STU#: STU00210472

PROTOCOL TITLE: Development & Preliminary Clinical Validation Blue Light Phototherapy Systems for T-Cell Mediated Skin Diseases

PRINCIPAL INVESTIGATOR:
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VERSION DATE:
1.0

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	FDA approved device (DusaPharm Blue) BLU-U by DusaPharma model 4170 Wavelength: 417±15 nm
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	20
Funding Source	T-Cellerate, LLC
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☐ No

OBJECTIVES:

Objective 1: To determine the efficacy of using blue light therapy to treat patients with Grover's disease or psoriasis vulgaris (also known as plaque psoriasis). We will be using the PASI scale to determine the severity of psoriasis vulgaris before and after receiving blue light treatments. The hypothesis is that blue light will reduce the erythema, scaling, and induration of psoriatic plaques and the erythema, pruritus, and number of papules for patients with Grover's disease.

Objective 2: To determine the histopathological changes of skin biopsies and immunohistochemistry of skin-based T-cell markers in patient's receiving blue light therapy in both Grover's disease and psoriasis. To examine the serological markers of immune function and correlate them with histopathological or clinical signs of improvement.

BACKGROUND:

Transient acantholyic dermatosis (Grover's disease) is a rare skin disorder that presents most commonly as small, pruritic, erythematous papules on the trunk, particularly the central chest and back in males older than forty or fifty. The etiology is largely unknown, but the disease is thought to be associated with sweating and heat. The time course of Grover's disease is variable: some patients present with a self-limited two to four week eruption or a persistent non-resolving pattern. A clinical diagnosis can be made, but it is often confirmed through skin biopsy demonstrating typical features.[1]

Psoriasis vulgaris is a common chronic inflammatory skin disorder that presents as erythematous, well-demarcated plaques with overlying silvery scale. It is associated numerous co-morbidities including obesity, cardiovascular disease, and autoimmune disease. Psoriasis is caused by the complex interactions of numerous inflammatory cells (T-cells and dendritic cells) and cytokines (TNF-alpha, Il-23, Il-12) that leads to abnormal differentiation in the epidermis, vascular dilation, and inflammatory cell recruitment.[2]

Blue light therapy in psoriasis has been studied in 2 randomized clinical trials, which have shown improvement in erythema and the LPSI score before and after therapy[3-4]. Although these studies studied the clinical response of psoriasis to blue light, neither examined histopathological or serological evidence of the immune system after blue light therapy. This study will also control for confounding variables such as 10% salicylic petroleum gel and moisturizes that were used in these two studies.

Standard of care treatment for Grover's disease include high potency topical steroids, application moisturizers, or emollients. Grover's disease patients may also minimize symptoms by avoiding triggers such as sweating or heat.

Standard of care for psoriasis include use of emollients, topical steroids, topical vitamin D, tar, calcineurin inhibitors, UV light phototherapy, and systemic therapies include methotrexate, retinoids, and biologic agents.

STUDY ENDPOINTS:

Objective 1 endpoint

- Recruitment of at least n=10 individuals with Grover's disease
- Recruitment of at least n=10 individuals with psoriasis vulgaris
- Demonstrate device safety as evidenced by absence of adverse events

- Demonstrate preliminary skin efficacy as demonstrated by clinical photo evaluation, patient reported outcomes with Dermatology Life Quality Index (DLQI) and skin histopathology with both Grover's disease and psoriasis vulgaris.
- Obtain user comfort and experience with phototherapy system using psychometric survey.

Objective 2 endpoint

- Elucidate keratinocyte and skin T-cell expression, and viability with blue light phototherapy
- Elucidate changes in circulatory T-cells based on flow cytometry and serum cytokines with blue light therapy.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
The DUSA BLU-U (Model 4170) is a Blue Light Photodynamic Therapy Illuminator is intended to provide phototherapeutic light to the body. Blue light therapy is indicated for dermatological conditions such as actinic keratosis (AK) or inflammatory acne vulgaris. The BLU-U is approved by the FDA (K031805) as a Class II medical device.
The BLU-U Illuminator to be used in this study is owned by the Northwestern Memorial Hospital Department of Dermatology and stored at the Dermatology Clinic in Chicago.

PROCEDURES INVOLVED:
Patients with Grover's Disease or Psoriasis vulgaris will be enrolled on the study.

In the informed consent process a Dermatologist will discuss Standard of Care treatment options for Grover's Disease or psoriasis vulgaris. If the patient wishes not to participate in this study the SOC treatment will be available to them. If the patient chooses to participate in this study, they may elect to do SOC treatment at any time (ending participation early) or after the phototherapy study visits are complete. Patients receiving SOC phototherapy (other light type, with activator creams, etc) may participate in this study by blocking a small site from their SOC phototherapy which will be treated with the Blue Light therapy in this trial. The Department of Dermatology has standard of care procedures for blocking specific sites during SOC phototherapy. These procedures will be followed if a patient that is enrolled on the study is simultaneously receiving SOC phototherapy for their condition. The clinical research team will consult with the phototherapy team for any patient that is receiving phototherapy.
No procedures in this study are standard of care for Grover's Disease or psoriasis vulgaris. If the symptoms of resolve before all phototherapy sessions are completed, the patient will have their final assessment and will have completed the study.

After informed consent a patient will be scheduled to start the study sessions immediately (if not on medications) or after a period of two weeks without using medications related to their skin condition. A site on the body will be identified for treatment with Blue Light, this will be the same site treated throughout the study.

The study visits will take approximately 30 minutes and will be done three times a week (at least 23 hours apart) over five weeks (15 visits total). Each session will consist of 16

minutes of Blue Light phototherapy with the BLU-U device over the affected area. Before starting the first, seventh and after the last session the patient will have a single, 6mm, punch biopsy of a characteristic lesion on the treated side only and a blood draw not exceeding 30 cc or two tablespoons in a visit. Tissue and blood, samples will be collected under the Dermatology Tissue Acquisition and Biorepository (IRB# STU00009443) protocol upon completion of the consent form for STU00009443.

During the first and last study visit the patient will be asked to complete surveys relating to their comfort and experience with the phototherapy symptoms and psychometric surveys of skin-related symptoms and skin-related quality of life.
In addition photographs will be taken of the afflicted areas before the first treatment, on the first visit, third visit after every 3 treatments until the end of the study as outlined in the table below.

Procedure Table

	Blue Light Phototherapy	Biopsy of lesional treated area	Blood Draw	Psychometric and Skin QoL survey	Photographs of afflicted skin area
Visit 0 - Consent					X
Visit 1 - Baseline	X	X	X	X	X
Visit 2	X				
Visit 3	X				X
Visit 4	X				
Visit 5	X				
Visit 6	X				X
Visit 7	X	X	X		
Visit 8	X				
Visit 9	X				X
Visit 10	X				
Visit 11	X				
Visit 12	X				X
Visit 13	X				
Visit 14	X				
Visit 15	X	X	X	X	X
Early completion (If condition resolved before final visit)	X	X	X	X	X

In this single arm, prospective clinical trial patients with Grover's disease (n=10) will be invited to participate. A baseline biopsy of a characteristic lesion will be performed. Patients will be asked to complete a baseline psychometric survey of skin-related

symptoms and skin-related quality of life. Patients will then be asked to present to the phototherapy unit at Northwestern Dermatology for 15 total sessions of blue light therapy divided into 3 sessions a week for 5 weeks. The target irradiance is 14 mW/cm^2 with a total dose of 9 J/cm^2 requiring ~16 min per treatment. At each treatment session, clinical photos will be taken along with blue-light dosimeter readings at various locations of the body. At the mid-point of the study (7 sessions), an additional biopsy will be taken of a characteristic lesion. At the end-point of the study (15 sessions), a final biopsy will be taken of a characteristic lesion. If the lesion(s) is/are resolved a biopsy will be done adjacent to a previous biopsy. Patients will be asked to complete psychometric surveys relating to their comfort and experience with the phototherapy symptoms. In addition, they will complete psychometric surveys of skin-related symptoms and skin-related quality of life to compare against baseline. Subjects on the therapy will be asked to refrain from using systemic treatments throughout the trial with a 2-week washout period before the start of the trial. Topical treatments may be used, except in the area that is identified for treatment with Blue Light phototherapy provided by this study.

In a parallel single arm, prospective clinical trial patients with psoriasis vulgaris (n=10) will be invited to participate. A baseline biopsy of a characteristic lesion will be performed. Patients will be asked to complete a baseline psychometric survey of skin-related symptoms and skin-related quality of life. A baseline PASI-75 (a well-accepted clinical endpoint for psoriasis severity) will be conducted and across every treatment visit. Patients will then be asked to present to the phototherapy unit at Northwestern Dermatology for 15 total sessions of blue light therapy divided into 3 weekly sessions. The target irradiance is 14 mW/cm^2 with a total dose of 9 J/cm^2 requiring ~16 min per treatment. At each treatment session, clinical photos will be taken along with blue-light dosimeter readings at various locations of the body. At the mid-point of the study (7 sessions), an additional biopsy will be taken of a characteristic lesion. At the end-point of the study (15 sessions), a final biopsy will be taken of a characteristic lesion. Patients will be asked to complete psychometric surveys relating to their comfort and experience with the phototherapy symptoms. In addition, they will complete psychometric surveys of skin-related symptoms and skin-related quality of life to compare against baseline. A final PASI-75 will be scored. Subjects on the therapy will be asked to refrain from using any systemic treatments throughout the trial with a 2-week washout period before the start of the trial. Topical treatments may be used, except in the area that is identified for treatment with Blue Light phototherapy provided by this study.

In partnership with Northwestern University's Skin Biology Disease Research Center (one of only 6 in the country), all skin biopsy results will be processed for standard histology as well as immunohistochemistry. All biopsies will be stained for T-cell biomarkers including CD4, CD3, CD5, CD7, CD8 with cell populations counted for biopsies taken at baseline, at the midpoint and at completion of 15 sessions of blue light therapy. Keratinocyte apoptotic biomarkers will also be collected.
Serological markers will be drawn both at baseline and after treatment from blue light in both the Grover's disease and psoriasis cohorts for immune-cell related cytokines (TNF-α, C-reactive protein, IL-6, E-selectin, and ICAM-1)

Procedures performed to lessen the probability or magnitude of risks:
Blue Light phototherapy sessions will be done in a private clinic room to maintain privacy of the patient. The researchers and patient will wear protective eyewear during use of the BLU-U device. Eyewear will block light with wavelengths of at least 500nm and shorter with an Optical Density (OD) of two or greater as recommended by the DUSA, the manufacturer of the BLU-U.

Photographs taken for the study will not include the full face and will exclude identifying marks such as tattoos. The intent of photographs is to document the efficacy of the treatment and any improvement of the disease.

Standard, sterile technique will be followed for both blood draws and punch biopsies.

Pictures of the psoriatic lesions and Grover's disease will be recorded and stored on research only devices (tablets/iPads). Those images will only be stored and accessed by research personal devices. The photographs will be used to assess whether the blue light therapy has improved the skins disease is psoriasis and Grover's disease.

DATA AND SPECIMEN BANKING
The biopsies and blood draws will not be stored for future use, and will be immediately used to histopathological examination and serological markers. Specimens will only be handled by the research team and the laboratory conducting pathological and histological testing. All research specimens will be labeled with a unique patient identifier, collection date and time.

Upon completion of consent, the biospy samples will also be shared with Dermatology Tissue Acquisition and Biorepository (IRB# STU00009443).

SHARING RESULTS WITH PARTICIPANTS
The results of the biopsies, and serological markers of the immune system will not be shared with the patient. At the end of the study a dermatologist will give an assessment of the patients condition and follow up care instructions if necessary.

STUDY TIMELINES
An individual will participate in the study for approximately 5 weeks. It will take approximately 1 year to enroll all study participates. The data to complete primary analyses is January 2021.
All recruiting will occur at either Northwestern Memorial Hospital (Arkes Pavilion in the outpatient dermatology offices).

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria
1. Patient's aged 18-89 at time of enrollment
2. Previous diagnosis of psoriasis vulgaris or Grover's disease

3. All Groups: Subjects who are able and willing to give informed consent for this study and the Dermatology Tissue Acquisition and Biorepository (STU00009443).

Exclusion Criteria

1. All Groups: Subjects who are younger than 18 years of age or older than 90 years of age
2. Patients who receive systemic treatment within 2 weeks washout period before or during planned phototherapy
3. Patients using topical treatment on the area identified for treatment in this study
4. Patients prescribed any of the following drugs for issues not related to their psoriasis or Grover's disease
    - topical steroids
    - calcineurin inhibitors
    - methotrexate
    - retinoids
    - biologic agents
5. Unable to schedule phototherapy sessions
6. We will not recruit the following populations: adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, prisoners and other vulnerable populations.

RECRUITMENT METHODS

Patients will be recruited from the Department of Dermatology clinics at the time of their regular appointments and asked if they would like to learn more about this research study. We may also ask NMH Dermatologists to refer patients with psoriasis or Grover's disease or review medical records to search for eligible patients.
Eligible patients may be contacted by phone to gauge interest in the study and will be consented in person in the NMH Department of Dermatology.

An additional method of identifying patients will be through the Electronic Data Warehouse (EDW). The EDW at NU is updated daily. An algorithm can be set up based on the eligibility criteria of the trial to identify potential patients that have psoriasis or Grover's disease. Eligible patients will be sent an introductory email about the study and given 1 week or more to respond. If the team does not hear back from the patient or the patient does not respond indicating disinterest in the study, the clinical research team may follow up with a scripted phone call and schedule an appointment if the potential research subject is interested in the study.
Recruitment will be monitored carefully with weekly meetings of study coordinator and study PI. Barriers to recruitment will be identified and addressed to ensure recruitment remains on track.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Subjects will be offered $25 or $50 USDs (payable via check) for their participation in each study visit involving Blue Light Therapy. Study visits involving blood draws and biopsies will pay $50. All other visits will compensate $25.

Total compensation that a patient can earn in this study is $450 dollars.

WITHDRAWAL OF PARTICIPANTS

If the patient shows adverse signs from the blue light therapy, they will be withdrawn from the study. Participants will be free to withdraw from the study at any time. Participants may be withdrawn from the research without their consent if they are unable or unwilling to schedule and attend blue light phototherapy sessions.

RISKS TO PARTICIPANTS

Blue light: Hyperpigmentation has been a reported side effect of direct blue light therapy.

Biopsies: Present a small risk for scarring and infection

Blood draw: it might be uncomfortable, but there is otherwise very little risk

Photographs: Faces will be obscured, but there is a possibility that subjects may be able to be identified from the photographs that will be taken for the study.

Survey: Some questions may make patients uncomfortable or upset. Patients do not have to answer these questions if they do not want to.

Study procedure: As patients are asked to refrain from other skin treatments for two weeks before this study and during the study their symptoms may be worse. These conditions on the skin do not lead to long term sequelae when not treated for 1-2 months, but will be closely monitored during the study.

POTENTIAL BENEFITS TO PARTICIPANTS

The potential benefit is that blue light therapy may improve the clinical manifestation of Grover's disease and psoriasis.

DATA MANAGEMENT AND CONFIDENTIALITY

Subject identifiable medical information obtained as a result of this study is considered confidential and disclosure to third parties other than the principal investigator and the co-investigators is prohibited. All reports and communications relating to subjects in this study will refer to each subject only by their initials study identification number. Data generated as a result of this study are available to inspection on request by Food and Drug Administration or other government regulatory agency auditors, and the Northwestern University Institutional Review Board (IRB).

Subject identity will be protected through use of a coded list of identifiers, which will be maintained separately from the data set. Source documents and CRFs are kept in a

secured area (in a locked cabinet in a locked room) in the Department of Dermatology and all electronic data is password protected so that only authorized personnel can have access.

Photographs may be taken of the psoriatic lesions and Grover's lesions for research purposes only. Photographs will be labeled only by subject initials and identification number. All photos will be stored on a password protected server accessed by a password protected computer.

Data stored and used for future research will be de-identified. Data will not be used for future research outside of the scope of this study.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS
This study is minimal risk.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
Faces will not be photographed, but there is a possibility that subjects may be able to be identified from the photographs should there be identifying tattoos or marks. Areas with any identifying tattoos or marks will not be photographed.

This study is minimal risk.

COMPENSATION FOR RESEARCH-RELATED INJURY
This study is minimal risk. If a patient has complications or injury related to blood draw or biopsy, they will receive standard of care treatment to resolve their injury.

ECONOMIC BURDEN TO PARTICIPANTS
There are no costs to the participants involved in the study

CONSENT PROCESS
Prior to study entry, a written informed consent must be obtained from the subject. A copy of the signed consent form must be retained in the study file.

To protect participant confidentiality, we will conduct all research-related discussions and informed consent procedures in a private room. If a private room is not available, a designated area far enough away from other patients such that they cannot hear the conversation will be used. We will obtain written informed consent from the participant in English, using the IRB-approved consent form, prior to conducting any study procedure. The study procedures, risks, and benefits will be discussed and the study team will answer all questions prior to obtaining consent. All versions of the consent forms will be approved by the relevant ethics committees prior to study initiation.

Eligible participants who do not wish to participate in this study will continue to receive care according to local clinical standards

NON-ENGLISH SPEAKING PARTICIPANTS

Non-English speaking participants will not be included in this study.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

The following PHI will be collected, and is also listed on the consent form for study enrollment:

- All information in a medical record
- Results of physical examinations
- Medical history
- Patient Demographics
- Patient address, phone number and email address

Entry of any data into a Northwestern Memorial Healthcare Corporation entity (for example, Galter Pavillion or Prentice Women's Hospital) clinical record during the duration of the research study is also PHI that may be collected and listed in the consent form.
PHI from the above categories may be obtained from the following entities: Northwestern Medical Group (NMG) and Northwestern Memorial Hospital (NMH).

Any research information shared with outside entities during the study will not contain the name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The Department of Dermatology Clinical Trials Unit has many active clinical trail and standard of care protocols treating patients with UV or Blue light therapy. A board-certified dermatologist will be responsible for overseeing the conduct of the study and review of patient eligibility, the patients condition, and the efficacy of the blue light phototherapy treatment.

REFERENCES

1. AOCD, Grover's Disease, https://www.aocd.org/page/GroversDisease?
2. Psoriasis. (2019, March 13). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/psoriasis/symptoms-causes/syc-20355840
3. Br J Dermatol. 2013 Aug;169(2):266-82. doi: 10.1111/bjd.12355

4. Kleinpenning MM, Otero ME, van Erp PE, Gerritsen MJ, van de Kerkhof PC. Efficacy of blue light vs. red light in the treatment of psoriasis: a double-blind, randomized comparative study. Journal of the European Academy of Dermatology and Venereology. 2012 Feb;26(2):219-25.
5. Pfaff S, Liebmann J, Born M, Merk HF, Von Felbert V. Prospective randomized long-term study on the efficacy and safety of UV-free blue light for treating mild psoriasis vulgaris. Dermatology. 2015;231(1):24-34.