample size was fixed and the power was variable. Scenario D5 to D8 relate to these assumptions.

Finally scenario D2 was chosen. 37 patients per group are required (41 patients if accounting for 10% loss to drop-out, non-compliance and/or follow-up).

13.3. Randomization procedure

After a maximum of 24 weeks (48 PUVA treatments) patients without complete remission will discontinue active study participation but they will be followed up in an observatory arm. Patients with complete remission after 12 weeks (24 PUVA treatments), 16 weeks (32 PUVA treatments), 20 weeks (40 PUVA treatments) or maximum of 24 weeks (48 PUVA treatments) will be randomized by a computerized randomization service to receive either PUVA-maintenance therapy (*Arm A*) or no maintenance therapy (*Arm B*) (Appendix: Figure 1). Randomization will be done using Randomizer, Medical University of Graz, Austria (https://www.randomizer.at/random).

14. ETHICAL AND LEGAL ASPECTS

Acknowledgement / approval of the study

Approval from the ethics committee (EC) must be obtained before starting the study.
The clinical trial shall be performed in full compliance with the legal regulations according to the Drug Law (AMG - Arzneimittelgesetz) of the Republic of Austria.
An application must also be submitted to the Austrian Competent Authorities (CA) (Bundesamt für Sicherheit im Gesundheitswesen (BASG) represented by the Agency for Health and Food Safety (AGES PharmMed) and registered to the European Clinical Trial Database (EudraCT) using the required forms. The timelines for (silent) approval set by national law must be followed before starting the study.

Changes in the Conduct of the Study

Protocol amendments

Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Study Termination

If the sponsor or the investigator decides to terminate the study before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator, sponsor or (designated CRO on behalf of the sponsor) will notify the relevant CA and EC. Documentation will be filed in the Trial Master and Investigator Files.

Clinical Study Report (CSR)

Within one year after the final completion of the study, a full CSR will be prepared by the sponsor and submitted to the EC and the competent authority.

15. SIGNATURES

15.1 Sponsor

Herewith I confirm that the clinical trial will be performed in accordance with ICH-GCP, the Declaration of Helsinki, local legislation and the present study protocol.

_____ _____

Name **Date**

15.2 Investigator

Herewith I confirm to have read and to comply with the present study protocol and to ensure that enrolled patients will be followed and treated according to the study protocol.

_____ _____

Name **Date**

16. References

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Appendix (Tables and Figures)

Table 1:

TNM Cutaneous Lymphoma

TNM classification for mycosis fungoides (including "B" system for CTCL to incorporate Sezary syndrome); according to the ISCL/EORTC revision to the staging of mycosis fungoides and Sezary syndrome [OLSEN (a)]

Skin

T1 Limited patches/plaques (<10% of total skin surface)
T2 Extensive patches/plaques (>10% of total skin surface)
T3 Tumours
T4 Erythroderma

Nodes

N0 No clinical lymphadenopathy
N1 Clinically enlarged lymph nodes but histologically uninvolved
N2 Lymph nodes not enlarged but histologically involved
N3 Clinically enlarged lymph nodes and histologically involved

Visceral

M0 No visceral involvement
M1 Visceral involvement

Blood

B0 No peripheral blood Sezary cells (<5%)
B1 Peripheral blood Sezary cells (>5% of total lymphocyte count)
B2 High blood tumor burden

Clinical Staging system for CTCL (mycosis fungoides)

Clinical Stage T N M B

IA T1 N0 M0 B01
IB T2 N0 M0 B01
IIA T1-2 N1 M0 B01
IIB T3 N0-1 M0 B01
III T4 N0-1 M0 B01
IVA T1-4 N2-3 M0 B0-2
IVB T1-4 N0-3 M1 B0-2

Table 2:

Karnofsky scale for performance status

Index Performance scale
100 Normal; no complaints.
90 Able to carry on normal activities; minor signs or symptoms of disease.
80 Normal activity with effort.
70 Cares for one self. Unable to carry on normal activity or to do active work.
60 Ambulatory. Requires some assistance in activities of daily living and self care.
50 Requires considerable assistance of frequent medical care.
40 Disabled; requires special care and assistance.
30 Severely disabled; hospitalization indicated though death not imminent.
20 Very sick; hospitalization and active supportive treatment.
10 Moribund
0 Dead

Table 3:

Modified Severity Weighted Assessment Tool (mSWAT)

	Percentage of diseased area		
Body region (%BSA)	**Patch**	**Plaque**	**Tumor**
Head (7 %)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior trunk (13%)			
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	**1**	**2**	**4**
Subtotal lesion BSA x weighting factor			
		mSWAT score =	

mSWAT score = Summation of Subtotal lesion BSA x Weighting factor products above (Patch + Plaque + Tumor)

Table3: BODY CHART

Erforderliche Parameter fehlen oder sind falsch.

Table 4: Summary of visits and assessments

	Within 4 weeks [f]	Treatment			Optional (4 opt.) [g]						End of PUVA maintenance	Observatory Patient [h]	Follow up [p]
Visit No.	1	2	3	4a	4b	4c	4d	5	6	7	8	8	
Weeks	**-4 to 0**	**+3 [j]**	**+6 [k]**	**+12**	**+16**	**+20**	**+24**	**+16, +20, +24 or +28 [l]**	**+24, +28, +32 or +36 [m]**	**+36, +40, +44 or +48 [n]**	**+48, +52, +56 or +60 [o]**		
ASSESSMENTS													
Medical History	x											x	
Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Report	x	x	x	x	x	x	x	x	x	x	x		x
Clinical examination	x	x	x	x	x	x	x	x	x	x	x	x	x
mSWAT + Body Chart	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology	x	x	x	x	(x)	(x)	x		x	x	x		
Serum biochemistry	x	x	x	x	(x)	(x)	x		x	x	x		
Antinuclear antibody + Ro-La	x												
Cytokine analysis	x		x	x	(x)	(x)	x		x		x		
Disease monitoring laboratory investigations including TCR-R+FOXP3 mRNA [a]	x		x	x	(x)	(x)	x		x		x		
FACS analysis [b]	x		x	x	(x)	(x)	x		x		x		
Treg functional assay [b]	x		x	x	(x)	(x)	x		x		x		
CELL free DNA [only for Graz]	x		x	x	(x)	(x)	x		x		x		
Skin biopsy	x		x	(x) [q]	(x) [q]	(x) [q]	x		optional		optional		optional
Ophthalmologic examination	x												
DLQI [c]	x			x			x		x	x	x		x
HADS [d]	x			x			x		x	x	x		x
Photographic assessment [e]	x		x	x	optional	optional	x	optional	optional	optional	optional		optional
Pregnancy test (ß-HCG blood or urine test strip) (monthly) [i]	x	x	x	x	x		x		(x)	(x)			
Randomization [g]				x [g]	x [g]	x [g]	x [g]						

[a] TCR-R: T-cell receptor rearrangement and FOXP3 mRNA	[b] To analyse on site if procedure is available	[c] DLQI: Dermatology Life Quality Index
[d] HADS: Hospital Anxiety and Depression Scale	[e] Photographic assessment: optional in case of recurrence	[f] Before treatment start (within 4 weeks)
[g] Randomization: time of randomization at V4a, V4b, V4c or V4d if complete remission	[h] For patients who were not randomized in Group A or B	[i] Pregnancy test: has to be taken once a month till Randomization and after Randomization in Study Arm A
[j] 3 weeks after treatment start	[k] 6 weeks after treatment start	[l] Time of visits: depends on the numbers of optional visits
[m] 12 weeks after start of maintenance therapy	[n] 24 weeks after start of maintenance therapy	[o] 36 weeks after start of maintenance therapy
[p] every three months in the first year, every 6 months in the second year and once a year in years 3 to 5 after PUVA maintenance therapy		[q] Skin biopsy: in the case of complete clinical response at the time of randomization

Table 5: Cytokines and chemokines will be analyzed, including:

IL-1a, IL-1b, IL-4, IL-6, IL-9, IL-10, IL-13, IL-12p35, IL-12p40, IL-12p70, IL-17A, IL-17F, IL-23, IL-23p19, TGF-β1, IFN-γ, TNF-α, G-CSF, GM-CSF, MCP-1, RANTES, KC, IP-10, MIP-1a and others

Figure 1:

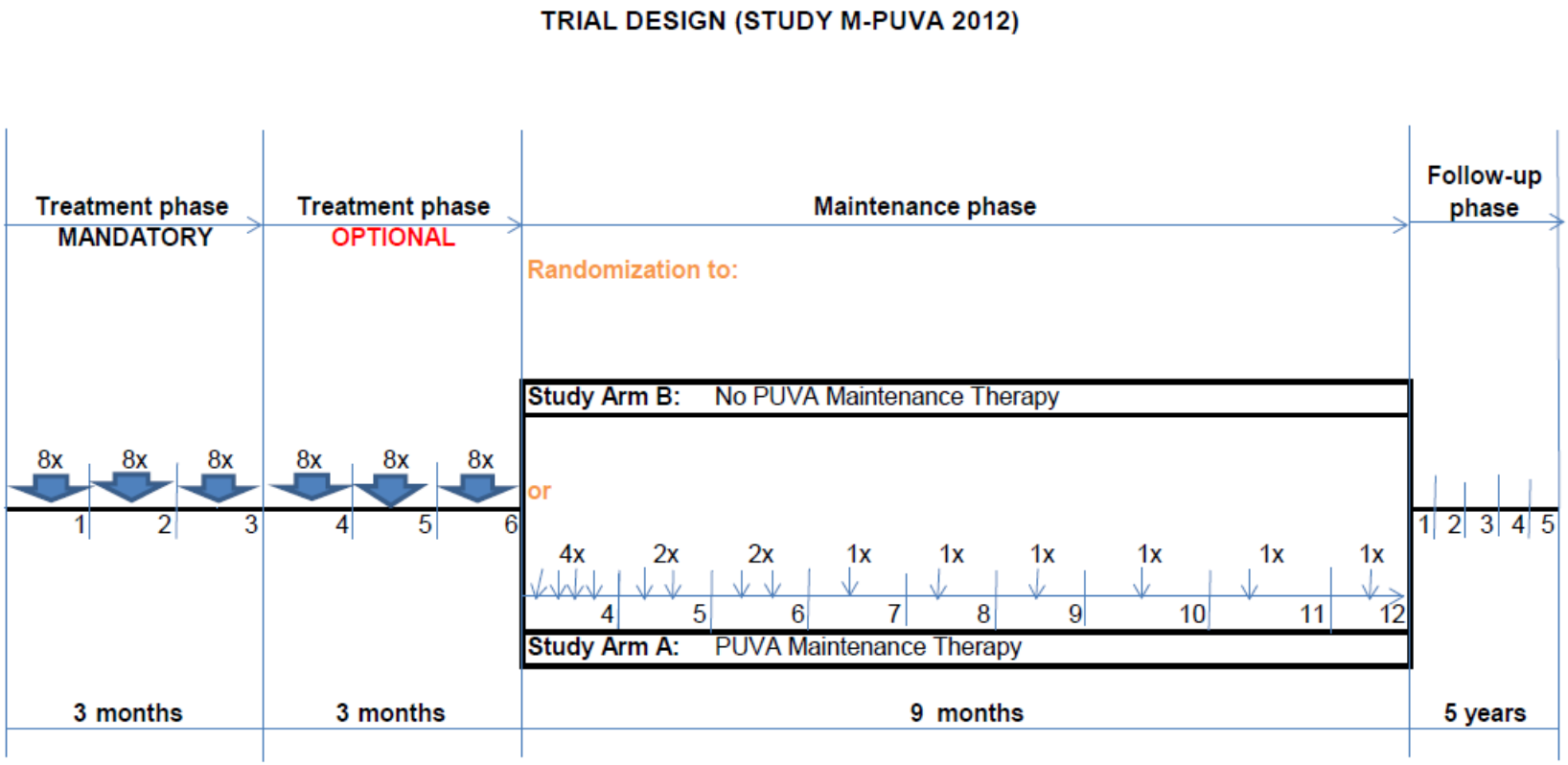
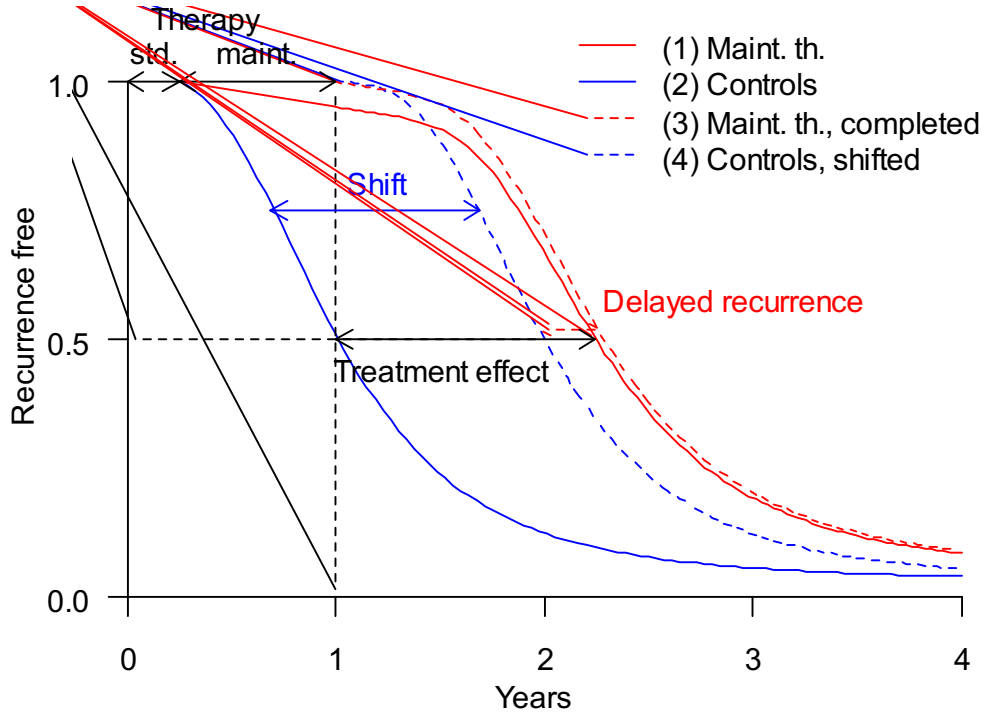


Figure 1: ↓ PUVA exposure: Month 1-3 (and optional Month 4-6): 2x/week, Month 4: 1x/week, month 5-6: 1x/2 weeks, month 7-12: 1x/month

Follow-up: year 1: 1 visit/3 months, year 2: 1 visit/6 months, year 3-5: 1 visit/year

Figure 2:


Therapy
std.
maint.
(1) Maint. th.
(2) Controls
(3) Maint. th., completed
(4) Controls, shifted
Shift
Delayed recurrence
Treatment effect
Recurrence free
1.0
0.5
0.0
0
1
2
3
4
Years