UVA-1 for treatment of skin tightening and improvement of hand function in scleroderma: a randomized, intra-patient, dominant/non-dominant hand clinical trial.

Background:

Systemic sclerosis (SSc), also called scleroderma, is a rare chronic autoimmune disease that can have a wide range of cutaneous, joint, and internal organ involvement. In the skin, SSc is characterized by enhanced fibroblast activity leading to hypertrophic dermal collagen that results in thickened, less flexible skin. (Hassani, 2016) SSc is often divided into two types based on extent of cutaneous involvement: diffuse SSc and limited SSc. The hand is a frequent area of involvement in both subtypes of SSc. Hand disability in SSc leads to a high burden on quality of life for patients as it limits both work and activities of daily living. Treatment for hand sclerosis remains limited with generally progressive disease despite aggressive treatment with anti-fibrotic medications, immunosuppressive agents, and topical approaches. Specific hand therapies include physiotherapy and injections of autologous adipose-derived stromal vascular fraction into the fingers with some success. (Guillaume-Jugnot, 2016; Liem, 2019)

Ultraviolet therapy has been used in dermatology for several decades. UVA-1 is a form of phototherapy that utilizes the longest wavelengths in the UV spectrum from 340-400 nm. It is able to penetrate deeper in the skin than other types of phototherapy and target different types of cells including fibroblasts. In sclerosing skin conditions UVA-1 appears to be superior to other forms of UV light. Medium to high dose UVA-1 also appears to be superior to low dose UVA-1 for sclerosing conditions. (Kreuter 2006).

UVA-1 has been reported to be beneficial to skin changes in SSc in several case reports and a few small studies. (Jacobe 2020) Interpretation of these reports has been difficult based on the small numbers of subjects involved and the non-blinded non-randomized nature of the reports. In a single controlled study with half-side comparison of 9 patients, the investigators could not demonstrate improvement with UVA-1 in the treated hand. (Thomas 2007) This study was limited by a small number of patients and the long disease duration prior to treatment (mean of 13 years). A more recent report of a patient with SSc for 2.5 years and severe acrosclerosis that responded to 21 sessions of UVA-1 with improved mobility and functionality renews interest in this treatment modality. (Cuenca-Barrales 2019)

If UVA1 therapy can significantly improve hand involvement in SSc with regards to functionality and disability, it may be a cost-effective and beneficial treatment for this patient segment with debilitating disease.

Purpose and Objectives:

1. To assess the efficacy of 30 sessions of ultraviolet-1 (UVA1) therapy in treating hand involvement of SSc in a prospective, randomized, investigator-blinded, intra-patient, UV-blocking glove-controlled, crossover clinical trial.
    a. To compare improvement in hand function as measured by the Hand Mobility in Scleroderma (HAMIS) test, in the UVA1-treated hand compared to control hand (gloved).
    b. To compare the improvement in hand function as measured by the Cochin hand functional disability scale (CHFDS) in the UVA1-treated hand compared to control hand (gloved).
    c. To compare the improvement in skin hardening based on durometer measurements in the UVA1-treated hand compared to control hand (gloved).
    d. To measure improvement in the physician measure of skin thickness on hands and fingers (0-3) scale after completion of 30 UVA1 sessions.

   e. To assess the duration of response after a complete 30-treatment course at 3 and12 months post treatment using the HAMIS, CHFDS, durometer, and physician skin thickness assessment.
2. Assess patient-reported outcomes before, during and after treatment using Skindex-16, Michigan Hand Questionnaire (MHQ), PROMIS-Physical Function (PROMIS-PF), Hand Disability in Systemic Sclerosis – Digital Ulcers(HDISS-DU) and Visual Analog Scale (VAS).

Sample size calculation:
We are planning a study of paired cases and controls with 1 control per case. Prior studies using UVA1 have reported 100% of patients with systemic sclerosis improving on high dose therapy (80-120 J/cm^2), although objective clinical measures were not reported. (Connolly, 2015) Studies using exercise-based therapies with specific objective endpoint assessments, specifically the HAMIS test, show ~4-point (15%) improvements in HAMIS test scores in treated groups as compared to controls and baseline with a standard deviation of ~6.5. (Bongi, 2009) Using a conservative estimate of 4-point (15%) improvement in HAMIS test scores from baseline to after 30 treatment sessions and a standard deviation of 6.5 points, a paired t-test can be used to calculate a sample size. A sample size of 21 patients will be needed to be able to reject the null hypothesis that improvement in HAMIS test scores is equal between treated and untreated sides with a power of 0.8 and an alpha (Type I error probability) of 0.05. A sample size of 28 patients will be needed to be able to reject the null hypothesis that improvement in HAMIS test scores is equal between treated and untreated sides with a power of 0.9 and an alpha (Type I error probability) of 0.05.

Assuming a dropout rate of 25%, the total number of participants required to reach the desired 28 person sample size for data analysis at 90% power is 35 to complete the study. The total number of participants required to reach the 21 person sample size for data analysis at 80% power is 27 patients to complete the study. This study will use 80% power, and we plan to enroll a total of 27 patients.

Study Design:
This study will use a single-blind, prospective, randomized (dominant/non-dominant hand) comparator design to assess the effect of high dose (80-120 J/cm^2) UVA1 therapy on hand function in scleroderma in a paired t-test design. This study will be placebo-controlled (with a UV-blocking gloved hand), cross-over, randomized clinical trial. Following the initial treatment period (30 treatments), patients will have the option to undergo the same high dose UVA1 treatment protocol on the untreated control hand. A follow up period of 12 months following completion of UVA1 therapy will prospectively follow patients to monitor for relapse of their disease to assess the durability of the clinical response to UVA1 therapy on hand scleroderma.

Inclusion criteria:
- -Must be able to understand and provide written informed consent
- -Scleroderma skin involvement affecting both hands approximately equally
- -Age of at least 18-years-old
- -Male or female
- -Ability to engage in twice weekly UVA1 sessions
- -No changes in systemic therapy during the first 100 days of the study period

Exclusion criteria:
- -On photosensitizing medication
- -Inability to complete study visits
- -UV light therapy in the 4 weeks prior to entering the study
- -Commercial tanning or excessive sun exposure in the 4 weeks prior to entering the study
- -Current pregnancy or planned pregnancy during the study period
- -Use of topical therapies other than emollients (suprapotent corticosteroids) in the 2 weeks prior to entering the study
- -History of intolerance to ultraviolet light

-Any other condition that will disqualify the patient from the study in the opinion of the investigator

Study Procedures:
Recruitment:
Patients attending regularly scheduled dermatology clinic visits will be approached by study personnel. Providers inside and outside of our institution regularly refer patients to be considered for studies and these patients will be pre-screened by study personnel (coordinators and investigators). We will not use cold calls based on chart review. We will additionally use an IRB-approved flyer, and patients who call in response will be pre-screened for the study.

Informed Consent:
Description of location(s) where consent will be obtained: University of Utah Midvalley Dermatology Clinic. This clinic has private patient rooms where consent will be obtained.

The consent process will be completed prior to conducting any study procedures. Typically, a summary of the study is presented by the study staff to patients who are interested and appear to be eligible for the study. There is no mandatory waiting period, but sometimes patients are informed of the study during clinic or over the phone, and an appointment is then scheduled in the dermatology clinic to conduct the formal consent process.

During this appointment, which is conducted in the clinic in a private and quiet study clinic room, the study staff will present an overview of the study. They are given a copy of the informed consent form (ICF) to read. A copy of the consent may be distributed to the patient to take home for review if an eligible patient expresses interest during a routine clinic visit. Otherwise, we allow them to read it in private on site, and we remain immediately available (outside the door of the clinic room) and ask them to alert us when they are finished. We will step in and monitor their progress periodically. The study staff will then review the ICF in detail with the patient and ensure that the patient's questions are answered. The PI is available, if necessary, to answer questions. If the patient feels they have had ample opportunity to review the ICF, understand the study, and want to participate, then the ICF is signed and dated by both parties.

If the participant wants more time to consider the study, the ICF, or other standard treatment options at any point in the process, they are encouraged to take the ICF home to discuss the study with family and/or friends.

Procedures:
This is a single-blinded, randomized, UV-blocking glove controlled, dominant/non-dominant hand, cross-over study to determine the efficacy of UVA1 in the treatment of hand scleroderma. Each participant will have at least one hand treated with UVA1 during the active treatment period of the study. The study will be performed at the University of Utah Dermatology Department using both the University of Utah E12 Clinic space as well as the Midvalley Clinic space. UVA1 lights boxes are located at both E12 and Midvalley locations. Personnel involved in the study will include the PI, the co-investigators, and the study coordinators. Approximately 27 patients will be enrolled to account for a 25% drop-out rate. The number needed to treat to show a difference in the treatment vs. control hands is 21. The study timeline is summarized in Table 1.

Screening:
For screening, subjects with qualifying scleroderma involving both hands will be asked to read and sign the informed consent document. They will be reminded that they are to take their time and, if

necessary, take it home for further consideration. Questions will be answered. Those meeting inclusion / exclusion criteria who have signed informed consent will be enrolled.

Table 1: Outline of study protocol from baseline to week 15, then up to 12-month post-treatment.

Treatment Arm								
	Informed Consent	Inclusion/ Exclusion criteria	History and Physical	Adverse Event Screening	UVA1 2-3 times weekly	Assessments	PROM	Photos
Screening	X	X						
Baseline		X	X	X		X	X	X
UVA treatment sessions 1-14					X			
UVA treatment session 15				X	X	X	X	X
UVA treatment sessions 16-29					X			
UVA treatment session 30				X	X	X	X	X
3-months post-treatment				X		X	X	X
12-months post treatment				X		X	X	X
Placebo/Control Arm								
	Informed Consent	Inclusion/ Exclusion criteria	History and Physical	Adverse Event Screening	UVA1 biweekly with glove occlusion	Assessments	PROM	Photos
Screening	X	X						
Baseline		X	X	X		X	X	X
UVA treatment sessions 1-14					X			
UVA treatment session 15				X	X	X	X	X
UVA treatment sessions 16-29					X			
UVA treatment session 30				X	X	X	X	X
3-months post-treatment				X		X	X	X
12-months post treatment				X		X	X	X

PROM = Patient-reported outcomes measurements

Table 2: Outline of study protocol for optional placebo arm treatment starting at week 15 (previously treated arm will be covered with UV-blocking glove).

	Adverse Event Screening	UVA1 2-3 times weekly	Assessments	PROM	Photos
Baseline	X		X	X	X
UVA treatment sessions 1-14		X			
UVA treatment session 15	X	X	X	X	X
UVA treatment sessions 16-29		X			
UVA treatment session 30	X	X	X	X	X
3-months post-treatment	X		X	X	X
12-months post treatment	X		X	X	X
	Adverse Event Screening	UVA1 biweekly with glove occlusion	Assessments	PROM	Photos
Baseline	X		X	X	X
UVA treatment sessions 1-14		X			
UVA treatment session 15	X	X	X	X	X
UVA treatment sessions 16-29		X			
UVA treatment session 30	X	X	X	X	X
3-months post-treatment	X		X	X	X
12-months post treatment	X		X	X	X

PROM = Patient-reported outcomes measurements

After answering questions and prior to the first treatment the Principal Investigator (PI) will examine the entire patient and assess for the diagnosis of systemic sclerosis with bilateral hand involvement and perform the following assessments: HAMIS, CHFDS, durometer measurements, and mRSS. (Please see efficacy assessment section for details of HAMIS, CHFDS, durometer, and mRSS). Photographs of the hands and other affected areas will be taken. The patient will be asked to identify their dominant (writing) hand and their answer will be noted. Using a random number generator, the patient will be randomized to undergo UVA1 treatment vs UV-blocking glove (control) on the dominant hand. The non-dominant hand will receive the other modality. A study coordinator will perform the randomization on the day of first treatment and the PI and sub-investigators (sub-I) will be blinded to the treatment assignment.

UVA1 Treatments:

Blinding:

A UV-blocking glove will be placed on the control hand as determined by the randomization process. Subjects will wear eyewear that occludes external light.

Evaluations for adverse effects will be carried out by the UVA1 operator (a nurse not involved in any assessments) and the blinded investigator at prescribed intervals. Evaluation of UVA1 efficacy on hand scleroderma will be assessed by a trained and experienced evaluator who is blinded as to the UVA1-treated side (covered / not covered). The efficacy evaluations will be carried out prior to treatments on days both evaluations and treatments are completed.

Dosing Schedule:

Prior studies with UVA1 have shown that high and medium dose protocols (>40-120 J/cm^2) are more effective than low dose (20-40 J/cm^2) to treat sclerosing skin conditions. (Hassani, 2016) Thus, we will set the initiation dose at 50 J. The hands will be positioned approximately 9 inches from the bulbs. The palmar surface of the hand will be exposed for half the treatment and the dorsal surface for half the treatment. If tolerating well after three treatments, the dose will be increased to 60 J for three treatments and then 70 J for the remaining treatments.

Patients will return to clinic two-to-three times per week for 30 treatments over a 100-day period to receive UVA1 treatments. If the patient experiences redness, burning, pain, or blistering at the treatment site, treatment will be held if active symptoms persist at the time of the next scheduled treatment. If the symptoms have resolved and the patient has healed by the next scheduled treatment, the UVA1 energy will be reduced by 10 J of the previously delivered dose. Dose escalation will then proceed by increasing the UVA1 energy after three well tolerated treatments.

Evaluations:

1. Efficacy evaluations will be performed at baseline, after 15 UVA1 treatment sessions, after 30 UVA1 treatment sessions, and at 3 and 12 months after completion of all UVA1 treatments. For each evaluation, one of the sub-Investigators who is blinded to the treatment assignments will generate and record the HAMIS, CHFDS, Durometer, and mRSS. Hands will be photographed. Patients will complete all PROM including using Skindex-16, Michigan Hand Questionnaire (MHQ), PROMIS-Physical Function (PROMIS-PF), Hand Disability in Systemic Sclerosis – Digital Ulcers(HDISS-DU), and Visual Analog Scale (VAS).

The blinded evaluator will also perform safety evaluation and document study-related adverse events.

a) Primary Efficacy Measure:
   The efficacy will be measured using the HAMIS test score to assess for improvement over time and as compared to the untreated hand. The primary endpoint will be assessed after 30 UVA1 treatments. The

primary endpoint is improvement in HAMIS score as compared to the untreated hand after 30 UVA1 treatment sessions.

b) Secondary Efficacy Measures:
Secondary efficacy measures include HAMIS test score improvement from baseline in treated and untreated hands after 30 UVA1 treatment sessions, as well as changes in CHFDS, Durometer measures, mRSS, Skindex-16, MHQ, PROMIS-PF, and VAS scores between baseline and after 30 UVA1 treatment sessions and (when applicable) between treated and untreated hands. Other secondary efficacy measures include change in HAMIS test scores CHFDS, Durometer measures, Physician assessment, Skindex-16, MHQ, PROMIS-PF, HDISS-DU, and VAS scores between completion of 30 UVA1 treatments and 3 and 12 months post-treatment in both hands as compared to baseline and after 30 UVA1 treatment sessions in each hand. Secondary endpoint measures also include time to disease worsening after treatment as defined by a 3-point (~10%) increase in HAMIS scores post-treatment.

Endpoint measure descriptions:
HAMIS is a hand function test developed for adults with systemic sclerosis. HAMIS consists of 9 items designed to measure all movements assessed in an ordinary range of motion (ROM)-measured hand test. Specific items test finger flexion and extension, thumb abduction, pincer grip, finger abduction/swelling, dorsal extension and volar extension of the wrist, and pronation and supination. Each item is graded on a 0-3 scale, where 0 corresponds to normal function and 3 denotes that the individual is unable to perform the item. Each hand is assessed separately. The minimum score for HAMIS is 0, representing normal hand function. The maximum score of HAMIS is 27, representing a high degree of dysfunction. (Sandqvist, 2000)

The **CHFDS** is a questionnaire with 18 questions concerning daily living activities, administered by a clinician, which each question scored on a scale from 0 (performed without difficulty) to 5 (impossible to do). The total score is obtained by adding the scores from all items (range 0-90), with lower scores indicating normal function and higher scores indicating poor function. This test was developed for rheumatoid arthritis but has been validated in scleroderma. (Rannaou, 2007)

A **Durometer** is an instrument for testing the hardness of various materials. It has been used in scleroderma to measure the hardness of affected skin as compared to normal skin.

The **physician assessment on skin thickness on the hand and fingers based on the modified Rodnan skin score (mRSS)** which is a standard outcome measure for skin disease in systemic sclerosis. The score is calculated by evaluating the skin thickness at 17 different body sites. Each site is graded from 0 to 3, with 0 representing normal skin and 3 representing severe skin thickness. The score is calculated by adding the scores at each site to arrive at a total score ranging from 0 (normal) to 51 (severe disease). (Khanna, 2017) In this study we will only calculate the score for the hands and fingers. Total possible score of 6 on each hand.

Skindex-16 is a 16-item validated assessment for the patient to identify the impact of their skin disease on three quality of life domains: symptoms, emotions, and physical functioning. Scores are normalized to a 0-100 scale with 0 representing no impact on quality of life and 100 representing maximal impact.

The **Michigan Hand Questionnaire (MHQ)** is a 37-item validated instrument exploring hand-specific outcomes across six domains: overall hand function, activities of daily living (ADLs), pain, work performance, aesthetics, and patient satisfaction with hand function. It asks questions separately about each hand, allowing for comparisons between hands. The raw score is converted to a 0-100 scale. For pain, a higher score indicates more pain, but for the other five scales, higher scores indicate better hand performance. The score for the affected hand is obtained by selecting either the right or the left hand score.

Hand Disability in Systemic Sclerosis – Digital Ulcers(HDISS-DU) is a patient reported outcome measure developed to capture the full spectrum of symptoms and disability related to digital ulcers, which are common and debilitating in scleroderma involving the hands. The instrument consists of 24 items. Responses are scored from 1 to 6 (6 scores), where 1 is 'yes, without difficulty', 2 is 'yes, with a little difficulty', 3 is 'yes, with some difficulty', 4 is 'yes with much difficulty', 5 is 'nearly impossible to do' and 'used unaffected hand only' (both responses were assigned the same score), and 6 is 'impossible'. The eighth response option 'did not do this activity in the past 7 days' is scored as missing. The overall HDISSDU score is calculated as the mean of non-missing item scores (with a missing data threshold of < 12 items) and ranged from a minimum score of 1 to a maximum score of 6, with increasing score corresponding to increasing disability.

PROMIS Physical Function (PROMIS-PF) is a computer adaptive test (CAT), wherein initial screening questions guide the need for additional questions following an iterative algorithm. For example, if a patient is unable to walk 100 feet without resting, an additional question about jogging 1 mile would not be asked. A weighted t-score results based on national averages with 50 as the mean score; >50 means higher physical function, <50 means lower physical function.

All PROs (Skindex-16, MHQ, PROMIS-PF) will be collected electronically at every visit.

Table 3 summarizes the efficacy measurement points during the study period.

	Baseline	Post 15 treatments	Post 30 treatments	Months 3 and 12 post-UVA1 treatment
UVA1 Treated				
HAMIS	X	X	X	X
CHFDS	X	X	X	X
Durometer	X	X	X	X
Thickness Score	X	X	X	X
Skindex 16	X	X	X	X
MHQ	X	X	X	X
PROMIS-PF	X	X	X	X
HDISS-DU	X	X	X	X
VAS	X	X	X	X
UVA1 Untreated				
HAMIS	X	X	X	X
CHFDS	X	X	X	X

Durometer	X	X	X	X
Thickness Score	X	X	X	X
DLQI	X	X	X	X
Skindex 16	X	X	X	X
MHQ	X	X	X	X
PROMIS-PF	X	X	X	X
HDISS-DU	X	X	X	X
VAS	X	X	X	X

Statistical Methods, Data Analysis and Interpretation:
HAMIS, CHFDS, Durometer, physician assessment of skin thickness, DLQI, Skindex 16, MHQ, PROMIS-PF, HDISS-DU, and VAS will be collected at the time points outlined in table 3 throughout the study (baseline, after 15 UVA1 treatments, after 30 UVA1 treatments, then months 3, and 12 following completion of all UVA1 treatments or if applicable, at an early termination visit and any unscheduled visits). The subject will complete his/her physical examination and evaluations before the site personnel perform any clinic assessments and before any other interaction with the site personnel has occurred to avoid biasing the subject's response.
The differences between the scores for each hand will be compared using paired Student's t-tests and between patients using independent Student's t-test to compare significance for each outcome measure between control and treatment arms. Student's t-test will also be used to compare significance between treatment points within each arm (treatment or control).
Statistical significance will be considered demonstrated if the p-value for the differences is less than 0.05.

References:

Hassani J, Feldman SR. Phototherapy in scleroderma. Dermatol Ther (Heidelb). 2016; 6(4): 519-53.

Sandler RD, Matucci-Cerinic M, Hughes M. Musculoskeletal hand involvement in systemic sclerosis. Semin Arthritis Rheum. 2020; 50(2): 329-334.

Guillaume-Jugnot P, Daumas A, Magalon J et al. Autologous adipose-derived stromal vascular fraction in patients with systemic sclerosis: 12-month follow-up. Rheumatology (Oxford). 2016; 55(2): 301-6.

Liem SIE, Vliet Vlieland TPM, Schoones JW, de Vries-Bouwstra JK. The effect and safety of exercise therapy in patients with systemic sclerosis: a systematic review. Rheumatol Adv Pract. 2019; 3(2).

Connolly KL, Griffith JL, McEvoy M, Lim HW. Ultraviolet A1 phototherapy beyond morphea: experience in 83 patients. Photodermatol Photoimmunol Photomed. 2015; 31(6): 289-95.

Kroft EB, van de Kerkhof PC, Gerritsen MJ, de Jong EM. Period of remission after treatment with UVA-1 in sclerodermic skin diseases. J Eur Acad Dermatol Venereol. 2008; 22(7): 839-44.

Bongi SM, Del Rosso A, Galluccio F, et al. Efficacy of connective tissue massage and McMennell joint manipulation in the rehabilitative treatment of the hands in systemic sclerosis. Clin Rheumatol. 2009; 28(10): 1167-73.

Sandqvist G, Eklund M. Hand Mobility in Scleroderma (HAMIS) test: the reliability of a novel hand function test. Arthritis Care Res. 2000; 13(6): 369-74.

Rannou F, Poiraudeau S, Berezne A, Baubet T, Le-Guern V, et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum. 2007: 57(1): 94-102.

Khanna D, Furst DE, Clements PJ, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017; 2(1): 11-18.

Prasad S, Coais J, Jacobe H. Utilizing UVA-1 Phototherapy. Dermatol Clin. 2020 (38) 1:79-90.

Kreuter A, Hyun J, Stucker M, et al. A randomized controlled study of low-dose UVA-1, medium-dose UVA-1, and narrowband UVB phototherapy in the treatment of localized scleroderma. JAAD. 2006;22(5)247-53.

Mouthon L, Poiraudeau S, Vernon M et al. Psychometric validation of the hand disability in systemic sclerosis-digital ulcers (HDISS-DU) patient reported outcome instrument. Arthritis Res Ther. 2020 Jan 6;22(1):3.