A Phase 0, single-center study to characterize the response of a UV-B skin challenge on the skin of healthy volunteers and cutaneous lupus erythematosus (CLE) patients

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Abstract: cutaneous lupus erythematosus (CLE) is an autoimmune disease that can occur isolated to the skin or as a manifestation of Systemic Lupus Erythematosus (SLE). The current concept regarding the onset of the disease comprises an autoimmune background predisposing to CLE triggered by factors such as UV light. UV exposure causes cellular stress which leads to induction of inflammatory cytokines, including type I interferon (IFN). The UV-B "sun burn" model is a skin inflammation model in which erythema is induced on the skin by irradiating the skin with UV-B light in a well-controlled and reproducible manner. UV-B exposure drives an increase in skin perfusion, followed by infiltration of immune cells into the skin. The objective of this phase 0 study is to characterize the dermal immune response of healthy volunteers and CLE patients following a UV-B skin challenge on non-lesional skin for later integration into a phase 1 proof-of-mechanism study with a novel immunomodulatory agent. This is a single-center study in which 10 healthy volunteers (HV) and 6 CLE patients will be included to characterize the dermal immune response following a UV-B challenge. After the screening visit, in which the minimal erythema dose (MED) will be determined, the skin of the upper back will be challenged with two-times MED UV-B irradiation on 1cm^2 squares on the back in challenge period 1. Skin punch biopsies of 4mm will be taken 3h, 6h and24h post challenge in HV to determine the optimal biopsy time point. This time point will be used in the UV challenge study for the CLE patients. The site that will be biopsied 24h post challenge will serve as imaging site to characterize the inflammatory response following UV-B irradiation with several non-invasive imaging tools. Imaging will also be performed on unchallenged skin as control. Two weeks after the first challenge period, the second challenge period will commence in which one 1cm^2 square on the back will be challenged with two-times MED UV-B irradiation and biopsied 24h after the challenge to test repeatability. Pharmacodynamic endpoints will include immunohistochemistry or immunofluorescence of the target and biomarkers, transcriptome analysis by RNAseq, laser speckle contrast imaging, Antera 3D multispectral imaging, trans-epidermal water loss, optical coherence tomography and clinical photography. This Phase 0 study will establish the UV-B sunburn model as clinical model of UV-B sensitivity and immune activation in HV subjects and CLE patients.

Non-Interventional Study Design:

Subjects will undergo a UV-B challenge on two separate occasions which are two weeks apart. Subjects will also undergo UV-B irradiation during screening for MED determination.

MED Determination: the subjects are first exposed to 6 different doses of UV-B, to determine the Minimal Erythemic Dose (MED) using the six different slots of the UV-B lamp. 24 hours (± 2 hours) after the exposure of the 6 doses, the erythemic response of the skin to UV-B is assessed by two observers. The MED is determined visually by observing which dose produces the first clearly discernible erythema.

Healthy Volunteer Part: for the healthy volunteers, during the challenge period 1 at day 1 three of each 1 cm2 of the subject's skin of the upper back is exposed to two-times MED (Figure 1). During the challenge period 2 at day 15, one 1cm2 square on the back is challenged with two-times MED UV-B irradiation

Patients: for the CLE and/or SLE patients, non-lesional skin of the back is challenged with two-times MED UV-B irradiation on one 1cm2 square on two occasions which are 14 days apart (Figure 2).

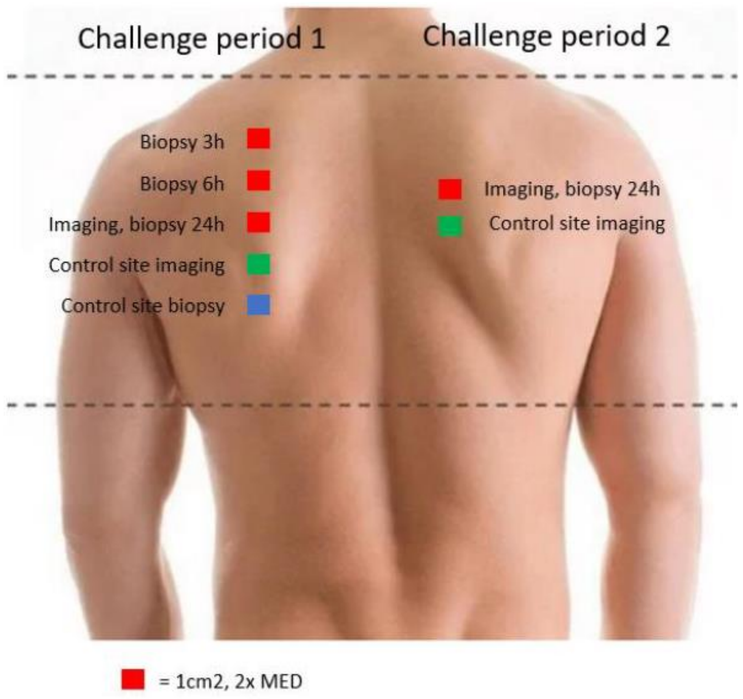


Figure 1. Schematic overview of study design healthy volunteers

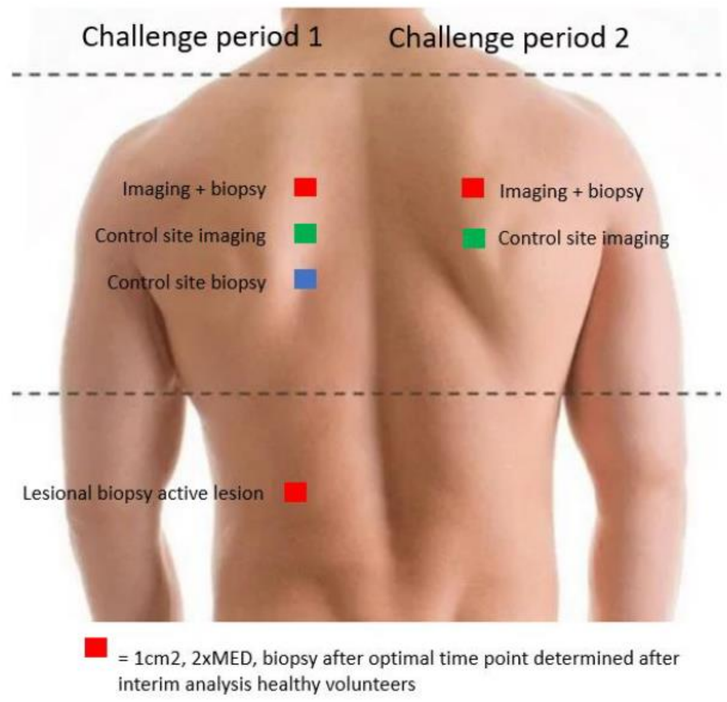


Figure 2. Schematic overview of study design CLE patients

Tolerability/Safety Endpoints:

Adverse events (AE) will be collected throughout the study, at every study visit.

Pharmacodynamic Endpoints:

Skin punch biopsies:

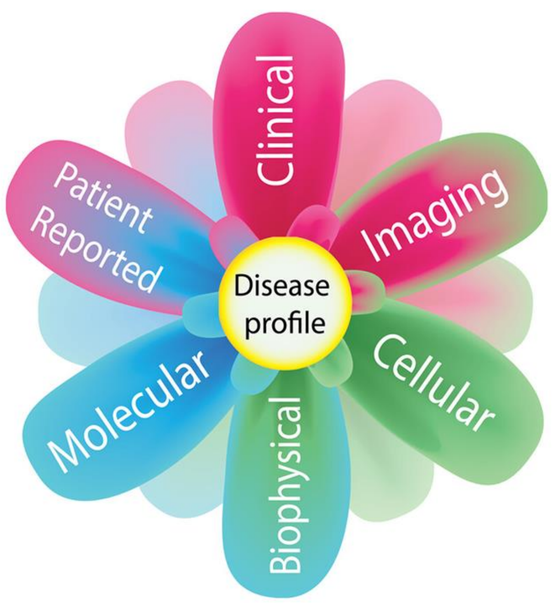
- Immunohistochemistry
- RNA-sequencing

Imaging of UV-B challenged skin:

- Laser Speckle Contrast Imaging (microcirculation)
- 3D multispectral imaging (3D skin morphology, erythema, hemoglobin level)

Imaging of target lesion and control non-lesional skin (CLE patients only):

- Laser Speckle Contrast Imaging (microcirculation)
- 3D multispectral imaging (3D skin morphology, erythema, hemoglobin level)
- Trans-epidermal water loss (skin barrier function)
- Optical Coherence Tomography (skin morphology, epidermal thickness, blood perfusion)
- Clinical (2D) photography



Blueprint for mechanistic and clinical pharmacology studies

Adapted from: Wouter et al, A multimodal, comprehensive characterization of a cutaneous wound model in healthy volunteers, Experimental Dermatology, 2023, 32(7): 1028

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