NCT number: NCT04601532

Official Title: Randomized Controlled Trial Assessing a Novel Glycopolymer Compound in the Treatment of Superficial Partial-Thickness Burns

Study Protocol Document Date: 8/17/2020

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Abstract: Current effective dressings for burn wounds contain silver (nanoparticulate or ionic), hypochlorite, hydrogen peroxide, sulfa agents, chlorhexidine, iodine or other dilute antiseptics meant to provide some measure of antimicrobial protection. However, all of these materials have some proven limitations in facilitating wound healing and also have notable local and systemic adverse effects. None of the current clinical treatments enhance healing and/or reduce scar formation. The purpose of this study is to test the safety and effectiveness of SynePure™ Wound Cleanser when used in combination with Catasyn™ Advanced Technology Hydrogel for the treatment of superficial partial-thickness burn wounds.

This study is an investigator initiated, single site, University of Pittsburgh, prospective, parallel group, randomized controlled trial comparing SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel (intervention group) to the current gold standard treatment Silvadene (control group). Both groups will receive the same care other than the treating agent. Subjects will be recruited from the UPMC Mercy Burn Center adult patient pool who have sustained superficial partial-thickness burn wounds that comprise ≤10% of total body surface area (TBSA).

1.0 Objective and Specific Aims:

Primary Objective: To test the effectiveness of SynePure Wound Cleanser when used in combination with Catasyn Advanced Technology Hydrogel for the treatment of superficial partial-thickness burn wounds as compared to standard of care treatment.

Secondary Objective: To test the ongoing safety of SynePure Wound Cleanser when used in combination with Catasyn Advanced Technology Hydrogel for the treatment of superficial partial-thickness burn wounds as compared to standard of care treatment.

Hypothesis: SynePure Wound Cleanser when used in combination with Catasyn Advanced Technology Hydrogel is safe in humans and improves time to heal and infection rates in superficial partial-thickness burn wounds when compared to standard of care treatment.

Specific Aims:

1) Compare re-epithelialization rates between treatment groups.
2) Compare rates of infection, complication and progression of the wound to deep partial/full thickness between treatment groups.
3) Compare healed wound characteristics, Patient Reported Outcomes and Health-related Quality of Life Outcomes between treatment groups.

2.0 Background and significance:

2.1 Background:

Burn wounds are associated with significant morbidity and mortality as well as Quality of Life impairments for the patient. Burn wounds can be particularly problematic as they can compromise skin integrity potentially allowing microbial invasion and subsequent infection. In fact, thermal destruction of the skin provides an ideal environment for microbial colonization.[1] If left untreated, the infection can spread to a systemic level, further jeopardizing the patient.

Topical management via dressings provide a barrier against microbial infection. The current gold standard for burn wound dressings is silver (nanoparticulate or ionic) and it has shown some efficacy in treating infections but it does not demonstrate an ability to prevent infections and some treatment guidelines even recommend against its use.[2-3] Although silver dressing is preferred for military use, a retrospective review spanning 10 years of use

in military environments showed that silver was not more effective than other antimicrobial topical treatments[4] and a meta-analysis with over 2500 surgical patients found silver sulfasalazine was associated with increased infection rates and hospital length-of-stays were two days longer on average.[5]

Other current effective dressings for burn wounds include hypochlorite, hydrogen peroxide, sulfa agents, chlorhexidine, iodine or other dilute antiseptics meant to provide some measure of antimicrobial protection. However, all of these have some proven limitations in facilitating wound healing and also have notable local and systemic adverse effects (see ref 6 for review). Finally, none of the current clinical treatments, have demonstrated evidence of enhanced healing and/or reduced scar formation.

Synedgen has developed SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel. These products are Food and Drug Administration (FDA) 510(k) cleared wound care medical devices formulated with a novel biocompatible chitosan derivative, poly (acetyl, arginyl) glucosamine. SynePure is optimized for the cleansing and debridement of wounds and thermal injuries, and Catasyn serves as a protective gel dressing. Together, these products reduce inflammation in wounds, aggregate bacteria and disrupt bacterial biofilms, and accelerate healing. SynePure and Catasyn are nontoxic, biocompatible, shelf-stable up to two years, easy to use, and may be used in any care setting from the battlefield to a tertiary hospital.

Synedgen optimized Catasyn's formulation, completed GLP biocompatibility studies, and performed engineering and qualification runs for in-house cGMP manufacturing of the product. Catasyn's constituent glycopolymer preparation was optimized and validated under cGMP. Together with collaborators at the University of Miami, the studies necessary to determine the optimized schedule for the treatment of full-thickness burns were completed. Work done in collaboration with the University of Pittsburgh Medical Center further established the efficacy of SynePure and Catasyn's efficacy in a pig model of infected thermal injury. In this study, using SynePure and Catasyn together twice a day, three days a week demonstrated 4-6 day faster healing of methicillin-resistant Staphylococcus aureus burns through reduced infection, increased epithelialization, and faster wound closure as compared to standard of care (Silvadene).[7] Similar results were observed in partial thickness injury infected with Pseudomonas aeruginosa**.**[8]

We have also explored SynePure and Catasyn's activity by gene array analysis to better understand the gel's capacity to accelerate healing and control inflammation. Confirmation of SynePure and Catasyn's reduction in wound bacterial colonization was confirmed in both our partial-thickness and full-thickness wound porcine models. All toxicology studies performed to date have shown no toxicity and no adverse events have been observed in multiple animal studies including a variety of animal species and several routes of drug administration.

Significance:

SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel demonstrates an improvement in healing, scarring, fibrosis, and infection of burn wounds and complex open wounds. Its toxicity profile, ability to remove biofilms, healing, and anti-inflammatory properties make a compelling case for further testing of SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel as a new agent to facilitate healing and limit scarring in burn wounds.

3.0 Research Design and Methods:

The study is a prospective, parallel group, randomized controlled trial comparing SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel (intervention group) to the current gold standard treatment Silvadene (control group). Subjects will be randomized 1:1, either to the treatment group or the standard of care (Silvadene) control group.

Prior to the candidate's referral into the study, as part of standard of care in the burn center, the burn wound is debrided and cleansed in the hydrotherapy area, and then assessed to categorize the burn (superficial, partial thickness,).

Procedural Summary:
1. After informed consent process is completed, the study investigator examines and screens the participant to confirm the diagnosis of a superficial-partial thickness burn and all other eligibility inclusion/exclusion criteria. Medical history, medical record review with participant report, medication profile collections, vital signs, demographics, physical exam with burn wound and surface area assessments are completed at this time. Upon completion of these assessments' all findings are reviewed and participant eligibility is determined based on study inclusion and exclusion criteria.

2. Should participant be deemed eligible to continue in research; randomization is performed to determine group assignment with randomization to either the intervention group (SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel) or the control group (Silvadene). Prior to application of treatment agent and dressing application, 2D photographs will be taken of the burn area for later evaluation.

3. During the Initial treatment visit (Day 0), after randomization, the treatment agent is applied (SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel or Silvadene) to complete secondary dressing with a dry gauze and Kerlix wrap application.

4. Patient education on wound care and daily dressing change per routine care. Dressing to be changed daily by patient or provider. Education also provided as to the treatment agent to be applied daily with the dressing change (SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel or Silvadene).

5. Participants will be asked to complete Subject report questionnaires related to the burn wound, symptoms experienced and effects of injury on their activities of daily living.

6. The research coordinator will call the participant twice at timepoint Day 1 and Day 3 to assess participant safety, complications/adverse events and address any questions or concerns that the participant may have encountered.

7. Follow-up Visits (Visits 2-8) will occur in the UPMC Mercy Burn Center and will consist of wound evaluation, brief history and physical assessment, vital signs, recording of status change since last visit/interaction, medication review, and adverse event collection. 2D photographs will be obtained of burn wound area at time of physical assessment and Subject report questionnaires and wound dressing assessment /treatment agent application (if wound has not yet healed). Reference to the Schedule of Events included with Protocol for additional detail of study procedures.

Recruitment:
Subjects presenting to the study site for treatment of superficial partial thickness burns will be considered for enrollment. Physicians and licensed clinicians within the burn center area, familiar with the study's inclusion/exclusion criteria will assess for potential patients as they arrive to the

Burn Center Clinic for treatment, a part of their burn practice. If the patient is an appropriate candidate and willing to be considered for the study, he/she will be referred to the research team.

After informed consent has been obtained, the study investigators will conduct screening procedures to determine study eligibility. Should the participant meet criteria, he/she will proceed to randomization on Day 0 prior to treatment application. Enrolled subjects will be randomly assigned per a predefined 1:1 randomization scheme to either the interventional group or control group.

Active Treatment:
During the initial treatment visit (Day 0), the wound will undergo hydrotherapy debridement per routine care and at which time 2D photographs of the wounds will be obtained prior to randomization. Participants assigned to each group will have their treatment applied per their randomization status, either SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel (intervention group) or Silvadene (control group). They also will be given written instructions on how to apply the treatment at home and a sufficient supply to last until their next visit.

Consent and Screening procedures:
All screening procedures will be performed at the UPMC Mercy burn center in a private room after this informed consent document is signed. These screening procedures will take approximately 2-3 hours.

- Informed consent
- Review of medical records related to the injury, past surgeries, and general health events
- Demographic information and allergy collection
- Physical assessment inclusive of an evaluation to your burn wound area
- Medication collection
- Vital sign measurement (such as temperature, heart rate, blood pressure and respiration rate) collection
- Pregnancy Test (Urine Dip)

Initial Treatment Visit 1 (Day 0):
After all screening procedures have been completed and reviewed by the investigators and eligibility will be determined. Should the participant be determined to be eligible to continue participation, the initial treatment procedures will be continued and all procedures may occur on the same day as the screening visit. This visit will be performed at the UPMC Mercy Burn Center. The total length of time for this visit will take approximately 2-3 hours of time.

- Randomization process with assignment to 1 of 2 treatment groups where either SynePure Wound Cleanser with Catasyn Advanced Technology Wound Hydrogel OR Silvadene will be applied. Both groups will then receive a secondary dry dressing covering consisting of gauze and Kerlix wrap.
- 2D photographs will be obtained focusing on the burn injury area, prior to the wound being dressed.
- Written instructions will be provided describing how to apply the wound treatment and dressings daily in between to the participant. Should the participant be in hospital during the healing of the burn wound these daily dressings will be performed by either a member of the clinical staff or the research team.

- Completion of Subject Self-report questionnaires that pertain to the burn wound, pain, and other symptoms that experience. Potential effects and relationship to the participant's quality of life and activities of daily living
- Adverse events collection

After this initial visit, the research team will reach out to the participant by phone on Day 1 and Day 3 of the study schema to determine if there are any questions, issues or concerns that the participant may be experiencing. Additionally, they will remind and confirm the next in person visit to the clinic.

Follow-up Visits (Visits 2-8):
These Visits will occur in the UPMC Mercy Burn Center and have a duration of 1-2 hours to complete. These visits will consist of wound evaluation to assess for healing, brief history and physical assessment, vital signs, recording of status change since last visit/interaction, medication review, and adverse event collection. 2D photographs will be obtained of burn wound area at time of physical assessment and prior to wound dressing /treatment agent application (if wound has not yet healed) and subject report questionnaires consisting of SF-12, Wound Experience and Satisfaction questionnaires, Vancouver Scar Scale, POSAS Questionnaires (described in the following section). During the study visit, continued instructions for at home dressing and treatment application will be reinforced.

Subject Reported Questionnaires:
Vancouver Scar Scale Score: The VSS[9] is a scale to assess the extent of scarring for a given wound by scoring the pigmentation, vascularity, pliability and height of the scar. Each domain is individually scored then the domains are summed to give a total score that range from zero (0) to 13 with zero (0) representing a 'normal' presentation. Validity and reliability of the scale have been documented[10-12] and is commonly used in wound healing research.

SF-12: The SF-12[13], an abbreviated version of the SF-36, is a patient self-reported twelve questions survey of general health, physical functioning, role functioning (physical and emotional), bodily pain, vitality, mental health, and social functioning. The scale is comprised of two scores: physical component summary (PCS) and mental component summary (MCS). Scores are summarized and normalized. While the survey demonstrates moderate validity and reliability,[14] the survey is ideal for use as it is brief and commonly used, so comparisons between studies are possible.

POSAS: The patient and observer scar assessment scale[15-16] is used to measure scar quality. It is composed of a patient reported section and an observer reported section. Each section consists of six items that are scored numerically on a ten-step scale. These are then summed together to make up the total score. There is also an overall opinion section for both the patient and the observer. While validity and reliability are marginal for the POSAS, scores have shown little variance from the gold standard, the Vancouver Scar Scale, and it has the distinct advantage of incorporating the patient's perspective.

Wound Experience Questionnaire: The wound experience questionnaire[17] consists of three sections regarding the patient's wound. The questionnaire is used for wounds early into the healing process and wounds that have dressings. This has been primary used in patients with surgical wounds but can be adapted to wounds not specifically operative, such as burns. Validity and reliability evidence have not been published but the questionnaire has the unique capability to assess a primary focus of this study. In addition to assessing patient satisfaction with the healing process, the questionnaire also assesses patient satisfaction with the wound dressings as distinct categories.

3.1 Data Collection and Statistical Consideration:

Sample Size Estimation:

In this study, the minimal median difference of three (3) days to healing is determined to be the clinically relevant difference. Given an assumed median time of 15 days to healing for the Silvadene comparator group[18], a corresponding hazard ratio of 0.8 for the intervention group is anticipated. a sample of 45 in each group (90 total) is required to detect a statistically significant difference [confidence level ($\alpha \leq 0.05$) – 95%; Power – 80%]. Assuming a 10% attrition, it is recommended to enroll up to 100 subjects to achieve a sample of 90 subjects. This will be easily accomplished in our outpatient burn clinic, with a 400-patient annual volume, and we will use a 3-week evaluation period so that the trial can be accomplished in a year.

Analytic Plan:

Descriptive statistics will be presented as means and standard deviations for continuous data and as counts and percentages for dichotomous and categorical data. Time-to-event curves with Kaplan-Meier (KM) estimates will be used to compare overall median time to wound healing between treatment groups. Comparison of KM curves will be performed using the log rank test as the curve is assumed to be non-parametric or semi-parametric, and the baseline hazard is not related to the group assignment. Relevant clinical and demographic variables may be assessed for their independent contribution in time-to-event outcome using univariate screening and the hazard is assumed to be relatively constant across the study window. Multiple regression modeling (Cox Proportional Modeling) and adjusted KM curves will be assessed as appropriate. Variables will be included in the multivariate analysis if the univariate screening p-value is < 0.10 and multivariate parameters will be presented as hazard ratios with their corresponding 95% confidence intervals.

Infection, complication, and progression rates will be compared using the Chi-squared test or the Fisher exact test if the data is very unequally distributed within the contingency table, which is anticipated for infection rates. Repeated Measure Analysis of Variance (ANOVAs) will be performed to assess differences in PROs with the days since wounding as the Within-Subjects factor and treatment groups as the Between-Subjects factors. Bonferroni post-hoc analyses may be performed for all statistically significant main effects. Baseline demographic and clinical characteristics will be compared between treatment groups with Independent samples t-test for continuous data and Chi-squared test for dichotomous and categorical data.

Analysis will be performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and statistical significance will be determined at $p \leq 0.05$ with the exception of univariate screening as previously described.

Outcome definitions:

1. Healed wound: 90% reepithelialization (skin and mucous membrane replacement) of the wounded area.
2. Infection: characterized by local new inflammation, heat, purulence as well as new or increased pain, redness and swelling
3. Complications other than infection: gangrene, necrosis, periwound dermatisis and/or edema, hematoma, or any other complication determined to be related to the wound and/or treatment

4. Progression; recategorization of the wound to a more advanced state deep partial thickness, full thickness. Failure to heal with 21 days of injury also may be determined as progression by the investigator.

4.0 Human Subjects:

4.1 General Characteristics:

Inclusion criteria:

- 18 years of age or older, Male and Female
- Ability to provide informed consent
- Patients who have sustained superficial, partial thickness burn wounds ≤ to10% of total body surface area (TBSA)
- Patients otherwise in good general physical and mental health, as per the investigator's clinical judgment

Exclusion criteria:

- Inability to provide informed consent
- Deep partial-thickness burns and full-thickness burns
- Radiation, chemical or electrical burn injury
- Patients with burns primarily located to the face, genitals, or span across joints
- Patients whose burn injury was ≥ to 48 hours prior to entry into the UPMC Mercy Burn Clinic.
- Patients with uncontrolled cerebrovascular disease, cardiovascular disease, concurrent endocrine, hepatic or renal disease, or other severe conditions for whom, in the investigators' discretion would render study participation unsafe
- Current pregnancy
- Patients with concurrent burn related injuries or inhalation injury that would put the patient at increased risk, per physician discretion
- Any condition to which in the investigator's discretion would render study enrollment a safety concern for the patient.

All patients who present to the UPMC Mercy ER or Burn Center, whose burns are assessed to be superficial, partial thickness burns, and who also meet the study's eligibility criteria in the opinion of the referring physician will be considered for participation.

The racial, gender and ethnic characteristics of the proposed subject population reflects the demographics of Pittsburgh and the surrounding area and/or the patient population of the University of Pittsburgh Medical Center. We shall attempt to recruit subjects in respective proportion to these demographics. No exclusion criteria shall be based on race, ethnicity, gender, or HIV status.

The study will plan to enroll 115 subjects in order to randomize 100 subjects, to either the intervention group (SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel) or the control group (Silvadene). It is expected that some subjects will not meet screening criteria after they are consented, and will therefore not proceed forward to randomization.

4.4 Recruitment Procedures:

Subjects presenting at the UPMC Mercy burn center (whether initially seen at the Mercy Emergency Center, or at the outpatient burn clinic) for the treatment of burn wounds will be considered for enrollment. The potential candidate while in the hydrotherapy area, where

as standard of care, the burn wounds are debrided and assessed for depth classification will be introduced to the study. Appropriate candidates will be introduced by the treating physicians and clinical team to the research and will determine interest from the potential candidate in the research. If interest is expressed, the potential candidate will be introduced to the study team and the informed consent process will be initiated, should the candidate express willingness to proceed. Informed consent will be performed prior to any screening or intervention procedures.

The study investigator along with the research coordinator will discuss with the subject the nature of the research study, design schema, the risks and benefits, cost and payments and rights as a research subject participant. The potential subject will be provided with ample time to review the informed consent document and ask questions. Should the potential subject wish to take additional time to review the consent or discuss it with his/her family, or medical personnel he/she will be able to. The study investigator will provide the potential subject a private area within the burn center to conduct this informed consent document review prior to signing the informed consent.

Technical terms will be described using lay terminology and subjects will be permitted and encouraged to ask questions, and all will be answered to their satisfaction. In addition to the consent, the study schema lists the elements of each visit's requirements for participation in a visual and accessible way. Study investigators, or their clinical designee, will be responsible for obtaining informed consent and signing the informed consent document.

4.5 Risk/ Benefit Ratio:

As part of this study's goals are assessing the safety of the intervention treatment in patients with superficial partial-thickness burns, not all possible risks and adverse effects are known.

Risks associated with SynePure Wound Cleanser and Catasyn Advanced Technology Hydrogel include:

SynePure Wound Cleanser
Has been approved for external use in cleaning dermal wounds (including superficial partial-thickness burn wounds).

- There were no adverse events found upon topical application.

Catasyn Advanced Technology Hydrogel
Has also been approved for external use for dressing of wounds (including superficial and superficial partial-thickness burn wounds).

- There is a low risk of redness where the hydrogel is placed on the skin.

Risks associated with Silvadene include:

- Dermatologic
  - Skin discoloration
  - Burning sensation
  - Itching
  - Rashes
  - Skin photosensitivity (sensitivity to sunlight)
  - Skin necrosis (death of skin)
- Gastrointestinal reactions/ upset stomach

- Renal
  - Interstitial nephritis (inflamed kidneys)
- Hepatic
  - Hepatitis (inflamed liver)

Uncommon risks associated with Silvadene include:

- A small risk of adverse reaction associated with systemic absorption (This may lead to deposition of silver in your organs.
- Blood disorders
  - Agranulocytosis- dangerously low level of white blood cells, leading to immunocompromise
  - Aplastic anemia- body stops producing enough new blood cells
  - Thrombocytopenia- decreased platelet count
  - Leukopenia- decreased neutrophil count
  - Hemolytic anemia- destruction of red blood cells faster than they are produced
- Dermatologic and allergic reactions
  - Stevens-Johnson syndrome (SJS)
  - Toxic epidermal lysis (TEN)
  - Exfoliative dermatitis
- Hepatocellular necrosis
- CNS reactions
- Toxic nephrosis

Additional risks associated with the study protocol include:

- A breach of confidentiality.
- Distress or anxiety associated with completing the questionnaires

There is no known direct benefit to the study participants. There may be direct benefit due to an additional period of monitoring and therapy beyond typical standard of care. While there is no guarantee or benefit from this research, demonstrating safety and preliminary efficacy of these devices could provide a new approach in partial thickness burn treatment and could prevent decreased function and disability in civilian and military trauma.

5.0 Costs and Payments:

Costs: The study treatments (SynePure and Catasyn, and Silvadine) and will be provided by the manufacturer for this study, and research procedures will be completed at no cost to the participants. However, all standard of care procedures (i.e. recommended labs or scans) and costs associated with burn treatment visits will be charged to the participant's insurance, and they will be responsible for all associated test or visit co-pays as well.

Reimbursement: Participants may receive a parking voucher for the research visits (visits 3,4,6,7) should the actual visit exceed 2 hours in duration. Participants may also be reimbursed up to a total of $40.00 ($10.00 gift card for each completed research visit 3,4,6,7).

6.0 Appendices:

See attached informed consent form, schema table and subject dressing instruction, 510K clearance product files and package insert.

6.1 Qualifications of Investigators:

J. Peter Rubin, MD, Founding Chair of the Department of Plastic Surgery at the University of Pittsburgh. Dr. Rubin has a successful track record of implementing Department of Defense clinical trials under programs including the Biomedical Translational Initiative, the Armed Forces Institute of Regenerative Medicine, and the Office of Technology Transfer Clinical Trials Program. He is an internationally recognized board-certified plastic and reconstructive surgeon, as well as a scientific researcher with an active basic science laboratory (Co-Director of the Adipose Stem Cell Center) who holds funding from the National Institutes of Health. As **Principal Investigator**, Dr. Rubin will provide medical oversight for study subjects, study eligibility determination, the consenting process, research study procedures, overall protection of human subject risks and benefits, and performance of clinical trial conduct and compliance under Good Clinical Practice (GCP) standards.

Jenny Ziembicki, MD Medical Director, UPMC Mercy Burn Center: Dr. Ziembicki has a special interest in the development of UPMC Mercy's comprehensive outpatient burn therapy program, which allows patients a more expedient return to a productive lifestyle. As a **co-investigator** on this project she will provide clinical oversight for study subjects, will be responsible for collection of information assessing the research study eligibility criteria, the consenting process, research study procedures, overall protection of human subject risks and benefits, and performance of clinical trial conduct and compliance maintaining GCP standards. In addition, with the other burn center physician co-investigators, she will confirm the determination of ≥ 90% re-epithelization and time to heal for the participants' burn wounds.

Alain Corcos, MD, Division Chief & Trauma Medical Director, UPMC Mercy: Dr. Corcos is a board-certified surgeon whose research interests include wound dressing effects, and autologous noncultured cell-spray grafting in the treatment of burns. As a **co-investigator** on this project, with the other burn center physician co-investigators, he will confirm the determination of ≥ 90% re-epithelization and time to heal for the participants' burn wounds.

Garth Elias, MD, Clinical Associate Professor of Surgery: As a **co-investigator** on this project, Dr. Elias will assist Drs. Ziembicki and Corcos. With the other burn center physician co-investigators, he will confirm the determination of ≥ 90% re-epithelization and time to heal for the participants' burn wounds.

Francesco Egro, MD Resident, Department of Plastic Surgery at the University of Pittsburgh
Dr. Egro pursued his Bachelors of Science with Honors in Microbiology and his Medical Degree from the University of Bristol, United Kingdom. He then served as a research fellow at the Division of Plastic Surgery at Emory University under the mentorship of Dr. Albert Losken, where he conducted his research on breast oncoplastic surgery. Dr. Egro is currently a member of the American Society of Plastic Surgery, Royal College of Surgeons of England, and the American Burn Association, where he also serves on their Education Committee. Dr. Egro's clinical and research interests include microsurgery, burns, surgical education, and adipose-derived stem cells. Dr. Egro will serve as a **co-investigator** and assist the PI with medical oversight for study subjects, study eligibility determination, the consenting process, and research study procedures. In addition, he will assist with data analysis, manuscript writing and publication of results, and will serve to compile analysis of the burn wound photographs.

Patsy Simon, BS, RN, CCRC, CCRA, ACRP-PM Director, Regulatory and Clinical Affairs for the UPMC Center for Innovation in Restorative Medicine, Department of Plastic Surgery at the University of Pittsburgh: Ms. Simon has over 34 years of clinical nursing experience with over 20 years of expertise in clinical research trial conduct and compliance. She has regulatory expertise in federal, industry and investigator initiated clinical trials, with strong experience in federal IND and IDE application development and management. Ms. Simon's role on this project as a **co-investigator** will be in the development stage and concentration of research procedural feasibility, regulatory and

clinical management and clinical staff operations. She will oversee the development of compliance standards, quality management process as they pertain to the research execution and adherence to federal, state and local regulations, and ICH Good Clinical Practice (GCP) guidance during the conduct of the project.

Rebecca Parsons, PA-C Department of Plastic Surgery at the University of Pittsburgh: Ms. Parsons has 3 years of experience as a surgical physician assistant prior to her role in research. Before working in plastic surgery, she was employed by an orthopedic surgery group where she worked for three years as a first assist in a variety of orthopedic cases, including trauma care. She is also trained in both inpatient and outpatient perioperative care settings. Before obtaining her Master's Degree as a Physician Assistant, she graduated with a Bachelor's degree in Biochemistry from Grove City College. Her role on the study as a **co-investigator** will include assisting the physician investigators with screening and enrollment, administration of the study treatments, and follow up visit procedure completion.

Eleanor Shirley, M.A. Department of Plastic Surgery at the University of Pittsburgh: Ms. Shirley has 20 years of experience at the University of Pittsburgh as a senior research study coordinator, focused on surgical outcomes, mental health/quality of life and diabetes. She has experience in screening participants and recruitment, conducting certified assessments, data review/management and regulatory requirements. She has participated in grant writing and submission, and is cognizant of study fiscal issues, both pre- and post- award. Post data collection, she has served as a member on writing group committees and been a submitting author of study results for publication. Her role in the study as a **research coordinator** will include research training activities, quality management, regulatory compliance, oversight of recruitment after initial referral, screening and enrollment, study visits completion, data collection, analysis and transfer, and participant retention.

Shawna Reekie, Department of Plastic Surgery at the University of Pittsburgh: Ms. Reekie will serve as the primary coordinator for this clinical trial. Her role as a **research coordinator** will be to assist with recruiting patients, completing study visits, data collection, protocol adherence, patient retention, and submission of regulatory documents.

Alexandra McCloskey, MS, Department of Plastic Surgery at the University of Pittsburgh.
Ms. McCloskey has several years of experience as a research coordinator in multiple different disciplines. She has experience in screening patients and recruitment as well as maintaining regulatory documents and completing start-up processes. Her role as a **research coordinator** will be to assist with recruiting patients, completing study visits, data collection, protocol adherence, patient retention, and submission of regulatory documents.

6.2 References:

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NCT number: NCT04601532

Official Title: Randomized Controlled Trial Assessing a Novel Glycopolymer Compound in the Treatment of Superficial Partial-Thickness Burns

Study Consent Document Date: IRB Approved 12/20/2022

UNIVERSITY of PITTSBURGH
Department of Plastic Surgery

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: "Randomized Controlled Trial Assessing a Novel Glycopolymer Compound in the Treatment of Superficial Partial-Thickness Burns"

KEY INFORMATION

You are being asked to take part in a research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision.

- The purpose of this study is to compare the safety and effectiveness of SynePure™ Wound Cleanser and Catasyn™ Advanced Technology Wound Hydrogel against the standard of care therapy (Silvadene) for superficial partial-thickness burns.
- Superficial partial-thickness skin burns, previously called second-degree burns, involve the top two layers of skin, are painful with air movement or air temperature changes, are red and seep fluid, usually form blisters, and turn white when pressed. Superficial partial- thickness skin burns heal within seven to 21 days. The burned area may permanently become darker or lighter in color but a scar does not usually form. Sunburns that blister after several hours are good examples of superficial partial-thickness burns.Your study participation will last up toa maximum of 21 days and consist of up to a maximum of eight in-person visits.
- There will be 115 subjects enrolled into this study to enable 100 subjects to undergo the randomization assignment procedure
- Subjects will be male and female,18 years of age and older, with a diagnosis of superficial partial-thickness burn injury.
- The study will involve the application of either SynePure Wound Cleanser and Catasyn Advanced Technology Wound Hydrogel or the standard of care therapy (Silvadene), for treatment of your burn. Prior to treatment application, we will obtain 2D photographs and ask you to complete questionnaires pertaining to your burn symptoms, treatment satisfaction and quality of life.
- Risks include reactions to either of the study treatments, discomfort related to the questions being asked of you, and the potential of breaches in confidentiality of your personal information.
- You may or may not personally benefit from your participation in this study. You may experience improvement in burn wound healing, and/or a potential for reduction of infection rates; however, there is no guarantee that you will receive such a benefit. This study may help us to understand how SynePure Wound Cleanser and Catasyn Advanced Technology Wound Hydrogel compares to the standard of care (Silvadene) in terms of safety and effectiveness.

- If you decide not to participate in this experimental study, there are several other treatments or procedures, some of which you may wish to consider are below:
    - Participating in another study
    - Standard of care treatment

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Why is this research being done?
This research study will assess the safety and effectiveness of SynePure Wound Cleanser when used with Catasyn Advanced Technology Wound Hydrogel compared to the standard of care treatment (Silvadene) in superficial partial-thickness burns.

SynePure Wound Cleanser is being used under its FDA 510K clearance for its intended use and indication. Although Catasyn Advanced Technology Wound Hydrogel has FDA 510K clearance, for this study, it is being used under an abbreviated investigational device exemption submission, as a nonsignificant risk device and as an FDA regulated product. An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Studies of non-significant risk devices are subject to abbreviated IDE requirements. An IDE submission to the FDA is not required under the abbreviated requirements, but the requirements for labeling, IRB approval, informed consent, monitoring, records, reports and promotional practices contained in FDA regulations still apply (21 CFR 812.2(b)).

The primary purpose of this study is to assess the time to heal, or the number of days that it will take for your burn wound to heal when treated with either the intervention or the standard of care dressing. We will define for the purpose of this study, healing as ≥ 90% closure of the burn surface area.

The secondary purpose of this study is to examine the outcome of your healed burn wound. The characteristics to be reviewed include how easy the wound is to move, its color, skin pigmentation, and whether or not you develop a scar. You will be asked to describe your wound, in terms of pain, itching, dryness, and irritation, and also, to rate your wound on the impact it has on your daily living.

This study is designed with a randomized controlled procedure to assign your treatment group, meaning like a flip of a coin, you would have a 50% chance of receiving the study intervention treatment or a 50% chance of receiving the standard of care treatment. You will be aware of which group you are randomized into. We plan to consent up to 115 participants to enable 100 of these participants to be randomized into two-groups; 50 to the interventional group and 50 to the standard of care group.

How long will I be in this research?
We are looking to enroll male and female participants to this study, 18 years of age or older who have received a superficial partial-thickness burn. Your study participation may last up to a total of 21 days. The number of visits that you have will vary, and will be determined on your wound's individual healing time. If your wound does not heal by visit 8, the last planned study visit, you will end your study participation. However, your clinical care will continue with your burn physician at the UPMC Mercy burn center, and you will continue to receive standard of care treatment for your burn.

What treatments or procedures are available if you decide not to take part in this research study?
If you decide not to participate in this experimental study, there are other treatments or procedures you may wish to consider:

- Participating in another study
- Standard of care treatment for your burns

What procedures will be performed for research purposes?

If you decide to participate in this study, we will do some or all of the following tests to see if you are eligible for the study. The following procedures will be completed after you have discussed the study with your physician and signed the informed consent.

Consent and Screening Procedures:
All screening procedures will be performed at the UPMC Mercy Burn Center in a private room after this informed consent document is signed. These screening procedures will take approximately 2-3 hours.

- Informed consent
- Review of medical records related to your injury, past surgeries, and general health events
- Demographic information and allergy collection
- Physical assessment inclusive of an evaluation to your burn wound area
- Medication collection
- Vital sign measurement (such as temperature, heart rate, blood pressure, and respiration rate) collection
- Pregnancy test (urine dip)

Initial Treatment Visit 1 (Day 0):
After all screening procedures have been completed and reviewed by the investigators,eligibility will be determined. If you are found to be eligible, you may continue to the initial treatment procedures, and they may occur on the same day as the screening visit. This visit will also be performed at the UPMC Mercy Burn Center. The total length of time for this visit will take approximately 2-3 hours of additional time.

- Randomization process with assignment to 1 of 2 treatment groups, where either SynePure Wound Cleanser with Catasyn Advanced Technology Wound Hydrogel OR Silvadene will be applied.
- Both groups will then receive a secondary dry dressing covering, consisting of gauze and Kerlix wrap.
- 2D photographs will be obtained focusing on the burn injury area, prior to the wound being dressed.
- Written instructions will be provided describing how to apply the wound treatment and dressings daily in between your clinic visits. If you are randomized to the intervention group, you will be asked to remove your old dressing on a daily basis, and gently cleanse your wound with SynePure™ Wound Cleanser to remove all remaining product ointment from your skin (using up to 125 ml or the entire bottle provided). Then you will be asked to allow your wound to air dry for 1 minute. Afterwards, you will apply Catasyn™ Advanced Technology Hydrogel onto your wound (can use 2 ml twice daily, or up to 4 ml total which is a little less than a teaspoon). Finally, you will redress your wound, with the supplies provided to you by the study team. Should your dressing become dislodged, you will be asked to repeat the steps listed above. Should you be admitted to the hospital during the healing of your burn wound, these daily dressings will be performed by either a member of the clinical staff or the research team.

- You will be asked to complete a few questionnaires that pertain to your burn wound, pain, and other symptoms that you may experience, and finally, the potential effects that this injury has on your quality of life and activities of daily living.
- Adverse events collection

After your initial visit, the research team will reach out to you by phone within approximately 24 and 72 hrs of your initial visit, to determine if there are any questions, issues or concerns that you may have. Additionally, they will remind and confirm with you the next in person visit to the clinic.

Follow-up Visits (Visits 2-8):

Some of these follow-up visits will be conducted along with your weekly standard of care clinical visits (visits 2, 5 and 8), and some of these visits (visits 3, 4, 6, and 7) will be specifically for the purpose of this research study. These additional research visits will not be part of your clinical care and will not be billed to your insurance, nor will you incur a cost for any procedure performed. These visits may occur at either the UPMC Mercy Burn Center or the UPMC Aesthetic Plastic Surgery Center. The total length of time for each of these individual visits will be approximately 1-2 hours. Should you be unable to attend the research only visits (3, 4, 6, and 7) in person, you will be offered the option to complete them through telemedicine (a secure video call).

These visits will consist of a burn wound evaluation to assess for healing, brief history and physical assessment, vital signs, recording of status change since last visit/interaction, medication review, and adverse event collection as listed below:

- Vital signs (temperature, heart rate, respirations, blood pressure) collection
- Review of your medications
- Brief medical history, physical assessment, and assessment of your burn injury to determine healing
- 2D photographs will be taken of the injured area
- Treatment agent and secondary dry dressing- (for these procedures, you will be instructed to bring treatment and dressings to the clinic for the dressing change)
- Adverse event collection
- Questionnaires related to topics such as your burn wound symptoms, pain, and other symptoms that you may experience and finally the potential effects that this injury has on your quality of life and activities of daily living.

What are the possible risks, side effects, and discomforts of this research study?

As with any research or clinical procedure, there may be side effects that are currently unknown, and these unknown risks could be permanent, severe, life threatening, or may even cause death. You will be carefully observed and questioned pertaining to any side effects that you may be encountering. You should inform your study doctor about any side effects that you experience while taking part in the study.

As part of this study's goals are assessing the safety of the intervention treatment in patients with superficial partial-thickness burns like yours, not all possible risks and adverse effects are known.

SynePure Wound Cleanser
Has been approved for external use in cleaning dermal wounds (including superficial partialthickness burn wounds).

- There were no adverse events found upon topical application.
- There is a risk of adverse reaction if you have an allergy to shellfish

Catasyn Advanced Technology Hydrogel
Has also been approved for external use for dressing of wounds (including superficial and superficial partial-thickness burn wounds).

- There is a low risk of redness where the hydrogel is placed on the skin.
- There is a risk of adverse reaction if you have an allergy to shellfish

Silvadene

- Skin reactions are the most common adverse reactions. Skin reactions include: skin discoloration, burning sensation, itching, rashes, skin photosensitivity – sensitivity to sunlight, and skin necrosis – death of skin.
- Other less common advere reactions include: gastrointestinal reactions/upset stomach, inflamed kidneys, or inflamed liver.
- Rare risks are associated with systemic absorption, and may lead to deposition of silver in your organs.
    - Blood disorders (a possibility of lower white cells, red cells or platelets)
    - Erosive skin reactions (this could lead to blistering of your skin and more severe effects such as hospitalization and in rare cases, even death)
    - Liver failure, as a result of silver deposits in your liver
    - Rarely, effects on your brain/spinal cord, such as long terms nerve symptoms related to balance and spatial perception
    - Kidney failure, as a result of silver deposits in your kidney

Breach of Confidentiality

- Participation in this research study does involve the potential risk of a breach of confidentiality of your medical record information, photography, and associated privacy of the participants.
- Steps to minimize these risks include the following:
    - Removing direct patient identifiers (i.e. names, social security numbers, medical record numbers) from information stored in the study records
    - Securing, in a separate location, and limiting access to information linking subject ID numbers assigned to the study record information with direct patient identifiers
- Limiting access to information contained within the study records to study investigators/research team only.

Questionnaires

- Infrequently, questions encountered during research visits may be distressing or anxiety provoking due to their personal or sensitive nature. You will not be required to answer any questions that are particularly distressing to you.

Reproductive Risks

- Taking part in this study may result in unknown risks to an unborn baby, so you should not become pregnant while on this study. A urine pregnancy test will be completed during the screening portion of this study and if it is shown that you are pregnant, you will be excluded from participating.

What are the possible benefits from taking part in this research study?
You may or may not personally benefit from your participation in this study. You may experience improved healing in your burn wound and have less of a chance of developing an infection; however, this is not guaranteed. This study may help us to understand how SynePure Wound Cleanser and Catasyn Advanced Technology Wound Hydrogel compares to the standard of care (Silvadene) in terms of safety and effectiveness.

Alternative Treatments
If you choose not to participate in the study, this will not affect your treatment or care at the UPMC Mercy Burn Center. The center physicians will apply the current recommended treatment for a superficial partial-thickness burn following their standard of care treatment protocol.

You will be promptly notified if any new information we learn during this research study that may cause you to change your mind about continuing to participate in the study.

Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study?
Some of the services or items in this study are part of the regular treatment for your burn. These services would be performed or used even if you were not in this study. The costs for these services or items will be billed to your insurance. You will be responsible for any costs your insurance does not cover. If you have any questions about these costs, or what out-of-pocket expenses you may be responsible for, contact your insurance company. If you are uninsured, you will be responsible for these costs.

The study treatments (either SynePure Wound Cleanser and Catasyn Advanced Technology Wound Hydrogel OR Silvadene) will be provided at no cost to you.

Will I be reimbursed if I take part in this research study?
You will receive compensation for your research visits to defray the cost of parking, should the visit exceed 2 hours in duration. You may be reimbursed up to a total of $40.00 for completion of the research visits (Visits 3, 4, 6, and 7). This reimbursement will be in the form of a $10.00 loaded onto a University Vincent Mastercard for each of these completed research visits. Should your research visits be completed through telemedicine, you will **not** receive compensation for parking.

Who will pay if I am injured as a result of taking part in this research study?
If you believe that the research procedures have resulted in an injury to you, immediately contact Dr. J. Peter Rubin who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your researchrelated injury requires medical care beyond this emergency treatment,

you will be responsible for the costs of this follow-up care. Currently, there is no plan for any additional financial compensation. You waive no legal rights by signing this consent.

Who will know about my participation in this research study?
To protect the confidentiality of information we obtain from you and your medical records, we will keep all information about you in a secure location. All paper records that could identify you will be stored in locked file cabinets, and all electronic records will be stored in passwordprotected files. Access to this information will be limited to research team members and to those health care professionals who are providing clinical services as part of this research study.

Will this research study involve the use or disclosure of my identifiable medical information?
As part of this study, we are also requesting your permission to review your medical records to obtain past, current, and future medical information from hospitals and other medical facilities. We will obtain information concerning your diagnosis, age, past medical history, diagnostic or surgical procedures that may have been done as part of your care for your burn and any associated injuries you may have experienced. Should we receive this information, we may use this information to determine whether you meet the conditions for participation in this study.

Although we will do everything in our power to protect your privacy and confidentiality of your records, just as with the use of your medical information for health care purposes, we cannot guarantee the confidentiality of your research records, including information that we obtained from your medical records. This research study will result in identifiable information that will be placed into your medical records held at UPMC, namely this consent form.

Per University of Pittsburgh policy all research records must be maintained for at least 7 years following final reporting or publication of a project. Data resulting from this research study may be shared with other investigators in the future, and all information will be de-identified prior to the sharing of this information.

Who will have access to identifiable information related to my participation in this research study?
This identifiable information will be made available to members of the research team for an indefinite period of time. That medical information, as well as information obtained during this research study, may be shared with other groups including authorized officials from the Department of Defense or Synedgen, the Food and Drug Administration (FDA), the University of Pittsburgh Human Research Protection Office (HRPO), and authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to your identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of:
(1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or
(3) assessing internal hospital operations (i.e. quality assurance).

Any information that is entered into your medical records will be available to you, in accordance with the UPMC Notice of Privacy Practices.

Authorized representatives of US and foreign government regulatory agencies such as the U.S.
Food and Drug Administration (FDA) may review and or obtain your identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While these agencies understand the importance of maintaining the confidentiality of your identifiable research and medical record information, UPMC and the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by them.

Your doctor may also be involved as an investigator in this research study, but you are not under any obligation to participate in any research study offered by your doctor. Before agreeing to participate in this research study, or at any time thereafter, you may wish to discuss participation in this study with another health professional, to obtain a 'second opinion' about study participation.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Is my participation voluntary?
Your participation in this research study is completely voluntary. You may want to discuss this study with your family and friends and your personal physician before agreeing to participate. If there are any words you do not understand, feel free to ask us. The investigators will be available to answer your current and future questions.

Whether or not you participate in this research study, it will have no effect on the standard of care that you receive or your current or future relationship with the University of Pittsburgh, UPMC or its affiliated health care providers or health care insurance providers.

May I withdraw, at a future date, my consent for participation in this research study?
You can, at any time withdraw from this research study; you can also withdraw your authorization for us to use your identifiable medical information for the purposes described above. This means that you will also be withdrawn from further participation in this research study. Any identifiable research or medical information obtained as part of this study prior to the date that you withdrew your consent will continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw from this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study, Dr. J. Peter Rubin (412-3838080) at the address listed on the first page of this form or his research colleagues. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. If you decide to withdraw from study participation after you have received the study agent, you

will receive standard-ofcare treatment as applicable and have follow-up assessments collected to ensure your safety upon termination from study participation.

If I agree to participate in this research study, can I be removed from the study without my consent?
If the investigators feel that you cannot complete the study requirements safely (for example, you develop complications such as infection, require surgery for your burn, are hospitalized or the classification of your burn is now deemed to be more severe- progressed to a full partial- thickness or deep-thickness burn, or non-compliance), they may withdraw you from the study. At the time of your withdrawal, the investigator will discuss with you the appropriate and requested follow up based on the specific event.

OPTIONAL CONSENT FOR PHOTOGRAPHS OF YOUR BURN WOUND

The research team is requesting permission to photograph any and all portions of your burn wound. These photos may be used for medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, email, television, internet, etc. Your identifiable features in these photographs will be blacked out (i.e., eyes, facial features, tattoos etc.), and the de-identified photo will be focused on your burn wound area. You are not required to give this permission and can refuse at any time after giving consent to these photographs being obtained.

I consent to the photography, as described above:

_____ _____

Participant's Signature Date

I **do NOT** consent to the photography:

_____ _____

Participant's Signature Date

VOLUNTARY CONSENT FOR STUDY PARTICIPATION

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified member of the research team or by Dr. J. Peter Rubin, at 412-383-8080. I understand that I may always request that my questions, concerns or complaints be addressed to Dr. J. Peter Rubin. At any

time, I may also contact the Human Protection Advocate of the HRPO Office, University of Pittsburgh (1-866212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form, I agree to participate in this research study, and allow the use and disclosure of my medical record information for the purposes described above. A copy of this consent form will be given to me.

_____

Printed name of Participant

_____ _____

Participant's Signature Date / Time

INVESTIGATOR CERTIFICATION:

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Licensed Physician-Investigator Signature Date/Time