Adjunctive ToeFX Photodynamic Therapy for Chronic Venous Leg Ulcers: A Single-Arm, Open-Label Pilot Feasibility Study

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1. Background and Rationale

Chronic venous leg ulcers (VLUs) are a common and costly manifestation of chronic venous insufficiency, affecting approximately 1% of the adult population over their lifetime and representing a substantial burden to patients and the healthcare system. VLUs are frequently painful, malodorous, and prone to infection, and they can significantly limit a patient's function, mobility, and quality of life. Despite standard of care (SOC) – compression therapy, regular debridement, moisture-balanced dressings, and infection management – approximately half of VLUs become chronic, and recurrence rates after healing remain high.

A major contributor to delayed healing is persistent local bioburden, including bacterial biofilm, which is resistant to many topical and systemic antimicrobial strategies and can perpetuate a chronic inflammatory wound environment. Strategies that reduce local bioburden without contributing to antimicrobial resistance are of particular interest in chronic wound management.

ToeFX has developed a non-thermal photodynamic therapy (PDT) platform that combines a methylene-blue-based photosensitizer (ClearToe® serum) with 660 nm light irradiation. Upon activation by light of the appropriate wavelength, the photosensitizer generates reactive oxygen species that are cytotoxic to a broad range of bacteria, fungi, and biofilm-associated organisms, while sparing host tissue at the fluences used clinically. This mechanism of photodynamic disinfection is well established in other clinical contexts, and the ToeFX platform is currently approved/registered for other indications. Its potential to reduce local bioburden and support a more favourable wound-healing environment has not yet been formally evaluated in venous leg ulcers.

This pilot study is intended to evaluate the feasibility (treatment adherence) and safety of ToeFX photodynamic therapy as an adjunct to SOC in a defined population of patients with chronic venous leg ulcers, while collecting preliminary clinical, wound-healing, and patient-reported outcome data to inform the design of a future, larger controlled trial.

2. Study Objectives

2.1 Primary Objective

To evaluate the feasibility and safety of adding weekly ToeFX photodynamic therapy to standard wound care in patients with chronic venous leg ulcers, as measured by:

- Treatment adherence: percentage of planned ToeFX treatment sessions completed per participant, and reasons for missed or discontinued sessions.
- Safety: incidence and severity of adverse events (AEs), serious adverse events (SAEs), device-related AEs, treatment-related AEs, and study discontinuations due to AEs.

2.2 Secondary Objectives

Exploratory clinical effectiveness will be assessed as follows:

- Percent and absolute change in wound area (cm^2) from baseline at Weeks 4, 8, and 12.
- Proportion of participants achieving complete epithelialization by Week 12.

- Time to complete wound healing.
- Change in wound bed characteristics using the Bates-Jensen Wound Assessment Tool (BWAT).
- Change in pain score (0–10 Numeric Rating Scale).
- Change in health-related quality of life (EQ-5D-5L).
- Patient satisfaction with treatment.
- Feasibility of integrating weekly PDT sessions into routine wound-care workflow (qualitative/operational observations).

3. Study Design

Study Type	Prospective, single-arm, open-label, single-centre pilot feasibility study
Design	All enrolled participants receive Standard of Care (SOC) + ToeFX photodynamic therapy. There is no separate control arm.
Number of Participants	20 participants (enrolled)
Treatment Period	Up to 12 weeks, once-weekly ToeFX treatment sessions
Study Endpoint per Participant	The earlier of: (a) complete wound healing, followed by a single confirmation visit 2 weeks later to verify sustained epithelialization and absence of wound breakdown; or (b) completion of the Week 12 / end-of-treatment assessment
Estimated Recruitment Period	2-3 months to enroll 20 participants
Estimated Total Project Timeline	9 months, including start-up, recruitment, final participant follow-up, and analysis

4. Study Population

4.1 Inclusion Criteria

1. Able to attend weekly visits for up to 12 weeks
2. Age ≥ 18 years
3. Presence of a chronic venous leg ulcer (CEAP C6) of the lower extremity
4. Ulcer duration ≥ 4 weeks
5. Ulcer size between 1 cm^2 and 20 cm^2 at baseline
6. Receiving standard-of-care compression therapy (or eligible to initiate compression therapy)
7. Ability to provide informed consent and comply with study procedures

4.2 Exclusion Criteria

8. Wound location or anatomy not compatible with ToeFX photodynamic therapy device
9. Systemic infection (e.g., fever, sepsis, spreading cellulitis) or wounds requiring systemic antibiotics
10. Necrotic tissue > 25% of wound bed, exposed bone/tendon, deep abscess, osteomyelitis, or gangrene
11. Severe ischemia (ABI < 0.5) or poorly controlled diabetes (HbA1c > 10%)
12. Heavy exudate requiring negative-pressure wound therapy
13. Known photosensitivity or allergy to methylene blue or light-based therapies
14. Immunosuppressive therapy, recent radiation or chemotherapy (within 3 months), or active malignancy
15. Pregnancy or lactation
16. Known Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency
17. Participation in another interventional study within 30 days of screening

5. Study Intervention

Adjunctive treatment	Topical application of ToeFX ClearToe® serum to the wound surface, followed by irradiation using the ToeFX light platform
Treatment schedule	Once per week for up to 12 weeks in addition to SOC
Exposure parameters	Red light ≈ 100 mW/cm², delivering ≈ 30–60 J/cm² (per current ToeFX PDT protocols)
Duration per session	~5 minutes of light exposure, plus pre- and post-treatment documentation (~30 minutes total visit time)
Early completion	If complete wound healing occurs before Visit 12, ToeFX treatment is discontinued and the participant returns for a single healing-confirmation visit 2 weeks later
Standard of care	Compression therapy, wound cleansing/debridement as clinically indicated, and moisture-balanced dressings, continued throughout the study per the treating clinician's judgment

6. Study Procedures by Visit

6.1 Screening

Patients with a chronic venous leg ulcer seen in clinic will be made aware of the study and asked whether they wish to be considered for participation. Patients who provide written informed consent will be screened for eligibility, including a review of medical history, ulcer characteristics, and confirmation of inclusion/exclusion criteria. Eligible patients will be enrolled. Patients who are

ineligible or decline further participation after screening are considered screen failures; the reason will be documented.

6.2 Baseline / Treatment Visit 1 (TV 1)

At this visit, the following activities will take place:

Standard of Care Activities

- Medical history
- Review of current medications
- Physical exam
- Wound assessment
- Routine wound cleansing/debridement (as clinically indicated)
- Compression therapy assessment/application

Study-Specific Activities

- Demographics
- CEAP classification (Clinical manifestations, Etiology, Anatomic distribution, Pathophysiology)
- Wound photography and wound area measurement
- Bates-Jensen Wound Assessment Tool (BWAT)
- Pain score (Numeric Rating Scale (NRS) 0-10)
- ToeFX treatment
- Documentation of treatment and adherence
- Completion of EQ-5D-5L questionnaire

The order of events for wound assessment, cleaning and treatment will be as follows: wound assessment and BWAT, CEAP classification, routine wound cleansing and debridement as clinically indicated with a final saline rinse, wound photography and wound area measurement, ToeFX treatment, wound dressing and compression therapy application.

6.2.1 ToeFX Treatment

Following wound cleaning and debridement as clinically indicated, the wound will be rinsed with saline then coated with ClearToe® serum, allowing about a minute for the gel to soak in. A second coat of ClearToe® serum may be applied at the clinician's discretion, again allowing it to soak in for about a minute. The ToeFX photodynamic therapy device will be placed so that the blue light is directed at the wound. Light therapy will be administered for 5 minutes. The clinician will then apply wound dressings and compression therapy as usual.

6.3 Treatment Visits 2-11

Treatment Visits (TVs 2–11) will occur weekly (+/- 2 days) for 12 weeks or until wound healing. If wound healing is observed at Visits 2-11, this visit becomes an End-of-Treatment Visit.
The following activities will take place at each Treatment Visit:

Standard of Care Activities

- Removal of dressing and standard wound assessment

- Routine wound cleansing/debridement (as clinically indicated)
- Application of standard wound dressing
- Assessment and application of compression therapy

Study-Specific Activities

- Review of medical history and adverse events
- Wound imaging and wound-area measurement
- Wound assessment: BWAT
- Pain score (NRS 0-10)
- ToeFX treatment (as described above)
- Documentation of treatment and adherence

6.4 End-of-Treatment

End-of-Treatment Visit will be conducted at Visit 12 or earlier if wound healing is observed. The visit will include all routine Treatment Visit assessments, as well as completion of a Patient Satisfaction Questionnaire and the EQ-5D-5L.

6.5 Healing Confirmation Visit

If wound healing is observed at any point during TVs 2-12/at EOT Visit, a Healing Confirmation Visit (HCV) will take place two-weeks (+/- 3 days) after healing is observed. Clinician will confirm complete epithelialization without wound breakdown. Visit will include the following activities:

- Review of medical history and adverse events
- Wound imaging and wound-area measurement
- BWAT
- Pain score (NRS 0-10)

7. Schedule of Events

Study Activity	Screening	Baseline & Treatment Visit 1 (Day 0)	Treatment Visits 2–11 (1 x/wk)	EOT / Visit 12	Healing Confirmation Visit
Visit Window	**Day -14 to Day 0**	**Day 0**	**Visits every 7 days +/- 2 days**	**12 weeks +/- 2 days post-TV1**	**2 weeks +/- 3 days post EOT Visit**
Informed consent		**X**			
Confirm inclusion / exclusion criteria	**X**	**X**			
Medical history, demographics, ulcer history	**X**	**X**			

Medication review		**X**	**X**	**X**	
Physical exam	**X**	**X**	**X**	**X**	
CEAP classification	**X**	**X**	**X**	**X**	
Compression therapy assessment / initiation	**X**	**X**	**X**	**X**	
Wound imaging and wound area measurement		**X**	**X**	**X**	**X**
BWAT		**X**	**X**	**X**	**X**
Pain score (NRS 0-10)		**X**	**X**	**X**	**X**
EQ-5D-5L		**X**		**X**	
Wound cleansing / debridement (as clinically indicated)		**X**	**X**	**X**	
ClearToe® serum application + ToeFX light treatment		**X**	**X**	**X***	
Standard wound dressing / compression application		**X**	**X**	**X**	
Adverse event assessment		**X**	**X**	**X**	**X**
Treatment adherence documentation		**X**	**X**	**X**	
Patient Satisfaction Questionnaire				**X**	

*If wound remains unhealed.

8. Outcome Measures

8.1 Primary Endpoints

- Treatment adherence: % of planned ToeFX sessions completed per participant
- Safety: incidence/severity of AEs, SAEs, device- and treatment-related AEs, and AE-related discontinuations

8.2 Secondary Endpoints

- Percent and absolute change in wound area (cm^2) at Weeks 4, 8, and 12
- Proportion achieving complete epithelialization by Week 12
- Time to complete wound healing
- Change in BWAT score

- Change in pain score (0–10 NRS)
- Change in EQ-5D-5L
- Patient satisfaction

9. Study Withdrawal

Participants may withdraw from the study at any time, for any reason, without providing a reason and without any effect on their ongoing clinical care. Participants may also be withdrawn at the investigator's discretion if continued participation is determined by the principal investigator and/or treating clinician determines continuing is not in their best interest. Reasons for withdrawal will be documented. Participants who withdraw will be offered guidance on continuing wound care outside the study.

10. Risks of Treatment

There is a minimal risk of localized, self-limiting skin reaction for patients with allergies to methylene blue or methyl methacrylate. There is a chance that the treated skin will remain blue for several days post-treatment before fading naturally. Subjects may experience discomfort on application of the ClearToe serum as the brush applicator applies the serum directly onto the wound. Subjects may also experience discomfort due to feeling some minimal heat with application of the blue light.

11. Statistical Analysis

A sample size of 20 participants was selected to provide a reasonable estimate of treatment adherence and safety while remaining feasible for a single-site pilot.

All enrolled participants who receive at least one ToeFX treatment session will be included in the feasibility and safety analyses. Participants who consent but do not receive any study treatment will be excluded from analysis, and the reason will be documented and reported.

Feasibility endpoints (treatment adherence) will be summarized descriptively as proportions with 95% confidence intervals. Safety data (AEs/SAEs) will be summarized as frequencies and percentages, by relatedness and severity. Continuous secondary outcomes (e.g., wound area, BWAT, pain score, EQ-5D-5L) will be summarized as mean ± standard deviation (if approximately normally distributed) or median with interquartile range (if not), at each assessment timepoint, with descriptive within-participant change from baseline. Categorical variables will be presented as frequency and percentage. No formal inferential statistical testing of efficacy is planned. As a pilot feasibility study, this protocol is not powered for formal hypothesis testing of efficacy; secondary outcomes are exploratory and intended to inform the design and sample size of a future controlled trial.

12. Data Management and Privacy

This trial will be registered at ClinicalTrials.gov. Each participant will be assigned a unique study ID; all study data will be de-identified for analysis purposes. Study data will be secured in locked cabinets and/or access-restricted electronic files with access limited to authorized study personnel.

Standardized wound photographs will be stored securely, identified only by study ID, in folders with restricted access. Effort will be made to avoid capturing identifying features (e.g., face, tattoos); any unavoidably captured identifying features will be censored to the extent possible while preserving the wound information needed for assessment.

A separate Key File linking study ID to participant name, medical record number, and contact information will be retained apart from study data. Study documents will be retained by the Principal Investigator for a period consistent with institutional policy and applicable regulatory requirements.

13. Sponsor-Investigator and Device Status

13.1 Sponsor-of-Record and Investigator-Initiated Status

This is an investigator-initiated study. The Principal Investigator / institution will act as sponsor-of-record for regulatory purposes, with ToeFX Inc. providing the study device, consumables, training, and study funding under a clinical trial agreement.

13.2 Health Canada Investigational Testing Authorization (ITA)

The current working assumption is that this study does not require a separate Health Canada Investigational Testing Authorization (ITA) for the ToeFX device, on the basis that the platform is already licensed/registered in Canada for other approved indications and this study evaluates an additional indication under REB oversight with informed consent.

14. Adverse Events

14.1 Definitions

Adverse Event (AE): any unfavourable and unintended sign, symptom, or disease experienced by a participant during the study, including an abnormal finding on examination, whether or not considered related to study treatment.

Serious Adverse Event (SAE): any AE that results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly, or is another medically important event that jeopardizes the participant or requires intervention to prevent one of the above outcomes.

14.2 Reporting and Management

AEs will be assessed at every study visit through participant interview and clinical examination, and participants will be instructed to contact study staff if an AE occurs between visits. For each AE, the investigator will assess relatedness to the study device/treatment and severity. All SAEs will be reported to the Principal Investigator within 24 hours of study staff becoming aware of the event. All fatal or life-threatening SAEs will be reported to the REB of record within 7 calendar days, and all other related or possibly related and unexpected SAEs within 15 calendar days, consistent with the REB’s reporting requirements.

14.3 Safety Monitoring Plan

The Principal Investigator will review all AEs/SAEs on an ongoing basis. An interim safety review will be performed after the first 5 participants have completed 4 weeks of treatment, and again after all participants complete study treatment and follow-up. Given the small sample size and pilot nature of this study, a formal independent Data Safety Monitoring Board (DSMB) will not be created.

15. Sponsor, Roles, and Study Support

Intellectual property arising from the ToeFX device and ClearToe® serum remains with ToeFX Inc. Publication of study results will follow data analysis.

16. References

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