A Prospective, Multicentre, Randomised, Assessor Blinded Study Comparing the Efficacy, including Patient Reported Outcomes of Two Different Daily geko™ Treatment Durations in Conjunction with Standard Care, with each Other and to Standard Care Alone, in Patients with Venous Leg Ulcers.

Protocol No.: FSK-VLU- 004

Date: 22May2020

Version: 12.2

Investigational Product: geko™

Indication: Venous leg ulcers

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Confidentiality Statement

Firstkind Ltd

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PROTOCOL APPROVAL SIGNATURES

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet GCP and all applicable regulatory guidelines and statutes.

Rachel Fallon
Rachel Fallon (Jun 8, 2020 16:43 GMT+1)

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INVESTIGATOR SIGNATURE PAGE

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical study. I also agree to comply with the Investigational Review Board (IRB) requirements for testing on human patients. I agree to ensure that the requirements for obtaining informed consent are met.

Investigator's Signature	Date

Print Name

Site Number

Abbreviations

ABPI	Ankle-Brachial Pressure Index
ADL	Activities of Daily Living
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CRF	Case Report Form
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for AEs
CV	Curriculum Vitae
CWIS	Cardiff Wound Impact Schedule
DFU	Diabetic Foot Ulcer
DVT	Deep Vein Thrombosis
EOT	End of Treatment
ICF	Informed Consent form
IEC	Institutional Ethics Committee
ITT	Intent-to-Treat
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GP	General Practitioner
HCV	Healing Confirmation Visit
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Investigational Review Board
LHR	Linear Healing Rate
MLU	Mixed Leg Ulcer
NA	Non-adherent
QoL	Quality of Life
PAR	Percentage Area Reduction

PET	Polyethylene Terephthalate
PI	Principal Investigator
PP	Per Protocol
PWAT	Photographic Wound Assessment Tool
RV	Run-in Visit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Standard Care
SOP	Standard Operating Procedure
TV	Treatment Visit
VAS	Visual Analogue Scale
VLU	Venous Leg Ulcer

Synopsis

Name of Sponsor/Company: Firstkind Ltd, Hawk House, Peregrine Business Park, Gomm Road, High Wycombe, Buckinghamshire, HP13 7DL, UK	
Name of Study Product: geko™ neuromuscular stimulator **Comparator Product:** Multilayer, multicomponent compression therapy intended for the treatment of VLU (Standard Care)	
Protocol Number: FSK-VLU- 004	**Indication:** Venous Leg Ulcers (VLUs)
Title of Study: A Prospective, Multicentre, Randomised, Assessor Blinded Study Comparing the Efficacy, including Patient Reported Outcomes, of Two Different Daily geko™ Treatment Durations in Conjunction with Standard Care, with each Other and to Standard Care Alone, in Patients with Venous Leg Ulcers.	
Study Centre(s): Multinational, multicentre study with centres in the United Kingdom & Europe,	
Planned Number of Subjects: A total of 60 participants will be randomised in the study	
Indication for Use: Indicated for use as an adjunct to Standard Care (SC) in the treatment of Venous Leg Ulcers (VLUs)	
Objective: The objective of this study is to compare the efficacy of a daily geko™ device treatment duration of 12 hours, in conjunction with SC, to SC alone, in patients with venous leg ulcers.	
Endpoints: **Primary Efficacy** The primary efficacy endpoint is linear healing rate (LHR) of the study ulcer from first Treatment Phase visit (TV1) to the End of Treatment (EOT) as compared with LHR from first Run-in Phase visit (RV1) to TV1. • EOT is defined as Treatment Phase visit 5 (TV5), withdrawal or that Treatment Phase visit at which 100% re-epithelialisation without drainage is first determined by the Principal Investigator (PI) or designee, whichever comes first. Each participant will be used as his/her own control. Wound area will be measured by a blinded independent wound expert using digital images taken at RV1, TV1 and at EOT. "Healing" of the study ulcer is determined by the PI or designee. "Healing" is defined as 100% re-epithelialised without drainage as confirmed at the Healing Confirmation visit (HCV).	

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Secondary Efficacy

The overall secondary efficacy endpoints are:

- Weekly LHR of the study ulcer measured by an independent blinded wound expert using digital images taken at each weekly visit until EOT.
- Wound healing status at baseline and EOT assessed by an independent blinded wound expert using the Photographic Wound assessment Tool (PWAT) to evaluate digital images taken at RV1, TV1 and EOT and at HCV, if scheduled.
- Incidence of healing at EOT, as determined by the by the PI or designee.

The participant reported secondary efficacy endpoints are:

- Time from TV1 to clinically significant pain reduction measured using a Visual Analogue Scale (VAS) instrument. For the purpose of this protocol a clinically significant reduction of pain is a mean reduction of ≥ 20.65 mm or a mean decrease of ≥ 10-20% in pain as measured on a 0-100 mm VAS.
- Time from TV1 to first instance of no study ulcer pain measured using VAS.

  (No pain = < 5mm on VAS when VAS scores: 0-4 mm = no pain; 5-44 mm = mild pain; 45-74 mm = moderate pain; and 75-100 mm = severe pain) (1).
- Pain score at EOT measured using VAS
- Change from TV1 in Quality of Life (QoL) at EOT, assessed using the Cardiff Wound Impact Schedule (CWIS)
- Change from TV1 in QoL at EOT, assessed using EQ-5D-5L
  - Wound closure as reported by participants during the Follow-up Phase (FP1-FP3)

Safety Assessments

Safety will be assessed using the following parameters:

- Incidence of AEs
- Incidence of SAEs
- Incidence of study ulcer infection
- Incidence of study treatment related AEs (including geko™, compression bandaging and any dressings used to treat the study wound)
- Incidence of investigational device (geko™) related AEs
- Pain in the ulcer site (sudden onset of pain or increase in pain during the study Treatment Phase)

Trial Design: This study is designed as a prospective, multicentre, randomised, assessor blinded study designed to compare the efficacy, including participant reported outcomes, of a geko™ treatment in

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conjunction with SC, to SC alone, in the treatment of patients with VLUs. There are two arms in the study consisting of: 1) Participants randomised to receiving SC only; 2) Participants randomised to receiving SC and geko™ 12 hours daily.

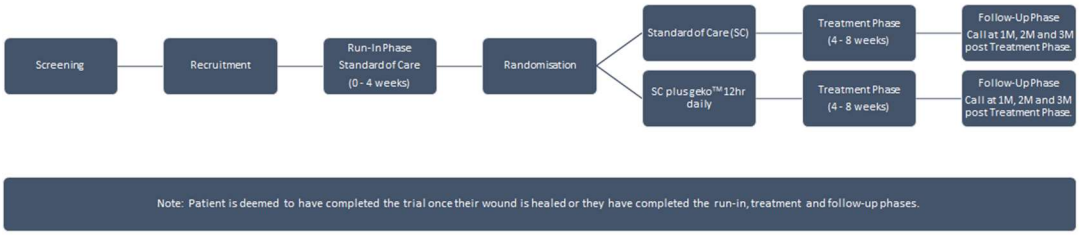
A non adherent (NA) wound contact dressing and/or an absorbent dressing may be used if required, at the Investigator's discretion in addition to SC. All dressing use and reason for dressing use will be recorded.

Multilayer, multicomponent compression therapy intended for the treatment of VLU based on local best practice will be used.

The study will be a multinational, multicentre study with study centres in the UK & Europe

The study will have a four-week Run-in Phase, a four-week Treatment Phase, 3 months Follow-up Phase and a Healing Confirmation visit (HCV) as applicable.

At or up to 21 days before RV1, written informed consent from the participant will be obtained by the Investigator or suitably qualified designee before the performance of any protocol-specific procedure.



Randomisation

This is a multi-centre randomised study. Participants will be allocated to treatment groups using Adaptive Covariate Randomisation using an on-line randomisation tool.

The randomisation will be applied centrally across the sites.

Blinding

The independent wound expert measuring the wound area and assessing the healing status of the wound will be blinded to the treatment assignments.

The Run-in Phase (RV1 to RV5) is designed to determine each participant's LHR when treated with SC alone. Participants will be seen and evaluated on a weekly basis.

The Treatment Phase (TV1 to TV5)

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Participants will be seen and evaluated on a weekly basis. Efficacy evaluations each week will include Investigator assessment of wound healing and measurements of ulcer size using digital photos. Safety evaluations during the Treatment Phase will consist of adverse event assessments at each visit.

The Follow-up Phase (FP1-FP3)

Participants will be contacted at week 13, week 17 & week 21 to find out when their wound is healed.

Healing Confirmation Visit (HCV)

Participants whose ulcer presented with 100% re-epithelialisation without drainage as determined by the PI or designee will be scheduled for a Healing Confirmation Visit (HCV) in a minimum of 7 days time after which they will exit the study whether or not healing is confirmed.

Duration of Treatment: The duration of the Treatment Phase is four weeks.

Total Study Duration: The total study duration is a maximum of nine weeks: four weeks Run-in Phase and four weeks Treatment Phase followed by a HCV in a minimum of 7 days time if applicable. Participants who completed TV5 will have further 12 week Follow-up phase.

Inclusion Criteria: Potential subjects are required to meet all of the following criteria for enrolment into the study and subsequent randomization.

1. Male or female aged ≥ 18 years and able to provide written informed consent.
2. Intact healthy skin at the site of geko™ device application.
3. Patients who have a chronic venous leg ulcer determined to be due to underlying venous disease following evaluation in a multidisciplinary clinic setting or by a vascular surgeon, GP or Nurse specialist
4. A VLU of approximately ≥ 3cm^2 and ≤ 39 cm^2 at study enrolment i.e. Run In Phase Visit 1 (RV1). The largest ulcer within the given size range will be designated the study ulcer and the only one included in the study. If other ulcerations are present on the same leg they have to be more than 2 cm apart if they are two separate wounds. .
5. Study ulcer (current episode of ulceration in case of ulcer recurrence) has been present for at least 6 weeks but no more than 5 years prior to study entry.
6. Ankle-Brachial Pressure Index (ABPI) of 0.75-1.24 inclusive measured at study entry or within 8 weeks of study entry.
7. No active index wound infection for a minimum of 48 hours prior to study entry (i.e. RV1).
8. No systemic antimicrobial treatment for a minimum of seven days prior to study entry prescribed for index wound infection (i.e. RV1).

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9. Patient understands and is willing to participate in the study and is able to comply with study procedures and visits.

Exclusion Criteria: Potential subjects meeting any of the following criteria will be excluded from enrolment and subsequent randomisation:

1. Known allergy to any of the protocol-stipulated treatments, or non-tolerance of multilayer, multicomponent compression therapy intended for the treatment of VLU.

2. History of significant haematological disorders (e.g. Sickle Cell disease).

3. History of Deep Vein Thrombosis (DVT) within six months preceding study entry

4. History of Pyoderma Gangrenosum or other inflammatory ulceration.

5. Pregnancy or breast feeding.

6. Use of investigational drug or device within four weeks prior to study entry that may interfere with this study.

7. Use of any neuro-modulation device.

8. Surgery during three months prior to study entry (such as abdominal, gynaecological, hip or knee replacement)

9. Trauma to the lower limbs that would prevent geko™ from stimulating the common peroneal nerve.

10. No involuntary movement of the lower leg/foot at the maximum tolerable device setting.

11. Any medication deemed by the Investigator to potentially interfere with the study treatment (e.g. systemic steroids).

12. Participation in any other clinical study.

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Statistical Analysis:

Sample Size Determination and Rationale:

The new sample size calculation is:

Based on a pair-wise comparison of geko™ 12h run-in vs treatment:

From the interim data, there is a mean difference of 0.58 mm/week between run-in and treatment and a standard deviation of 0.97 mm/week.

Assuming requirements of 80% power and p=0.05 (2-sided) 25 subjects would be needed in the geko™ 12H group. (30)

Little benefit is foreseen in continuing the geko™ 6h group, as statistical significance is not expected at the projected number of subjects in this trial.

From the results of the Interim Analysis the new Treatment Groups are:

Group	Description
SC	Standard care (multilayer, multicomponent compression intended for the treatment of VLU)
geko 12h	geko™ version XW, W-3 or variant (12 h daily neuro-stimulation) and SC

Analysis Populations:

The **Intent-to-Treat (ITT) population** is defined as the set of randomised participants who have at least one post-randomisation efficacy assessment for wound healing. The ITT population will be the primary population for the analysis of primary and secondary endpoints.

The **Per Protocol (PP) population** is defined as the set of participants who meet the ITT population requirements, defined above, and who were not associated with a major protocol violation/deviation. This population will be identified before the database lock.

The **Safety population** is defined as the set of participants receiving treatment after randomisation. This population will be used for the analysis of safety parameters.

Analysis Methods:

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analysing the efficacy and safety data from this study.

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1. Introduction

1.1 The Problem

Leg ulcers pose a significant burden on patients and health providers. In approximately 50-60% of cases, the aetiology is venous insufficiency (2) in which event they are referred to as venous leg ulcerations (VLUs) (3; 4). Older age, obesity, previous leg injuries, deep venous thrombosis, and phlebitis are the key risk factors (5). VLUs usually require weeks or months to heal and not uncommonly wound care specialists see patients who have suffered for years. In addition, VLUs are often recurrent (6; 7).

Ulcer pain is a common characteristic of VLUs and has a significant negative impact on patients' quality of life. A study by Phillips in 1994 found that 65% of patients with VLU complained of severe pain and 68% of patients stated that their ulcer had a negative emotional and psychological impact on them including feelings of fear, social isolation, anger, depression, anxiety and negative self-image (8).

1.2 The Pathophysiology: Venous Leg Ulceration

The venous ulcer pathophysiology is not entirely clear. Primary mechanisms for ulcer formation such as venous incompetence and associated venous hypertension have been described. Elongation of capillaries, micro-thrombosis, fibrin cuffs around vessels and leukocyte leakage are pathological microvascular changes seen with and attributed to venous hypertension (9).

The venous system of the lower extremity consists of superficial and deep veins connected by perforating veins. Normally, valves within the veins ensure the direction of blood flow from the superficial into the deep venous system and back to the heart. Pumping action of the musculature of the lower extremities aids the deep venous flow during physical activity. Factors such as immobility; ineffective pumping of the calf muscle; and venous valve dysfunction from trauma, congenital absence, venous thrombosis, or phlebitis may lead to venous incompetence (10; 11). Subsequent, chronic venous stasis causes pooling of blood in the venous circulatory system which in turn triggers further capillary damage and activation of inflammatory process. Leukocyte activation, endothelial damage, platelet aggregation, and intracellular oedema have been shown to contribute to VLU development and impaired wound healing (10) Oedema of the lower extremities followed by hyper-pigmentation, venous stasis dermatitis, hemosiderin deposits, loss of hair, thicken nails, atrophie blanche and lipodermatosclerosis, are all typical findings in patients with longstanding venous insufficiency.

1.3 The Treatment: Venous Leg Ulceration

Addressing oedema and improving the microcirculation in the skin is key in order to treat venous ulceration. Reduction of the oedema is best achieved using compression bandages and healing rates in venous leg ulcers are significantly improved by the application of compression therapy (12). High level compression (40 mmHg at the ankle) is more effective at healing venous leg ulcers than low compression (13). High level compression should only be applied

in the absence of significant arterial disease. The threshold normally employed for the use of high level compression is an ankle brachial pressure index (ABPI) of 0.8. Normal adult values range between 0.9 and 1.2. Levels lower than 0.8 indicate presence of arterial disease.

High level compression can be achieved using a variety of bandaging systems or compression hosiery. However, generally only approximately 45% of patients treated with optimal compression therapy (14) will heal within 12 weeks.

Hypoxia is a key factor that limits wound healing (15). Anything that negatively affects the delivery of oxygen to tissues, such as poor vascularisation, will interfere with healing and the link between compromised circulation and ulceration has been well established and well described (16). Thus an adjunct therapy which increases blood flow, circulation and/or delivery of oxygen could be a valuable aid in healing of VLUs.

1.4 geko™ neuromuscular stimulator

The geko™ device, manufactured by Firstkind Ltd (High Wycombe, United Kingdom), is a small disposable, battery powered, neuromuscular stimulation device designed to enhance blood flow in the lower limbs and improve healing of leg ulcers as an adjunct to standard care. It is made from mylar (polyethylene terephthalate (PET)) and is enclosed in a polypropylene casing. It is self-adhesive with a hydrogel layer that will stick it to the skin. geko™ is applied externally to the leg on the outer/posterior aspect of the knee. This positioning enables integral electrodes to apply a stimulus to the common peroneal nerve. These nerves control the contraction of a complex of muscles in the lower leg.

The stimulation of these nerves by the geko™ device causes the muscles to contract isometrically and will not affect normal movement of the limb nor patient mobility. Contraction of the lower leg muscles will boost venous return, local blood circulation and help prevent venous thrombosis. The geko™ device has ten stimulation levels to balance maximal effect of stimulation with patient comfort. The optimal stimulation level, which may vary between patients, is achieved when a stimulus results in a dorsi-flexion of the foot.

The geko™ device is fully insulated by a protective moulding and there is no risk of shock. It has charge-balanced waveforms that yield no build-up of charge in the patient. Therefore, provided the device is used in accordance with the instructions for use galvanic effects such as electrical burns cannot occur. The device is powered by battery, and is thus totally isolated from the mains electricity supply. The primary lithium coin cell battery powering the device is removable for disposal.

1.5 Summary of Prior Clinical Studies

The geko™ has been tested clinically to evaluate its safety and efficacy in human use. These studies did not give rise to any safety concerns for geko™.

Increases in venous, arterial and microcirculatory volume flow in the lower limb has been demonstrated in healthy volunteers. Venous flow was shown to increase by up to 100% (17; 18; 19), arterial flow by up to 75% (19) and microcirculatory by up to 400% (17; 19; 20) 21)

The geko™ has also been shown in a series of case studies to increase the rate of healing in venous leg ulcers, and it has been shown to be safe to use as a medical device. There were reports of skin irritations in these case studies. These types of adverse reactions are however anticipated in patients with venous leg ulcers as a result of increased sensitivity due to compromised blood circulation and metabolism in the skin.

Skin irritation has been shown to be more likely in patients who wear the device in excess of the recommended use. One study followed 12 patients with 18 heard to heal or none healing VLUs and showed a change in healing rate from 0.06% per week at baseline to 9.35% per week whilst using the geko™. Over the course of the study, 44% of wounds healed and 39% decreased in size (20).

Another series of case studies looked into the therapeutic effect of the geko™ device on wound healing outcomes over an eight-week period. Thirty patients with non-healing wounds (> 3-month duration) of either VLU, mixed aetiology leg ulcer (MLU) or diabetic foot ulcer (DFU) aetiology were recruited from a local outpatient wound clinic in the South Wales area. During the eight-week period two participants (8%) achieved complete re-epithelialisation between baseline and end of study. The mean wound surface area decreased over time (7.6 cm^2) and an increase of 21% in the mean percentage of granulation tissue was observed in the wound bed. Pain levels reduced in 52% of patients who completed the study. The Investigators concluded that their findings support the use of geko™ in patients with painful VLUs and MLUs (21).

1.6 Study Rationale, Benefits and Risks

This study is designed to evaluate the efficacy of two geko™ daily treatment durations in conjunction with Standard Care (SC), consisting of multilayer, multicomponent compression therapy intended for the treatment of VLU, compared with each other and to that of SC alone in participants with VLUs. geko™ has been shown to facilitate wound healing in earlier studies (See Section 1.5 Summary of prior clinical studies) and patients receiving the geko™ 6h or 12h daily in addition to SC may experience faster wound healing as well as greater pain reduction than patients treated with SC alone. We believe that treatment with geko™ will in conjunction with SC potentially lead to faster healing and re-epithelialisation than treatment with SC alone for patients with VLU.

A potential risk for participants randomised to the geko™ daily treatments is the possibility of eczema at the application site. This, however, is unlikely based on previous experience with geko™ (20). Potential adverse events for all research participants in this study are intrinsic to the nature of VLUs, including but not limited to: pain and infection at the wound site, and maceration of the surrounding skin.

Not all patients may respond to the geko ™ stimulus. Therefore, patients with no involuntary movement of the lower leg/foot at the maximum tolerable device setting will be excluded from the study.

2 Study Objective

The objective of this study is to compare the efficacy of a daily geko™ device treatment durations of 12 hours, in conjunction with SC, to SC alone, in patients with venous leg ulcers.

2.1 Efficacy Endpoints

2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is linear healing rate (LHR) from TV1 to EOT as compared with LHR from RV1 to TV1. LHR will be calculated by linear regression of the 4 measurements in each phase, with linear wound edge advance being based on the change with respect to time of wound area divided by perimeter, according to Vidal's method (22) [Each participant will be used as his/her own control, i.e. a participant's healing trajectory before introduction of treatment will be compared to his/her healing trajectory after introduction of treatment. Wound area and perimeter will be measured by a blinded independent wound expert using digital images taken at baseline (RV1), first treatment visit (TV1) and at EOT.

2.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Weekly LHR measured by an independent blinded wound expert using digital images taken at each weekly visit until TV5, withdrawal or healing whichever comes sooner.
- Wound healing status at baseline and EOT assessed by an independent blinded wound expert using PWAT to evaluate digital images taken at RV1, TV1 and at withdrawal, healing or at the end of the Treatment Phase (TV5), whichever comes sooner.
- Incidence of healing at EOT, as determined by the Investigator

"Healing" of the study ulcer is determined by the PI or designee. "Healing" is defined as 100% re-epithelialised without drainage as confirmed at the Healing Confirmation visit (HCV).

2.1.3 Participant Reported Secondary Efficacy Endpoints

The participant reported secondary efficacy endpoints are:

Time from TV1 to clinically significant pain reduction measured using a Visual Analogue Scale (VAS) instrument. For the purpose of this protocol a clinically significant reduction of pain is a mean reduction of ≥ 20.65 mm or a mean decrease of ≥ 10-20% in pain as measured on a 0-100 mm VAS (23; 24).

Time from TV1 to first instance of no study ulcer pain measured using VAS.

(No pain = < 5mm on VAS when VAS scores: 0-4 mm = no pain; 5-44 mm = mild pain; 45-74 mm = moderate pain; and 75-100 mm = severe pain) (1).

Pain score at EOT measured using VAS

Change from TV1 in Quality of Life (QoL) at EOT, assessed using the Cardiff Wound Impact Schedule (CWIS)

Change from TV1 in QoL at EOT, assessed using EQ-5D-5L

Wound closure as reported by participants during the Follow-up Phase (FP1-FP3)

The two QoL instruments, the CWIS a wound specific QoL instrument, and the EQ-5D-5L, a standardised instrument for measuring generic health status, will be provided to the participants for completion at RV1, TV1 and at EOT. In case of withdrawal all attempts should be made to obtain final QOL assessments.

2.2 Safety assessment

Safety will be assessed based on incidence of adverse events (AEs), incidence of serious AEs (SAEs), incidence of study treatment related AEs, incidence of investigational device related AEs, ulcer infection, and incidence of pain in the ulcer site (sudden onset of pain or increase in pain during the study treatment).

3 Study Design

This study is designed as a prospective, multicentre, randomised, assessor blinded study designed to compare the efficacy including participant reported outcomes of two different geko™ treatment durations in conjunction with SC, with each other and with SC alone, in the treatment of patients with venous leg ulcers. There will therefore be two arms in the study consisting of: 1) participants randomised to receiving SC only; 2) participants randomised to receiving SC, and geko™ 12 hours daily.

The standard care therapy in this study is multilayer, multicomponent compression therapy intended for the treatment of VLU. A non-adherent (NA) wound contact dressing and/or an absorbent dressing may be used if required, at the Investigator's discretion in addition to SC. All dressing use and reason for dressing use will be recorded.

Multiple multilayer, multicomponent compression bandaging systems delivering levels of compression and with clinical data to support their use are commercially available. The compression bandaging system of choice based on local best practice will be used. Moreover, this will prevent any problems around consistency of method of application of compression.

The study will be a multinational, multicentre study with study centres in the UK and Europe

The study will have three phases: a four-week Run-in Phase, a four-week Treatment Phase and a twelve-week follow-up phase. A schematic picture of the study flow is provided below in Figure 1.

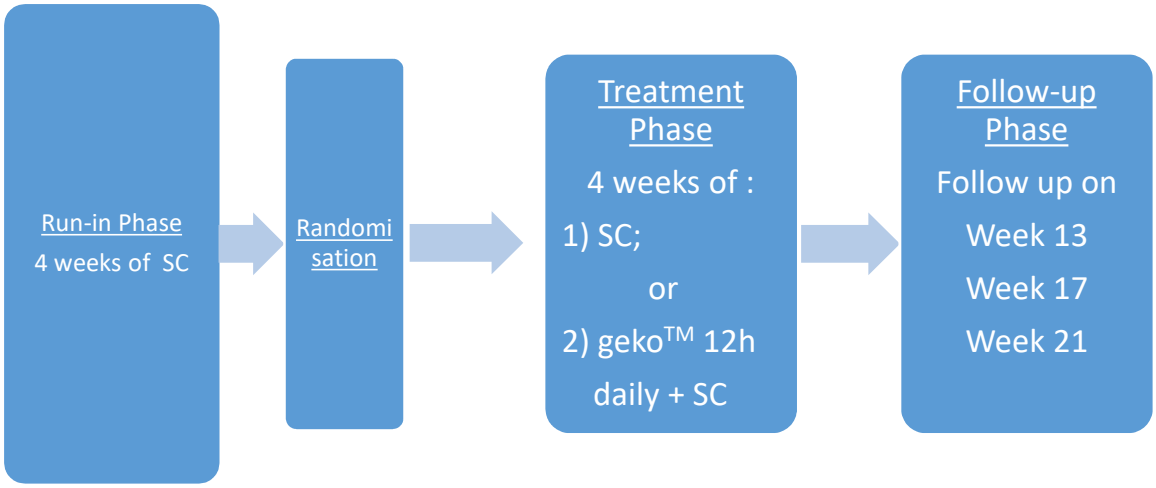

Figure 1: Study Schedule

At or up to 21 days before the first Run-in Phase Visit (RV1), the Investigator or suitably qualified designee will, prior to the performance of any protocol-specific procedure, obtain written informed consent from the patient.

During the Run-in Phase participants will be evaluated on a weekly basis. Efficacy evaluations each week will include Investigator assessment of wound healing and measurements of ulcer size using digital images. For the purpose of this study, healing is defined as 100% re-epithelialisation without drainage confirmed at the Healing Confirmation visit (HCV). The compression bandaging system of choice based on local best practice in the study centre in question will be used.

The results of the four-week Run-in Phase during which only SC will be used as treatment, will provide an SC only healing trajectory (LHR curve) (22) for each of the participants and each participant will serve as his/her own control.

At RV1, the Investigator will assess and confirm the patient's eligibility and select the study ulcer. Each participant will have only one VLU selected as the study ulcer. In the situation where a participant has more than one VLU at the RV1 visit, the Investigator will select the largest VLU that meets the eligibility criteria of the protocol as the study ulcer. If other ulcerations are present on the same leg they should be more than 2 cm apart from the study ulcer.

At the first Treatment Phase visit (TV1), once the Investigator has confirmed the participant's continued eligibility, randomisation and assignment to study treatment will take place.

The total maximum study duration is nine weeks, followed up by twelve weeks Follow-up Phase. All participants remaining in the study at the final Treatment Phase visit, TV5, will complete study visits unless they present with 100% re-epithelialisation without drainage as determined by the PI or designee, in which case they will be scheduled for a Healing Confirmation Visit (HCV) in a minimum of 7 days. All participants attending a HCV will complete study visits at this visit regardless if healing is confirmed or not.

3.1 Study Population

3.1.1 Number of Participants

A total of 60 patients will be randomised into the study

3.1.2 Inclusion Criteria

The inclusion criteria of the study are:

1. Male or female aged ≥ 18 years and able to provide written informed consent.

2. Intact healthy skin at the site of geko^{TM} device application.

3. Patients who have a chronic venous leg ulcer determined to be due to underlying venous disease following evaluation in a multidisciplinary clinic setting or by a vascular surgeon, GP or Nurse specialist.

4. *A VLU of approximately ≥ 3cm^2 and ≤ 39 cm^2 at study enrolment i.e. Run In Phase Visit 1 (RV1).* The largest ulcer within the given size range will be designated the study

ulcer and the only one included in the study. If other ulcerations are present on the same leg they have to be more than 2 cm apart if they are separate wounds.

5. Study ulcer (current episode of ulceration in case of ulcer recurrence) has been present for at least 6 weeks but no more than 5 years prior to study entry.

6. Ankle-Brachial Pressure Index (ABPI) of 0.75-1.24 inclusive measured at study entry or within 8 weeks of study entry

7. No active index wound infection for a minimum of 48 hours prior to study entry (i.e. RV1).

8. No systemic antimicrobial treatment for a minimum of seven days prior to study entry prescribed for index wound infection (i.e. RV1).

9. Patient understands and is willing to participate in the study and is able to comply with study procedures and visits.

3.1.3 Exclusion Criteria

The exclusion criteria of the study are:

1. Known allergy to any of the protocol-stipulated treatments, or non-tolerance of multilayer, multicomponent compression therapy intended for the treatment of VLU.
2. History of significant haematological disorders (e.g. Sickle Cell disease).
3. History of Deep Vein Thrombosis (DVT) within six months preceding study entry (i.e. RV1).
4. History of Pyoderma Gangrenosum or other inflammatory ulceration.
5. Pregnancy or breast feeding.
6. Use of investigational drug or device within four weeks prior to study entry (i.e. RV1) that may interfere with this study.
7. Use of any neuro-modulation device.
8. Surgery during three months preceding study entry (such as abdominal, gynaecological, hip or knee replacement) (i.e. RV1).
9. Trauma to the lower limbs that would prevent geko™ from stimulating the common peroneal nerve.
10. No involuntary movement of the lower leg/foot at the maximum tolerable device setting.
11. Any medication deemed by the Investigator to potentially interfere with the study treatment (e.g. systemic steroids.)

12. Participation in any other clinical study.

4 Study Schedule

The study is divided into three phases: the Run-in Phase, the Treatment Phase and Follow-up Phase. The schedules for the protocol-specified assessments and procedures in each phase are detailed below in the following sections.

One week equals 7 days and the allowed visit window is one week ± 3 days. Every attempt should be made to maintain participants on their original weekly treatment schedule. When determining the visit dates, the reference should always be to the RV1 or TV1 date and not the participant's previous visit.

There will be a Healing Confirmation Visit (HCV) scheduled in a minimum 7 days for participants who present with 100% re-epithelialisation without drainage of the study ulcer as determined by the PI or designee during the Treatment Phase.

4.1 Run-in Phase

Investigators should confirm that the patient has provided written informed consent. Thereafter procedures during the Run-in Phase should be performed in the following order:

- Confirm Participant response to geko^{TM} treatment by presence of involuntary movement of the lower leg/foot at the maximum tolerable device setting (RV1 only).
- Measure ABPI if a valid ABPI reading has not taken within 8 weeks of RV1
- Confirm eligibility (RV1 only). If the patient is not eligible, discharge the patient from the study as a screen failure. If the patient is eligible continue with the following procedures:
    - Record medical history and study ulcer history (RV1 only).
    - Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language (RV1 only).
    - Perform physical examination and assess Body Mass Index (BMI) (RV1 only).
    - Assess concomitant medications (Con Med) and update Con Med page in case report form [CRF] as appropriate).
    - Assess compression bandaging (See Section 9.8).
    - Record study ulcer location, history and duration (RV1 only).
      Note: 'Study ulcer location' is defined by the ulcer being on the left or right leg, by the location of the ulcer on the malleolus, low gaiter or high calf, and by the positioning of the ulcer as lateral, medial, anterior or posterior.
    - Administer the study ulcer pain VAS assessment.
    - Determine Venous Clinical Severity Score (RV1 only)
    - Assess for AEs. . Any AEs occurring during the Run In Phase are to be recorded on an AE form
    - Cleanse the study ulcer.
    - Obtain a digital image of the study ulcer (if debridement is planned, this is the Pre-debridement image). N.B., all study ulcer measurements will be performed using the pre-debridement images.

- At the discretion of the Investigator, perform debridement of the study ulcer to obtain a clean, granulating ulcer base with minimal adherent slough.
- If applicable, obtain a post-debridement digital image of the study ulcer
- Apply SC. A non-adherent (NA) wound contact dressing and/or an absorbent dressing may be used at Investigator's discretion if required in addition to the compression system.
- Record all dressing use
- Assess for any post-application AEs
- Schedule the next study visit in one week's time

The Run-in Phase ends with TV1 which is also the first visit of the Treatment Phase.

Table 1: Schedule of Events – Run-in Phase

Activity/Assessment	RV1	RV2	RV3	RV4	RV5/TV1
Informed consent	√				
Assessment of response to geko ™ treatment	√∞				
Ankle-Brachial Index (ABPI) if a valid ABPI reading has not been taken within 8 weeks of RV1	√				
Confirmation of eligibility	√				
Medical history	√				
CWIS, EQ-5D-5L and assessments	√				
Physical examination and BMI	√				
Concomitant medications	√	√	√	√	√
Assessment of compression bandaging	√	√	√	√	√
Study ulcer history	√				
Study ulcer pain (VAS) assessment	√	√	√	√	√
Venous Clinical Severity Score	√				√
Assess for AEs		√	√	√	√
Study ulcer cleaning	√	√	√	√	√
Study ulcer surrounding skin assessment	√				
Study ulcer image(s)	√⌘	√⌘	√⌘	√⌘	√⌘
Study ulcer debridement	√§	√§	√§	√§	√§
Application of compression	√¶	√¶	√¶	√¶	√¶
Assessment for post application AEs	√	√	√	√	√
Scheduling of next visit	√	√	√	√	√

∞ Presence of involuntary movement of the lower leg/foot at the maximum tolerable device setting

§ Study ulcer debridement at Investigator's discretion. N.B. All study ulcer measurements will be performed using the pre-debridement images.

⌘ If debridement is performed a pre-debridement and a post-debridement image is taken.

¶ A non adherent (NA) wound contact dressing and/or an absorbent dressing may be used at Investigator's discretion if required in addition to the compression system.

4.2 Treatment Phase

4.2.1 Treatment Visit 1 (TV1) – Prior to Randomization

The assessments on TV1 should be performed in the following order:

- Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language.
- Administer the study ulcer pain VAS assessment.

- Check for any changes in the participant's health. Any AEs during TV1 prior to randomisation are recorded in the participant's medical history. Following randomisation and during TV2-TV5, update the AE or Serious Adverse Events (SAE) CRF pages as applicable.
- Assess concomitant medications.
- Assess compression bandaging (See Section 9.8)
- Clean the study ulcer.
- Obtain a digital image of the study ulcer (if debridement is planned, this is the Pre-debridement image). N.B. All study ulcer measurements will be performed using the pre-debridement images.
- At the discretion of the Investigator, debride the study ulcer to obtain a clean, granulating ulcer base with minimal adherent slough.
- If applicable, obtain a post-debridement digital image of the study ulcer.
- Verify the participant's continued eligibility (See Sections 3.1.2 and 3.1.3).

If the participant is not eligible, discharge the participant from the study as a screen failure.

If a patient initially fails to meet inclusion/exclusion criteria he/she may later be reconsidered for participation, in which case the patient will be re-consented and assigned a new screening number at the time of re-screening. Patients who fail their first screening attempt may be re-screened once (i.e., up to two screenings) and be enrolled if they meet ALL inclusion and NO exclusion criteria at the second screening visit.

If the patient is eligible, perform the following procedures immediately

4.2.2 Treatment Visit 1 (TV1) – Randomisation and Post-randomisation

Perform the activities below in the following order:

- Randomise the participant. At the randomisation visit, the study ulcer needs to be ≥ 2 cm2 and ≤ 30 cm2. If other ulcerations are present on the same leg, they need to be at least 2cm away from the study ulcer
- Apply SC.
- Apply appropriate geko^{TM} to those participants randomised to either geko^{TM} group.
- Assess for any post-application AE.
- Provide the participant with geko^{TM} devices as applicable in accordance with the randomisation outcome
- Schedule the next study visit in one week's time.

NB. Each geko^{TM} device can only be used twice.

4.2.3 Treatment Phase Visits 2- 4 (TV2 – TV4)

Perform the assessments/activities in the following order:

- Administer the study ulcer pain VAS assessment.
- Check for any changes in the participant's health and update the AE or Serious Adverse Events (SAE) CRF pages if applicable.
- Assess concomitant medications.

- Assess compression bandaging (See Section 9.8).
- Assess study ulcer healing (to be performed by treating PI or designee)

If the study ulcer is 100% re-epithelialised without drainage:

- Obtain a digital image of the study ulcer site.
- Provide appropriate follow-up therapy for the healed ulcer and schedule the participant for a Healing Confirmation Visit (HCV) in a minimum of 7 days.
- Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language.
- Complete the remaining applicable visit procedures.

If the study ulcer is not 100% re-epithelialised without drainage:

- Clean the study ulcer.
- Check for signs of clinical infection. If clinical diagnosis of infection has been made, the participant should be treated with topical antimicrobials or oral antibiotics in accordance with local best practice. SC, or SC plus either geko™ treatment will continue at Investigator's discretion.
- Obtain a digital image of the study ulcer (if debridement is planned this will be the pre-debridement image). N.B. All study ulcer measurements will be performed using the pre-debridement images.
- Debride the study ulcer to obtain a clean, granulating ulcer base with minimal adherent slough, at the discretion of the Investigator.
- If applicable, obtain a digital image of the study ulcer (post-debridement image)
- Apply appropriate geko™ to those participants randomised to either geko™ group.
- Assess for any post-application Aes.
- Schedule the next study visit in one week's time.

Note that TV4 is the final scheduled study product application.

- Apply SC. A non adherent (NA) wound contact dressing and/or an absorbent dressing may be used at Investigator's discretion if required in addition to SC. All dressing use will be recorded.
- Assess and sign the participant diary card (geko™ groups only).

4.2.4 Final Treatment Phase Visit (TV5)

Perform the assessments/activities in the following order:

- Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language
- Administer the study ulcer pain VAS assessment.
- Assess and sign the participant diary card (geko™ groups only).
- Check for any changes in the participant's health and update the AE or SAE CRF pages if applicable.
- Assess concomitant medications.
- Assess compression bandaging (See Section 9.8).
- Assess study ulcer healing (to be performed by treating PI or designee)

If the study ulcer is 100% re-epithelialised without drainage:

- Obtain a digital image of the study ulcer site.
- Provide appropriate follow-up therapy for the healed ulcer and schedule the participant for a Healing Confirmation Visit (HCV) in a minimum of 7 days.
- Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language.
- Complete the remaining applicable visit procedures.

If the study ulcer is NOT 100% re-epithelialised without drainage:

- Complete the remaining visit procedures.
- Check for signs of clinical infection.
- Clean the study ulcer.
- Digital image of the study ulcer (if debridement is planned this will be the pre-debridement image). N.B., all study ulcer measurements will be performed using the pre-debridement images.
- Debride the study ulcer to obtain a clean, granulating ulcer base with minimal adherent slough, at the discretion of the Investigator.
- If applicable, obtain a digital image of the study ulcer (post-debridement).
- Provide appropriate follow-up therapy for the non-healed ulcer and exit the participant from the study.

Table 2: Schedule of Events – Treatment Phase

Activity/Assessment	TV1 (pre-rand)	TV1 (post rand)	TV2	TV3	TV4	TV5 /Final Visit
CWIS and EQ-5D-5L assessments	√					√
Study ulcer pain assessment (VAS)	√		√	√	√	√
Assess for AEs	√		√	√	√	√
Assess concomitant medications	√		√	√	√	√
Assess compression bandaging	√		√	√	√	√
Study ulcer exudate assessment	√		√	√	√	√
Venous Clinical Severity Score						√
Leg oedema assessment	√		√	√	√	√
Study ulcer healing assessment			√∞	√∞	√∞	√∞
Study ulcer cleaning	√		√	√	√	√
Study ulcer margin assessment	√		√	√	√	√
Study ulcer surrounding skin assessment	√		√	√	√	√
Study ulcer bed appearance	√		√	√	√	√
Signs of infection of study ulcer	√¶		√¶	√¶	√¶	√
Study ulcer image(s)	√⌘		√⌘	√⌘	√⌘	√⌘
Study ulcer debridement	√§		√§	√§	√§	√§
Confirm eligibility	√					
Randomisation		√				
Apply SC		√	√	√	√	√
Apply geko ™ as per randomisation		√	√	√	√	
Assess for post-application AEs		√	√	√	√	√
Assess and sign the participant diary card (geko groups only)			√	√	√	√
Provide the participant with the appropriate geko devices as applicable		√	√	√	√	
Schedule next visit		√	√	√	√	
∞ Study ulcer healing assessment to be performed by PI or designee. Participants with 100% re-epithelialisation without drainage will be scheduled for a Healing Confirmation Visit in a minimum of 7 days time.						
¶ If clinical diagnosis of infection has been made, the participant should be treated with topical antimicrobials or oral antibiotics in accordance with local best practice. Study treatment will continue as per Investigator's discretion						
⌘ If debridement is performed a pre-debridement and a post-debridement image is taken. N.B. All study ulcer measurements will be performed using the pre-debridement images.						
§ Study ulcer debridement at Investigator's discretion						

4.3 Healing Confirmation

Only those subjects whose study ulcer is 100% re-epithelialised without drainage as determined by the PI or designee during a TV, will be scheduled for a Healing Confirmation Visit (HCV). The HCV is to be scheduled a minimum of 7 days after the first determination of re-epithelialisation.

During the HCV perform the activities in the following order:

- Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language.

- Administer the study ulcer pain VAS assessment.
- Check for any changes in the participant's health and update the AE or SAE CRF pages if applicable.
- Assess concomitant medications.
- Assess compression bandaging (See Section 9.8).
- Assess study ulcer healing (to be performed by treating PI or designee).

If the study ulcer remains 100% re-epithelialised without drainage:

- Obtain a digital image of the study ulcer site.
- Provide appropriate follow-up therapy for the participant and the healed ulcer and exit the participant from the study.
- Complete the remaining applicable visit (TV5) procedures.

If the study ulcer remains 100% re-epithelialised without drainage at the HCV, the date of healing for the purpose of study results will be the date 100% re-epithelialisation without drainage was first determined by the PI or designee.

If the study ulcer is NOT 100% re-epithelialised without drainage:

- Complete the remaining visit (TV5) procedures.
- Check for signs of clinical infection.
- Clean the study ulcer.
- Obtain a digital image of the study ulcer.
- Provide appropriate follow-up therapy for the participant and the non-healed ulcer and exit the participant from the study.

4.4 Follow-up Phase

Participants who completed TV5 will be contacted after 4, 8 & 12 weeks to find out the status of the study wound.

At week 13, 17 and 21; a member of the research team (at the clinical site) will contact the patient to find out

- whether the wound is healed or not healed
- if healed (the date wound was healed)

4.5 Unscheduled Visits

Unscheduled visits may be required in addition to the visits detailed above. Additional visits are at the discretion of the Investigator. An example of an unscheduled visit is when a change of compression bandaging is required between scheduled visits. The details of these unscheduled visits with participants will be recorded in the medical records/source documents and on the CRF.

4.6 Missed Visits

If a participant misses a visit, the site is to make every effort to have the participant return as soon as possible to make up the visit. Once the participant is seen, he/she is to return to his/her original weekly visit schedule. For example, if a participant was seen regularly on Mondays but missed a scheduled Monday visit and came in on Wednesday, he/she should return the next Monday to maintain his/her weekly Monday visit schedule

5 Participant Completion and Withdrawal

5.1 Participant Completion

A participant whose study ulcer has healed will be considered as having completed the study. For the purpose of this study healing is defined as 100% re-epithelialisation with no drainage as determined by the PI or designee. The 100% re-epithelialisation and absence of drainage must be confirmed at a subsequent clinic visit (HCV) in a minimum of 7 days (See Section 4.3). If 100% re-epithelialisation of the study ulcer with no drainage is confirmed at the HCV, the date of healing will be the date the ulcer was first determined by the PI or designee as 100% re-epithelialised and without drainage.

5.2 Premature Withdrawal / Discontinuation from the Study

A participant who is randomised and has completed TV1 of the Treatment Phase but who does not complete the study, as defined in Section 5.1, has prematurely discontinued.

All participants have the right to withdraw at any point during the study without prejudice to his/her treatment. It will be documented whether or not a participant completed the clinical study. If for any participant, study treatment or observations were discontinued, the reason(s) will be recorded.

The Investigator can discontinue a participant at any time if it is considered medically necessary.

In addition, participants will be withdrawn from the study, at the Investigator's discretion, if any of the following occur:

A participant is significantly non-compliant with the requirements of the protocol.

A participant has revascularisation surgery on the leg with the study ulcer.

The study ulcer cannot be compressed.

The study ulcer merges with an adjacent ulcer.

The reason for treatment discontinuation or withdrawal from the study will be recorded in the source documents and on the appropriate page of the CRF. Every attempt should be made to complete the relevant CRF pages.

Before a participant is identified as lost-to-follow up, the site should make all reasonable efforts to contact the participant. These attempts must be documented and should include at a minimum one phone call and one letter/email.

Participants who meet the criteria for premature withdrawal during the Treatment Phase will have TV5 assessments performed.

In the event that a participant is prematurely discontinued from the study at any time due to an AE or SAE, the procedures stated in Section 5.2 must be followed.

5.3 Screen Failures

A patient who has signed a consent form, has been assigned a screening number, but is not randomised is classified as a screen failure. Patient number, demography and reason for screen failure will be collected.

6 Study Treatments

6.1 Method for Assigning Eligible Patients to Treatment

Eligible patients will be assigned to one of the following three treatment groups, based on the randomisation schedule:

- Group 1: SC only (multilayer, multicomponent compression intended for the treatment of VLU)
- Group 2: 12 hours daily treatment with geko™ (XW, W-3 or variant) plus SC (multilayer, multicomponent compression intended for the treatment of VLU)

6.2 Description of the Investigational Device

The geko™ device is CE marked (GB12/87339; SGS, United Kingdom Ltd). The geko™ device is made from mylar (polyethylene terephthalate (PET)), it is enclosed in a polypropylene casing and a hydrogel layer will stick it to the skin. In this study the XW, W-3 or variant will be used. (Refer to Appendix 1. for Fitting Instructions).

6.3 Participant Investigational Device Use

Each geko™ device can be used only twice. Participants randomised to the geko™ 12 hour daily treatment groups will at each visit be provided with a sufficient number of geko™ devices to last until the next scheduled Treatment Phase visit. Participants should ensure that they always have enough devices to carry them through to the next scheduled Treatment Phase visit. Participants randomised to either geko™ group will be provided with a diary card on which their geko™ usage will be recorded. The participants should bring the diary card with them at each site visit at which the cards will be verified and signed.

6.4 Labelling

The study supplies will be labelled in accordance with all applicable regulatory requirements. Each investigator will be supplied with sufficient supplies to conduct the study.

Each geko™ device will have a number which will be unique to the particular device. The unique device number will be recorded in the participant diary each time it is used to provide a check that the allocated treatment has been provided. At each study visit the study device usage will be assessed and new devices provided.

6.5 Device Storage, Handling, Application and Disposition

The investigational devices will be supplied in single use labelled packages.

The whole device with the battery in place can be disposed of in domestic waste.

Details on application of the geko™ device and Instructions for Use are available in Appendix 1.

6.6 Product accountability

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of investigational device receipt will be documented according to Sponsor's requirements.

An accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the dispensing and the destruction of the investigational product.

At the conclusion of the study the Investigator must agree to return all investigational products as instructed by Sponsor.

6.7 Participant Training and Instructions

Participants randomised to either geko™ group will be trained in the use of the geko™ device and be provided with Instructions for Use. Such participants will also be instructed to hand in the above mentioned diary card at each study visit for verification and signature by the Investigator.

All participants will be instructed to ring or visit the study site if there is any issue with the compression bandaging such as, but not limited to, pain, discomfort, and removal or soiling of the bandage.

All participants will be instructed to contact the Investigator if signs or symptoms of infection develop prior to their next scheduled visit.

7 Concomitant Medications

All medications and therapies administered or taken by the participant throughout the study will be recorded in the source documents and on the appropriate page of the Case Report Form (CRF).

For each medication the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose). Note: Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.
- Route of dosing
- Indication for use
- The start date
- The stop date (if applicable)

8. Excluded Therapies

The following treatments are prohibited throughout the study:

- Any neuro-modulation device
- Any other investigational treatment/medications

9 Description of Protocol Procedures and Assessments

9.1 Informed Consent

The Investigator or suitably qualified designee will obtain written informed consent for this study from all participants before the performance of any protocol-specific procedure.

In obtaining and documenting informed consent the Investigator must comply with applicable regulatory requirements and must adhere to Good Clinical Practice (GCP). The Investigator, or designee, must fully inform patients of all pertinent aspects of the study. Before written informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the patient ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study must be answered to the satisfaction of the patient. Prior to the patient taking part in the study, the written informed consent must be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

The signed informed consent must remain in the patient's files and be available for verification by the study monitor. The patient's medical record should clearly indicate that the patient is participating in this study.

9.2 Assessment of Eligibility

At the RV1 and TV1, the Investigator must assess a patient's continued suitability and eligibility for the study, especially with regards to the Inclusion and Exclusion criteria of this Protocol described in Sections 3.1.2 and 3.1.3. If a patient is not suitable or eligible for the study then the patient will be a screen failure.

9.2.1 Re-Screening

If a patient fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the patient will be re-consented and assigned a new screening number at the time of re-screening. Patients who fail their first screening attempt may be re-screened once again (i.e., up to two screenings per patient) and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the screening visit.

9.3 Demographics, Medical History, Study Ulcer History

9.3.1 Demographics

For the purposes of this study, demographic information will include:

- Dates of Informed Consent Form signature
- Date of birth
- Gender

- Use of tobacco products

9.3.2 Medical History

A medical history will be recorded at RV1 and will include:

- All ongoing medical conditions
- All previously resolved medical conditions related to Venous Insufficiency or Leg Ulceration or which are relevant in the opinion of the Investigator

Medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal
- Hepatic
- Neurological
- Endocrine
- Lymphatic
- Hematologic
- Immunologic
- Dermatologic
- Psychiatric
- Genitourinary
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Year of diagnosis
- History status (resolved or ongoing)

9.3.3 Study Ulcer History

- Duration of the current study ulcer

  Note: 'Duration' is defined as the length of time that the study ulcer has been open at this location (since the last time it was fully closed if the ulcer in question is a recurrent ulcer).

- Current compression bandaging system used for the study ulcer and length of time that this has been used
- Prior treatments that have been used on the study ulcer
- Age when the participant developed his/her first ulcer
- Total number of previous ulcers
- Location of the current study ulcer

  Note: 'Study ulcer location' is defined by the ulcer being on the left or right leg, by the location of the ulcer on the malleolus, low gaiter or high calf, and by the positioning of the ulcer as lateral, medial, anterior or posterior.

- Number of additional leg ulcers and location of each present at the screening visits
- History of VLU recurrence

  Note: 'Recurrence' is defined as the re-opening of an ulcer after healing.

- History of a DVT (deep vein thrombosis) in the study leg

9.4 Quality of Life Assessment Questionnaire (CWIS and EQ-5D-5L)

The Cardiff Wound Impact Schedule, CWIS, will be used to assess the "disease specific" QoL. A generic QoL questionnaire, the EQ-5D-5L questionnaire, will be used to assess the effects of treatments on the participants' QoL. Results may be used to derive a patient-reported outcome useful for health-related QoL claims on the investigational device treatment.

The questionnaires (and instructions for completing them) will be provided to all participants at the first Run-in Phase visit (RV1) and at TV1 prior to the application of randomised treatment. The questionnaires will also be provided and collected upon EOT, as part of the End of Study procedures.

The QoL assessments will be performed prior to any other study procedures, when scheduled, to minimise bias.

9.5 Physical Exam & Vital Signs

9.5.1 Physical Examination

The physical examination will be performed at study entry (RV1) and will include routine examinations for the following:

- Abnormalities of the extremities
- Neurologic abnormalities
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the participant or could impact safety or efficacy results for the participant; i.e. the abnormality is clinically significant.

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

9.5.2 Vital Signs

The following vital signs will be collected at study entry (RV1):

- Height

- Weight
- BMI (derived from the height and weight measurements)

9.6 Ankle-Brachial Pressure Index (ABPI)

Ankle Brachial Pressure Index (ABPI) is the ratio of blood pressure measured at the ankle to that measured at the arm. An ABPI < 0.8 indicates that there is a high probability that arterial insufficiency is present (positive predictive value 95% and negative predictive value 99%) in a general practice population). Compression therapy may be safely applied to patients with an ABPI >0.8 in addition to a comprehensive medical history.

If upon clinical examination the patient exhibits signs or symptoms that could suggest peripheral arterial disease, further investigations to determine vascular status may be warranted.

ABPI must be completed prior to any other study related procedures at the first Run-in Phase visit (RV1) unless a valid ABPI measurement has been taken within 8 weeks of the RV1 taking palce.

9.7 Pain Assessment Using Visual Analogue Scale (VAS)

Pain intensity of the VLU is to be assessed before any dressing changes or other wound manipulations at all study visits (Run-in Phase and Treatment Phase).

The Visual Analogue Scale (VAS) is a commonly used pain assessment tool suitable for the purpose of this study. Participants will be using the VAS instrument to record study ulcer pain. They will be asked to mark the point that best represented the pain intensity at the ulcer site on a horizontal line (100mm in length) anchored by word descriptors at each end, as "no pain" on the left side and "worst pain possible" on the right side of the line. Importantly, the participant marks on the line or by pointing to a position on the line the point that he/she feels represents his/her perception of his/her current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point indicated by the participant.

9.8 Assessment of the Compression Bandaging

The following questions will be asked to assess the compression bandaging during the Run-in and Treatment Phase visits:

1. Whether the bandage was in place at each visit (Yes/No)
2. If the bandage was not in place, the date it was removed and the reason for removal (slippage, strikethrough or other)
3. If the bandage is in place but needs to be changed at an unscheduled visit, the reason for removal/change must be recorded from the following:
    a. Maximum wear time

b. Participant withdrawn

c. AE

d. Slippage

e. Dressing change needed with details of dressing in question

f. Soiled

g. Participant request

h. Other

9.9 Study Ulcer Leg and Ulcer Assessments

The following assessments of the study ulcer/ study ulcer leg will be conducted as specified below.

9.9.1 Venous Clinical Severity Score

The Venous Clinical Severity Score (25) will be obtained only at the RV1, RV5 visit and at the last study visit. See Appendix 3 for details regarding scoring.

9.9.2 Leg Oedema Assessment (Study ulcer leg only)

The study ulcer leg oedema will be assessed during the study visits using a modification of the Guelph General Hospital Congestive Heart Failure Pathway leg oedema scale (26).

Leg Oedema Scale
• No
• 1+ : Mild pitting, slight indentation, no perceptible swelling of the leg
• 2+ : Moderate pitting, indentation subsides rapidly
• 3+ : Deep pitting, indentation remains for a short time, leg looks swollen
• 4+ : Very deep pitting, indentation lasts a long time, leg is very swollen

9.9.3 Study Ulcer Margin Assessment (Pre-debridement)

The study ulcer margins will be assessed during study treatment visits and the presence/absence of the following features will be recorded (27):

- Granulating
- Epithelialising
- Sloping
- Rolled
- Punched out

- Everted
- Purple
- Undermining
- Sinus
- Inflamed

9.9.4 Study Ulcer Bed Appearance (Pre-debridement)

The study ulcer bed appearance will be assessed during study treatment visits and the following features will be recorded:

- Percentage granulation tissue
- Quality of granulation tissue
- Percentage non-viable tissue

9.9.5 Study Ulcer Exudate Assessment

The Investigator will determine the amount and type, if any, of study ulcer exudate. In determining the amount of study ulcer exudate the Investigator should take into account the amount of exudate absorbed into the study ulcer dressing. The following categories will be used to quantify the amount of study ulcer exudate:

- No exudate
- Minimal amount
- Moderate amount
- Heavy/large/copious amounts

9.9.6 Study Ulcer Surrounding Skin Assessment

The study ulcer surrounding tissue within 4 cm of the ulcer edge will be assessed and presence/absence of the following features will be recorded:

- Tissue paper skin
- Peri-ulcer oedema
- Eczema
- Maceration
- Dry/scaly skin
- Erythema
- Healthy skin
- Inflammation
- Pustules
- Rash
- Skin abnormalities such as scarring

9.9.7 Study Ulcer Infection Assessment

The presence/absence of infection at the study ulcer site will be documented at each study visit. All participants who show evidence of an ulcer infection during the Treatment Phase must have the infection reported on an AE CRF. Any AEs during Run-in Phase are recorded in the participant's medical history.

The determination of presence/absence of ulcer infection will be made by the Investigator. The participant should be treated with topical antimicrobials or oral antibiotics in accordance with local best practice. SC, or SC plus geko^{TM} treatment will continue at Investigator's discretion during the Treatment Phase. Antibiotic interventions will be recorded on the Concomitant Medications Form and the event will be categorised as an AE, serious if it meets the definition of that category.

All participants will be instructed to contact the Investigator if signs or symptoms of infection develop prior to their next scheduled visit.

During an episode of infection, any modification of compression treatment is at the discretion of the Investigator and will be recorded in the CRF.

9.9.8 Investigator Assessment of Study Ulcer Healing

"Healing" is defined as 100% re-epithelialised without drainage determined by the PI or designee as confirmed at the Healing Confirmation visit (HCV). This means that in order to be considered as "healed", the study ulcer will need to remain closed without drainage for a minimum of 7 days from the date when it is first determined to be 100% re-epithelialised without drainage.

At each TV visit and at the HCV if scheduled, the PI or designee will assess the wound by answering the following questions:

- Is the study ulcer 100% re-epithelialised?
- Is there any drainage present?

When the Questions are asked at a TV visit, if question 1 is answered "yes" and question 2 is answered "no", the patient is scheduled for a Healing Confirmation Visit (HCV) in a minimum of 7 days. During the HCV questions 1 and 2 above are repeated. Question 1 must be answered "yes" and Question 2 must be answered "no" at the HCV for the study ulcer to be considered healed.

"If Question 1 is answered "yes "and Question 2 is answered "no", the date of healing will be the date the 100% re-epithelialisation without drainage was first determined by the PI or designee.

9.9.9 Study Ulcer Images

The study ulcer will be digitally photographed according to the schedules in this protocol using the Aranz SilhouetteStar^{TM}, a digital camera which is part of the Silhouette^{TM} system.

SilhouetteStar™ is a portable, non-contact device for imaging and measuring ulcers. This system will be used to measure the study ulcer area and to assess the study ulcer appearance.

Run-in Phase and Treatment Phase images of the study ulcer will be taken at each weekly visit, as well as at the HCV, if scheduled, will be used to measure and document ulcer size and healing status.

If debridement is performed, both pre and post-debridement images will be taken. The pre-debridement measurement will serve as the basis for all wound area related endpoints in this study.

All SilhouetteStar™ users must have training in the used system prior to undertaking any imaging and/or measurements for this study. A separate imaging and measurement manual with more detail about SilhouetteStar™ will be provided in the Operations Manual for the study.

If the index ulcer during the course of healing splits into a number of smaller wounds, the area's of the resulting wounds will be combined and used for analysis.

At end of study all images will be sent to an independent blinded wound expert for wound area measurements. The wound area measurements will be used for all PAR related analysis.

9.10 Recording of Device Usage

The participants randomised to the geko™study group will be provided with a participant diary for the purpose to record the daily geko™ device usage.

10 Statistical Analysis

10.1 General Statistical Considerations

This section presents general information concerning the statistical analyses which will be performed in this study, including for example, information about sample size, interim analysis, randomisation, treatment groups, endpoints, and the analysis methods and statistical tests to be performed. Detailed information on these and other related matters will be provided in the study Statistical Analysis Plan (SAP), as a separate document.

10.2 Sample Size Determination and Rationale

The sample size calculation is based on pilot data pooled from 2 two sources (The Canadian Bandaging Trial (28), and case series) and gives an estimate of effect size (delta/standard deviation) ranging from 0.80 to 1.1. In this design, each group is internally controlled by a four-week baseline, allowing pair-wise intra-group comparison, and normalised inter-group comparison. Assuming the more conservative figure for effect size, and assuming 50% effect size for the reduced dosage group, n=35 per group yields 90% power to establish an effect for geko^{TM} at the lower dosage.

Because of the short study duration, the discontinuation rate is predicted to be about at most 20%. To accommodate the potential discontinuations, the trial proposes to randomise 126 subjects (42 per treatment group).

10.3 Randomisation

This is a multi-centre randomised clinical study. Participants will be allocated to treatment groups using Adaptive Covariate Randomisation using an on-line randomisation tool (29).

The randomisation will be applied centrally across the sites.

10.4 Blinding

The independent wound expert measuring the wound area will receive the wound images without participant identification data or study visit data and he/she will therefore be blinded when measuring the wound area and assessing the healing status of the wound.

10.5 Interim Analysis for Sample Size Adjustment

An interim analysis will be conducted when approximately 60% have been enrolled.

The Interim Analysis will be directed and conducted by an independent statistician who is not involved in the study conduct other than the Interim Analysis. The main purpose of this Interim Analysis is to validate the assumptions in calculating the sample size (i.e., the effect sizes assumed in the initial sample size calculations). Using the observed difference of percentage reduction in area, and all other original assumptions noted above, the independent statistician will re-calculate the sample size. Based on the documented sample size re-calculation and the observed drop-out rate, the independent statistician's report will either recommend a new, increased sample size sufficient to achieve the study's objectives or will provide documentation that the current sample size is sufficient with no need to increase the sample size.

10.5.1 Procedure for Interim Analysis

The data to be used in the interim analysis and the treatment assignment of each randomised subject will be given to the statistician. Using this data, the independent statistician will calculate the following metrics for the primary end point:

1. Mean and standard deviation of LHR in each group.
2. The dropout rate at the time of the Interim Analysis, IA
3. The statistical power of the trial at the time of the IA (using a conditional power approach).
    a. If the statistical power is larger than 50%, then the sample size will be adjusted upward and no Type I error rate adjustment will be made to the final analysis.
    b. If the statistical power is less than 50%, the Type I error rate will be inflated and statistical adjustment will be made to the final analysis if the decision to increase the sample size is made. That is, the observed p-value, as well as the point estimate of the response rates, and the 95% CIs will be based on:

        p-value =2*{1- T2(n1+n2 - 1) (|z1 + z2|/√2)},

        Healing rate for each treatment group: $\hat{S} = (\sqrt{n1} \times \hat{S}1 + \sqrt{n2} \times \hat{S}2)/(\sqrt{n1} + \sqrt{n2})$,

        95% Confidence Intervals= $(\hat{S} - 2\ t\alpha/2{:}2(n1+n2 - 1)\sigma, \hat{S} + 2\ t\alpha/2{:}2(n1+n2 - 1)\sigma)$

        where n1, is the sample size in the treatment group before interim analysis and n2 is the sample size in treatment group after the interim analysis; T2(n1+n2 - 1) (.) is t distribution with 2 (n1+ n2-1) degrees of freedom. The $\hat{S}1$ is the healing rate of the n1 observation before the interim analysis and $\hat{S}2$ is the healing rate of the n2 observation after the interim analysis. The $(\sqrt{n1} + \sqrt{n2})\sigma$ is the observed pooled standard deviation before and after the interim analysis.
4. Using the observed metrics above, along with Type I Error Rate of 0.05, the sample size will be re-calculated and the independent statistician will provide the following to the sponsor and the statistician responsible for the trial:
    a. Re-estimation of sample size using the observed rate of healing and dropout rate
    b. The difference in percentage of healed subjects
    c. The healing rate in Treatment arms
    d. The healing rate in the Control arm
    e. The power used in calculating the new sample size

No other information will be shared with the sponsor or the statistician responsible for this trial.

10.5.2 Results of Interim Analysis

The new sample size calculation is:

Based on a pair-wise comparison of geko™ 12h run-in vs treatment:

From the interim data, there is a mean difference of 0.58 mm/week between run-in and treatment and a standard deviation of 0.97 mm/week.

Assuming requirements of 80% power and p=0.05 (2-sided) 25 subjects would be needed in the geko™ 12H group. (30)

Little benefit is foreseen in continuing the geko™ 6h group, as statistical significance is not expected at the projected number of subjects in this trial.

From the results of the Interim Analysis the new Treatment Groups are:

Group	Description
SC	Standard care (multilayer, multicomponent compression intended for the treatment of VLU)
geko 12h	geko™ version XW, W-3 or variant (12 h daily neuro-stimulation) and SC

10.6 Treatment Groups

The following treatment groups will be assessed:

Group	Description
SC	Standard care (multilayer, multicomponent compression intended for the treatment of VLU)
geko 12h	geko™ version XW, W-3 or variant (12 h daily neuro-stimulation) and SC

10.7 Description of Study Endpoints

10.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint for the study is LHR from TV1 to EOT as compared with LHR from RV1 to TV1. LHRs will be measured by a blinded wound expert using digital images at RV1, TV1, EOT, and at HCV if scheduled.

Each participant will be used as his/her own control, i.e. a participant's healing trajectory before commencement of treatment will be compared to his/her healing trajectory after introduction of treatment.

Since significant non-homogeneity may be expected in VLU participants and their respective healing trajectories, a pre-treatment run-in phase will be used to allow each participant to be used as his/her own control, i.e. a participant's healing trajectory before introduction of treatment will be compared to his/her healing trajectory after introduction of treatment. This allows an intra-group pair-wise comparison to evaluate the efficacy of each treatment regimen.

Additionally, for each participant, it enables generation of a treatment healing rate normalised relative to an initial healing rate. Inter-group (albeit un-paired) comparisons based on this normalised value are likely to be more sensitive than comparison of raw healing rates.

10.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Weekly LHR measured by an independent blinded wound expert using digital images taken at each weekly visit until EOT.
- Wound healing status at baseline and EOT assessed by an independent blinded wound expert using PWAT to evaluate digital images taken at RV1, TV1, EOS, and at HCV, if scheduled.
- Incidence of healing at end of study, as determined by the Investigator

"Healing" of the study ulcer is determined by the PI or designee. "Healing" is defined as 100% re-epithelialised without drainage as confirmed at the Healing Confirmation visit (HCV).

10.7.3 Participant reported secondary efficacy endpoints

Participant reported secondary efficacy endpoints are:

- Time from TV1 to clinically significant pain reduction measured using a Visual Analogue Scale (VAS) instrument. For the purpose of this protocol a clinically significant reduction of pain is a mean reduction of ≥ 20.65 mm or a mean decrease of ≥ 10-20% in pain as measured on a 0-100 mm VAS (23; 24).
- Time from TV1 to first instance of no study ulcer pain measured using VAS.

  (No pain = < 5mm on VAS when VAS scores: 0-4 mm = no pain; 5-44 mm = mild pain; 45-74 mm = moderate pain; and 75-100 mm = severe pain) (1).

- Pain score at EOT measured using VAS.
- Change from TV1 in QoL at EOT assessed using the CWIS.
- Change from TV1 in QoL at EOT assessed using EQ-5D-5L.

10.7.4 Safety Assessments

Safety will be assessed using the following parameters:

- Incidence of AEs

- Incidence of SAEs
- Incidence of study ulcer infection
- Incidence of study treatment related AEs (including geko™, compression bandaging and any dressings used to treat the study wound)
- Incidence of investigational device (geko™) related AEs
- Pain in the ulcer site (sudden onset of pain or increase in pain during the study Treatment Phase)

10.8 Participant Disposition

The disposition of all patients who sign an informed consent form (ICF) will be provided. The numbers of patients screened, randomised, completed, and discontinued during the study, as well as the reasons for all post-randomisation discontinuations will be summarised by treatment group, for all centres combined and each centre separately. Disposition and reason for study discontinuation will also be provided as a by-participant listing.

10.9 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarised by treatment group using appropriate descriptive statistics.

10.10 Analysis Populations

10.10.1 Intent to Treat Population

The Intent-to-Treat (ITT) population is defined as the set of randomised participants who have at least one post-randomisation efficacy assessment for wound healing. The ITT population will be the primary population for the analysis of primary and secondary endpoints.

10.10.2Per Protocol Population

The Per Protocol (PP) population is defined as the set of participants who meet the ITT population requirements, defined above, and who were not associated with a major protocol violation/deviation. This population will be identified before the database lock.

10.10.3 Safety population

The Safety population is defined as any participant receiving treatment after randomisation. This population will be used for the analysis of safety parameters.

10.11 Treatment Failures

Participants who are withdrawn or discontinue during the Treatment Phase and/or who do not achieve healing during the Treatment Phase will not be replaced and will be considered treatment failures.

10.12 Analysis Methods

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analysing the efficacy and safety data from this study.

All statistical tests will be two-sided and a 0.05% significance level maintained throughout the analyses.

10.12.1 Efficacy Analyses

Primary Endpoint: The primary efficacy endpoint is linear healing rate (LHR) from TV1 to EOT as compared with LHR from RV1 to TV1. LHRs will be measured by a blinded wound expert using digital images at RV1, TV1, and EOT.

Within treatment groups, treatment phase will be compared to run-in phase by paired non-parametric test (Wilcoxon signed rank). Effects will be compared between groups using non-paired non-parametric tests (Mann-Whitney).

Secondary Endpoints:

Weekly LHR shall be compared as above.

EOT healing status between groups shall be compared by Mann-Whitney U test on the PWAT scores. Weekly LHR can be tested using the same method (and same wording) as final LHR. Incidence of healing shall be compared between groups using Fisher's exact test.

Intra-group pain reduction measured on a visual analogue scale (VAS) will be analysed using paired t-test.

Inter group differences in time to clinically significant reduction in VAS shall be tested using Mann-Whitney u-test.

Intra-group changes to both Quality of Life (QoL) instruments in the study (CWIS and EQ-5D-5L) shall be tested using Wilcoxon signed rank test.

10.12.2 Safety Analyses

The Safety population will be used for the analysis of safety assessments.

For continuous variables data will be summarised by treatment using n, mean, SD, minimum and maximum values. For categorical variables data will be summarised by treatment using frequency and percentage.

10.12.2.1 Adverse Events

Adverse events will be coded using the latest version of MedDRA.

Separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

11 Adverse Events (Definitions and Reporting)

The Investigator or duly trained designee(s) will be responsible for detecting, documenting and reporting AEs and SAEs during this study as detailed in this section of the protocol.

11.1 Adverse Events

An adverse event (AE) is defined as any unfavourable or unintended sign, symptom, or disease that occurs or is reported by the participant to have occurred, or a worsening of a pre-existing condition. An AE may or may not be related to the study treatment.

AEs will be elicited through direct questioning and participant reports. Any abnormality in physical examination findings or laboratory results that the Investigator believes is clinically significant to the research participant will be reported as an AE. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

11.2 Reporting and Follow-up of Adverse Events

Report initiation for all AEs and serious adverse events (SAEs), (see Section 11.4) will begin at the time of the first run in phase visit and will be reported up until the final study visit. All events will be followed to resolution or until 30 days after the participant completes the study, whichever comes first. A final assessment of outcome will be made at that time.

AEs that emerge prior to the randomisation visit (TV1), will be recorded on an AE form. Aside from being used to determine participant eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to the patient receiving study treatment.

All AEs must be recorded in the participant's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is at the site of the study ulcer or at the site of the investigational device, whether the event is related to the study treatment, whether the event is related to the study ulcer, whether the event is considered to be an SAE (see Section 11.3), the impact the event had on study treatment (see Section 11.2.1), the Common Terminology Criteria for AEs (CTCAE) grade (intensity) of the event (see Section 11.2.2), the relatedness of the event (see Section 11.2.3), whether treatment was given as a result of the event (see Section 11.2.4), and the outcome of the event (see Section 11.2.5).

11.2.1 Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the participant is no longer in the treatment phase of the protocol.

11.2.2 Intensity Assessment

The guidelines outlined in CTCAE v4.03 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 3: Common Terminology Criteria for AEs v4.03 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.‡
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using telephone managing money etc	
† Self care ADL refer to bathing, dressing and undressing, feeding self, using toilet, taking medications, and not bed ridden.	
‡ Unlike the AE outcome assessment, a participant may have more than one Grade 5 event	

11.2.3 Relatedness Assessment

Adverse events will be assigned a relationship (relatedness) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relatedness of AEs to study treatment will be classified as follows:

- Not Related: No relationship exists between the AE and the treatment. The event is attributed to a pre-existing medical condition or an intercurrent event unrelated to the study product.
- Possibly Related: Follows the treatment, but may have developed as a result of an underlying clinical condition or treatments/interventions unrelated to the study product.
- Probably Related: Follows the treatment, but is unlikely to have developed as a result of the participant's underlying clinical condition or other treatment or other interventions.
- Definitely Related: Follows the treatment and physical evidence shows a convincing relationship to the treatment.

11.2.4 Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, therapy administered, surgery, or other (with a specification).

11.2.5 Outcome Assessment

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per participant is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given participant, only the primary cause of death will have an outcome of death.

11.3 Serious Adverse Events

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the participant is at immediate risk of dying from the adverse experience)
- Requires participant hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

11.4 Reporting of Serious Adverse Events

Once the Investigator becomes aware of an SAE, he/she must report the SAE to Sponsor within 24 hours.

Sponsor's SAE Contact:

Dr Kieron Day , PhD

Tel: +44 (0) 7921 106253

e-mail safety@firstkindmedical.com

A written SAE report must include a full description of the event. Additional supporting documentation may be requested and should be provided to Sponsor as and when it becomes available. Such documentation includes but is not limited to lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) or in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

11.5 SAE Follow-up

All events will be followed to resolution or until 30 days after the participant completes the study. A final assessment of outcome will be made at that time.

12 Direct Access to Source Data/Documentation

Participants will be identified on CRFs by a unique participant identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The participant identification number will be used if it becomes necessary to identify data specific to a single participant.

The monitors, auditors, personnel authorised by the Sponsor, the local IRB, and regulatory agencies are eligible to review medical and research records related to this study as a part of their responsibility to protect human participants in clinical research and will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that participant confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

13 Quality Control and Quality Assurance

13.1 Monitoring Requirements

In order to maintain knowledge of the progress of a study, the Sponsor's designated Clinical Research Associate (CRA)/monitor will visit the centres during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study participant original medical records (source documents) at regular intervals throughout the study. Participant original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but is not limited to, study, laboratory and diagnostic reports, wound images and tracings, quality of life questionnaire, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the CRFs, in accordance with applicable regulations. A Monitoring Log will be maintained at each study site which the monitor will sign, date and state the type of visit.

The Investigator should be aware that the study site and participant records might be inspected and audited by the Sponsor or representatives of Sponsor or relevant regulatory authorities.

13.2 Acceptability of Case Report Forms

A CRF must be completed for each participant who has signed an informed consent form. For patients who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed during or as soon as possible after the participant's visit. The Investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s CRA/ monitor, who will make a decision as to their acceptability.

13.3 Modification of Protocol

A modification or alteration to this protocol may not be undertaken without first obtaining the concurrence of Sponsor. Both the Lead Investigator and the Sponsor representative must sign and date the amendment prior to implementation. In addition, the Lead Investigator must report all protocol amendments to, and receive all required approvals from, the Institutional Review Board/Independent Ethics Committee (IRB/IEC) PRIOR to implementation of any protocol amendment at the study centre, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the participant; or
2. When the modification involves only logistics or administration.

In the event that a protocol change is proposed for all participants, the following procedure for a protocol amendment will be followed. An amendment must be in writing and it must be dated

by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to the appropriate regulatory authorities and notify other Investigators using this protocol.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor.

Any protocol amendments will be listed in the "Appendices" portion of the Table of Contents.

13.4 Reporting Protocol Deviations

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the participant will continue in the study. The Sponsor also has the right to discontinue the participant for protocol deviations/violations.

All protocol deviations must be documented in the CRFs.

14 Ethics and Regulatory Requirements

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, Good Clinical Practice (GCP) and currently applicable regulations.

No protocol changes will be implemented without the prior review and approval of the relevant IRB/IEC s, except where it may be necessary to eliminate an immediate hazard to a research participant (See Section 14.1).

Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable Good Manufacturing Practices (GMP) and the products provided for this study will be used only in accordance with this protocol.

14.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator will provide the IRB/IEC with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the participants or when the change involves only logistics or administration.

14.2 Investigator's Responsibilities

The Investigators are responsible for performing the study in full accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, Good Clinical Practice (GCP) and currently applicable regulations. Information regarding any study centres participating in this study that cannot comply with these standards will be documented.

14.3 Participant Informed Consent Requirements

Written and oral information about the study in a language understandable by the patient will be given to all patients by the Investigator and/or designee. Written informed consent will be obtained from each patient before any procedures or assessments that would not otherwise be required for the care of the patient are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the patient has been

given sufficient time to ask questions and consider participation in the study. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) is to be in compliance with Good Clinical Practice (GCP) guidelines. The Sponsor and/or designated Contract Research Organisation (CRO) will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the participant's study records, and a copy is provided to the participant. A second copy may be filed in the participant's medical record, if allowed by institutional policy.

15 Data Handling and Record Keeping

15.1 Recording and Collection of Data

The primary source document for this study will be the participant's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approved CRFs. The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the participant's visit.

The Principal Investigator (PI) will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the PI will need to again sign the Investigator signature page. Designated source documents will be signed and dated by the appropriate study personnel. Investigators must agree to complete and maintain source documents and CRFs for each participant in the study.

All research data will be entered, either electronically or manually, into a computerised database.

The PI will maintain a confidential list of study participants which will include each participant’s study number, name, date of birth and unique hospital identification number if applicable. This list will be kept by the PI and will not be collected by Sponsor. A notation will be made in the participant’s case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF. The PI must also maintain a separate screening log of all the patients screened for participation in the study; it should include gender; age; eligibility status; reason for ineligibility, if applicable; and study allocated participant number, if applicable.

15.2 Clinical Data Management

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor’s or CRO’s standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with applicable regulatory guidelines and the Sponsor’s SOPs as well as provisions of a study-specific Data Management Plan.

15.3 Archiving

All study documentation at the Study site and Sponsor site will be archived in accordance with Sponsor’s quality standards and SOPs.

The Study site will maintain all research records, reports, and case history reports for a period of 15 years after study closure.

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained at the Study site include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., participant's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Signed protocols and protocol amendments
- Product accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB/IEC
- Principal Investigator and co-Investigator(s) Curriculum Vitaes (CVs)
- Signed ICFs
- Patient screening and randomisation log
- SAE reports
- IRB/ICE approval letters and correspondence if applicable
- Completed QoL questionnaires
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Study site so that the conduct of the study can be fully documented and monitored.

16 Publication Plan

Manuscripts and abstracts will be prepared by both the Investigator(s) and the Sponsor. The results of the study may be published in scientific literature and may also be used in submissions to regulatory authorities. It is the intent of the Sponsor, and the Lead Investigator to publish or present the study results together with the other Investigators, unless specific permission is obtained in advance from the Sponsor to publish separate results. Co-authorship with any of the Sponsor's personnel will be discussed and mutually accepted upon submission of a manuscript or publication. Authorship will be decided upon in accordance with the ICMJE (International Committee of Medical Journal Editors) guidelines.

The publication process commences with Sponsor forming a Publication Committee. The Publication Committee will publish first. The Investigators can proceed with publication after publication by the Publication Committee.

All information concerning the Sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator and not previously published) is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. Investigators agree not to use it for other purposes without the Sponsor's prior written consent.

It is understood by the Investigators that the Sponsor will use the information developed in this clinical study in connection with the development of the geko^{TM}. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this study.

Publication and Disclosure: Because this is a multi-centre study, site and Investigator shall not independently publish, publicly disclose, present or discuss any results of or information pertaining to site's and Investigator's activities conducted under this agreement until such a multi-centre publication is released under Sponsor's direction; provided, however, that if a publication is not released within eighteen (18) months after completion of analysis of all study data from all studies conducted within the multi-centre study, site and Investigator shall have the right to publish the results of and information pertaining to site's and Investigator's activities conducted under this protocol and the clinical study agreement. Site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least sixty (60) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within sixty (60) days of its receipt, Sponsor shall advise site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair sponsor's ability to obtain patent protection. Sponsor shall have the right to require site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or

delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. Site and Investigator shall not publish, publicly disclose, present or discuss any results of or information: (a) pertaining to site's and Investigator's activities prior to completion of the study, even if the multi-centre study or the study is terminated before its completion and the final clinical study report is signed off, or (b) with respect to any endpoints or analyses other than those specified in this protocol.

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18 APPENDICES

Appendix 1: Instructions for Use and Fitting Instructions geko™ Devices

Sent under separate cover.

Appendix 2: Photographic Wound Assessment Tool (PWAT)

TABLE 1
PHOTOGRAPHIC WOUND ASSESSMENT TOOL

Domain	Assessment	Date Score
1. Edges	0 = Indistinct, diffuse, none clearly visible 1 = Distinct, outline clearly visible, attached, even with wound base 2 = Well-defined, not attached to wound base 3 = Well-defined, not attached to base, rolled under, thickened 4 = Well-defined, fibrotic, scarred or hyperkeratonic	
2. Necrotic Tissue Type	0 = None visible 1 = White/gray nonviable tissue and/or nonadherent yellow slough 2 = Loosely adherent yellow slough 3 = Adherent, soft, black eschar 4 = Firmly adherent, hard, black eschar	
3. Necrotic Tissue Amount	0 = None visible 1 = < 25% of wound bed covered 2 = 25% to 50% of wound covered 3 = > 50% and < 75% of wound covered 4 = 75% to 100% of wound covered	
4. Skin Color Surrounding Wound	0 = Pink or normal for ethnic group 1 = Bright red 2 = White or gray pallor or hypopigmented 3 = Dark red or purple 4 = Black or hyperpigmented	
5. Granulation Tissue	0 = Skin intact or partial-thickness wound 1 = Bright, beefy red; 75% to 100% of wound filled and/or tissue overgrowth 2 = Bright, beefy red; < 75% and > 25% of wound filled 3 = Pink, and/or dull, dusky red and/or fills ≤ 25% of wound 4 = No granulation tissue present	
6. Epithelialization	0 = 100% wound covered, surface intact 1 = 75% to < 100% wound covered and/or epithelial tissue extends > 0.5 cm into wound bed 2 = 50% to < 75% wound covered and/or epithelial tissue extends > 0.5 cm into wound bed 3 = 25% to < 50% wound covered 4 = < 25% wound covered	
TOTAL SCORE		
SIGNATURE		

Appendix 3: Venous Ulcer Clinical Severity Score

Pain	☐None ☐Occasional, not restricting activity or requiring analgesia ☐Daily, moderate activity limitation, occasional analgesia ☐Daily, severe limiting activities or requiring regular use of analgesia
Varicose veins	☐None ☐Few, scattered, branch varicose veins ☐Multiple: greater saphenous varicose veins confined to calf or thigh ☐Extensive: thigh and calf or greater saphenous and lesser saphenous distribution
Venous Edema	☐None ☐Evening ankle edema only (edema must be a daily occurrence) ☐Afternoon edema, above ankle (edema must be a daily occurrence) ☐Morning edema above ankle and requiring activity change, elevation (edema must be daily occurrence)
Skin pigmentation	☐None or focal low intensity (tan) (focal pigmentation over varicose veins does not apply) ☐Diffuse, but limited in area and old (brown) ☐Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple) ☐Wider distribution (above 1/3) and recent pigmentation
Inflammation	☐None ☐Mild inflammation, limited to marginal area around ulcer ☐Moderate inflammation, involves most of the gaiter area (lower 1/3) ☐Severe inflammation (lower 1/3 and above) or significant venous eczema
Induration	☐None, ☐Focal, circum-malleolar (<5cm)

	☐Medial or lateral (< lower 1/3), ☐Entire lower 1/3 or leg or more
Number of active ulcers	☐0, ☐1, ☐2, ☐>2
Active ulceration, duration	☐None, ☐< 3 months, ☐3 – 12 months, ☐> 12 months
Active ulcer, size (largest ulcer dimensions)	☐None, ☐< 2cm diameter ☐2 – 6 diameter, ☐> 6 diameter
Compression therapy	☐Not used or not compliant, ☐Intermittent use of bandages ☐Wears bandages most of the time, ☐Full compliance

Appendix 4: EQ-5D-5L Questionnaire

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

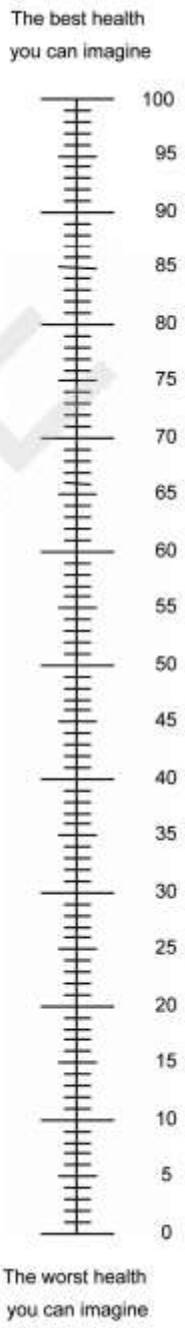
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 5: Cardiff Wound Impact Schedule (CWIS)

The following questionnaire is concerned with the effects that your wound has on your daily life. Please answer the questions carefully by placing a tick in the box which most closely reflects how you feel; it should take about ten minutes to complete.

If you are unsure about how to answer a question, please tick the answer which is closest to how you feel. All answers are confidential.

Personal Details

Patient Initials ☐☐☐ **Patient Number** ☐☐☐☐

Gender M ☐ F ☐ (Please circle)

Date of Birth D D M M M Y Y

Assessment Date D D M M M Y Y

Assessment 1st ☐ 2nd ☐ 3rd ☐ 4th ☐ 5th ☐ (Please circle)

Next Assessment Due D D M M M Y Y

Wound status Healed ☐ Not Healed ☐

Do you live on your own? Yes ☐ No ☐

How often do you see your family and friends?

Once a day ☐ Once a month ☐

Once a week ☐ Less than once a month ☐

Social Life

How <u>stressful</u> has this experience been for you?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Difficulty getting out and about	☐	☐	☐	☐	☐
Relying more on others	☐	☐	☐	☐	☐
Your family/friends being over protective	☐	☐	☐	☐	☐
Unable to enjoy your usual social life (eg hobbies)	☐	☐	☐	☐	☐
Limited contact with family/friends	☐	☐	☐	☐	☐
Not going out for fear of bumping your wound site	☐	☐	☐	☐	☐
Wanting to withdraw from people	☐	☐	☐	☐	☐

Social Life

Have you <u>experienced</u> any of the following during the past week?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Difficulty getting out and about	☐	☐	☐	☐	☐
Relying more on others	☐	☐	☐	☐	☐
Your family/friends being over protective	☐	☐	☐	☐	☐
Unable to enjoy your usual social life (eg hobbies)	☐	☐	☐	☐	☐
Limited contact with family/friends	☐	☐	☐	☐	☐
Not going out for fear of bumping your wound site	☐	☐	☐	☐	☐
Wanting to withdraw from people	☐	☐	☐	☐	☐

Well-being

To what extent do you agree/disagree with the following statements?

	Strongly Disagree	Disagree	Not Sure	Agree	Strongly Agree
I feel anxious about my wound(s)	☐	☐	☐	☐	☐
I feel frustrated at the time it is taking for the wound(s) to heal	☐	☐	☐	☐	☐
I am confident that the wound(s) I have will heal	☐	☐	☐	☐	☐
I worry that I may get another wound in the future	☐	☐	☐	☐	☐
The appearance of the wound site is upsetting	☐	☐	☐	☐	☐
I feel anxious about bumping the wound site	☐	☐	☐	☐	☐
I worry about the impact of the wound(s) on my family/friends	☐	☐	☐	☐	☐

Physical Symptoms and Daily Living

Have you <u>experienced</u> any of the following during the past week?

	Not at all/ Not applicable	Seldom	Sometimes	Frequently	Always
Disturbed sleep	☐	☐	☐	☐	☐
Difficulty in bathing	☐	☐	☐	☐	☐
Immobility around the home	☐	☐	☐	☐	☐
Immobility outside the home	☐	☐	☐	☐	☐
Leakage from the wound	☐	☐	☐	☐	☐
Pain from the wound site	☐	☐	☐	☐	☐
Discomfort from the bandaging/dressing	☐	☐	☐	☐	☐
Unpleasant odour or smell from the wound	☐	☐	☐	☐	☐
Problems with everyday tasks (eg shopping)	☐	☐	☐	☐	☐
Difficulty in finding appropriate footwear	☐	☐	☐	☐	☐
Problems with the amount of time needed to care for the wound site	☐	☐	☐	☐	☐
Financial difficulties as a result of the wound	☐	☐	☐	☐	☐

Physical Symptoms and Daily Living

How <u>stressful</u> has this experience been for you?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Disturbed sleep	☐	☐	☐	☐	☐
Difficulty in bathing	☐	☐	☐	☐	☐
Immobility around the home	☐	☐	☐	☐	☐
Immobility outside the home	☐	☐	☐	☐	☐
Leakage from the wound	☐	☐	☐	☐	☐
Pain from the wound site	☐	☐	☐	☐	☐
Discomfort from the bandaging/dressing	☐	☐	☐	☐	☐
Unpleasant odour or smell from the wound	☐	☐	☐	☐	☐
Problems with everyday tasks (eg shopping)	☐	☐	☐	☐	☐
Difficulty in finding appropriate footwear	☐	☐	☐	☐	☐
Problems with the amount of time needed to care for the wound site	☐	☐	☐	☐	☐
Financial difficulties as a result of the wound	☐	☐	☐	☐	☐

Overall Quality of Life

How would you rate your overall quality of life during the past week?

Please circle a number below (Score = number as circled)

How good is your quality of life?

My quality of life is the worst possible	0	1	2	3	4	5	6	7	8	9	10	My quality of life is the best possible

How satisfied are you with your overall quality of life?

Not at all satisfied	0	1	2	3	4	5	6	7	8	9	10	Very satisfied

Overall Comment(s)

Appendix 6: Participant Diary

Dear Participant,

Please use this sheet to keep a record of your geko™ use over the course of the study. If you are unable to use the geko™ device for any reason, please contact your doctor or research nurse as soon as possible. Please use the geko™ device daily as instructed. If you forget to use completely, record on this sheet that the geko™ device was not used. Do not try to squeeze in extra doses by using the geko™ device for longer periods the next day.

Participant ID - xxxxx

TVx - TVx					
Date dd/mm/yyyy	**Time you switched on the geko™ device (use 24hour format or include am/pm)**	**Time you switched off the geko™ device (use 24hour format or include am/pm)**	**Device setting (Please circle the setting used)**	**Label**	**Any comments**
		Device turned off by itself ☐	1 2 3 4 5 6 7 8 9 10	Please insert the label on geko™ device pouch here	
		Device turned off by itself ☐	1 2 3 4 5 6 7 8 9 10	Please insert the label on geko™ device pouch here	
		Device turned off by itself ☐	1 2 3 4 5 6 7 8 9 10	Please insert the label on geko™ device pouch here	
		Device turned off by itself ☐	1 2 3 4	Please insert the label on geko™ device pouch here	

			5 6 7 8 9 10		
		Device turned off by itself ☐	1 2 3 4 5 6 7 8 9 10	Please insert the label on geko™ device pouch here	
		Device turned off by itself ☐	1 2 3 4 5 6 7 8 9 10	Please insert the label on geko™ device pouch here	
		Device turned off by itself ☐	1 2 3 4 5 6 7 8 9 10	Please insert the label on geko™ device pouch here	

To be completed by the investigator

Date collected the completed diary –

Initials of the person collected –

Signature of the person collected –

Appendix 7: Protocol Amendments

Details of any protocol amendments following Ethics Committee approval to be recorded here

Change	Updated Protocol Version Number and Date	Details of Change
1	10.5 16/04/2018	Updates to inclusion/exclusion criteria, minor corrections
2	10.6 15/10/2018	Updates to inclusion exclusion criteria & adding Follow-up phase
3	10.7 14/01/2019	Removal of the words '*high level*' from '*multilayer, multicomponent high level compression therapy*'

5	10.8 16/08/2019	Minor spelling corrections and the following amendments: 1. Addition of details for Clinical Affairs Manager to page 2 2. Addition of Firstkind Ltd Head of Clinical Affairs to Protocol Approval Page 3. Addition of wording '*or within 8 weeks of study entry (i.e. RV1)'* to inclusion criterion 7, section 4.1 Run-in Phase, Schedule of Events and section 9.2 ABPI 4. Removal of wording from section 4.1 Run-in Phase '*Any AEs during run in phase are to be recorded in the participant's medical history'* 5. Removal of the wording '*and that occurred after initiation of the Treatment Phase of the study'* from section 11.1 6. Addition of the wording *'in the run in phase'* and *'AEs will be*

		recorded on an AE form' to section 11.2 7. Sponsor SAE contact details updated on page 61
6	28/08/2019	1. Addition of the wording '. *At the randomisation visit, the study ulcer needs to be ≥ 2 cm2 and ≤ 30 cm^2. If other ulcerations are present on the same leg, they need to be at least 2cm away from the study ulcer*' to section 4.2.2 2. Inclusion Criterion 6 - 0.8-1.2 replaced with 0.75-1.24
7	28/10/2019	1. Addition of Appendix 8 Sub-study 2. Addition of geko™ W-2, XW-2 & T-3 IFU to Appendix 1
8	V11.0	1. Change in Project Manager details 2. Analysis change from PAR to LHR 3. Interim Analysis changed from 60% randomized to 60% enrolled. 4. Addition of Vidal reference
9	V12.0	1. Removal of 6h geko™ 2. Results of Interim Analysis 3. Inc Criteria 4: Two separate wounds not allowed

Appendix 8: Sub-study to the VLU efficacy study at selected clinical sites to determine whether oedema prevents neuromuscular stimulation by the geko™ device in a sub-set of VLU patients.

Introduction

The VLU Efficacy Study has shown an un-expected number of patients who do not respond to the W-2 geko™ device. In the parent study, 24% of patients were found to be non-responders to stimulation by the device as evidenced by a lack of dorsiflexion, the involuntary movement of the lower leg / foot at the maximum tolerable device setting. This is in contrast to a study following orthopaedic patients after total knee replacement, where only 5% of patients were found not to respond to stimulation by the device (unpublished data).

It is thought that excessive oedema in the area of the geko™ device application site may be preventing neuromuscular stimulation in VLU patients in the parent study.

In this sub-study, the sub-set of non-responders from the parent study, instead of being excluded, may continue in the study and receive their standard care with the aim to reduce oedema during the Run-in Phase. Subjects will also be evaluated at the start of the Run-in Phase for their response to a higher out-put T-3 geko™ device and tested weekly
through-out the Run-in Phase with both W-2 or variant and T-3 geko™ devices. At the end of the Run-in Phase and following re-evaluation of their response to the W-2 or variant geko™ device, responders to the W-2 or variant geko™ device will re-join the treatment phase of the main protocol. Non-responders will be excluded at this stage.

It is hoped the results from this sub-study will show a positive correlation between treatment of excessive leg oedema and response to neuromuscular stimulation by the W-2 or variant geko™ device in VLU patients previously identified as non-responders in the VLU Efficacy Study.

This may be of two fold benefit to these patients:

1. Addressing oedema may ameliorate complications associated with untreated and persistent oedema, which can impede wound healing by obstructing blood flow throughout the body and to the wound site resulting in hypoxia, a key factor known to limit wound healing (15)
2. Treatment of oedema may also facilitate neuromuscular stimulation by the W-2 or variant geko™ device thus increasing blood flow, circulation and delivery of oxygen to the wound site (17, 19, 20, 21)

Study Objectives

This sub-study seeks to determine whether oedema in the area of the W-2 geko™ or variant device application site prevents neuromuscular stimulation by the device.

Subject Population

Subjects will be a sub-set of subjects enrolled in the parent study at selected sites, following the same Inclusion / Exclusion criteria as per Section 3 of the main protocol, but who **do not** respond to the W-2 or variant geko™ device i.e. subjects who do not have an involuntary movement (dorsiflexion) of the lower leg / foot at the maximum tolerable device setting without the compression bandaging in place. Subjects must also have evidence of oedema, as determined by the Venous Clinical Severity Score (see section 4.1 of main protocol and Castor EDC - step 13).

A total of 20 subjects may qualify for participation.

Obtaining a separate informed consent for participation in the sub-study is not required and a subject may withdraw their consent to participate in the sub-study at any time as per Section 5 of the main protocol.

The investigator can withdraw a subject from the sub-study, if in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with elements of the sub-study protocol that are critical for safety or necessary for the scientific integrity of the study. If the investigator withdraws a subject from the study, the investigators will explain the reason for withdrawing the subject.

Study Schedule

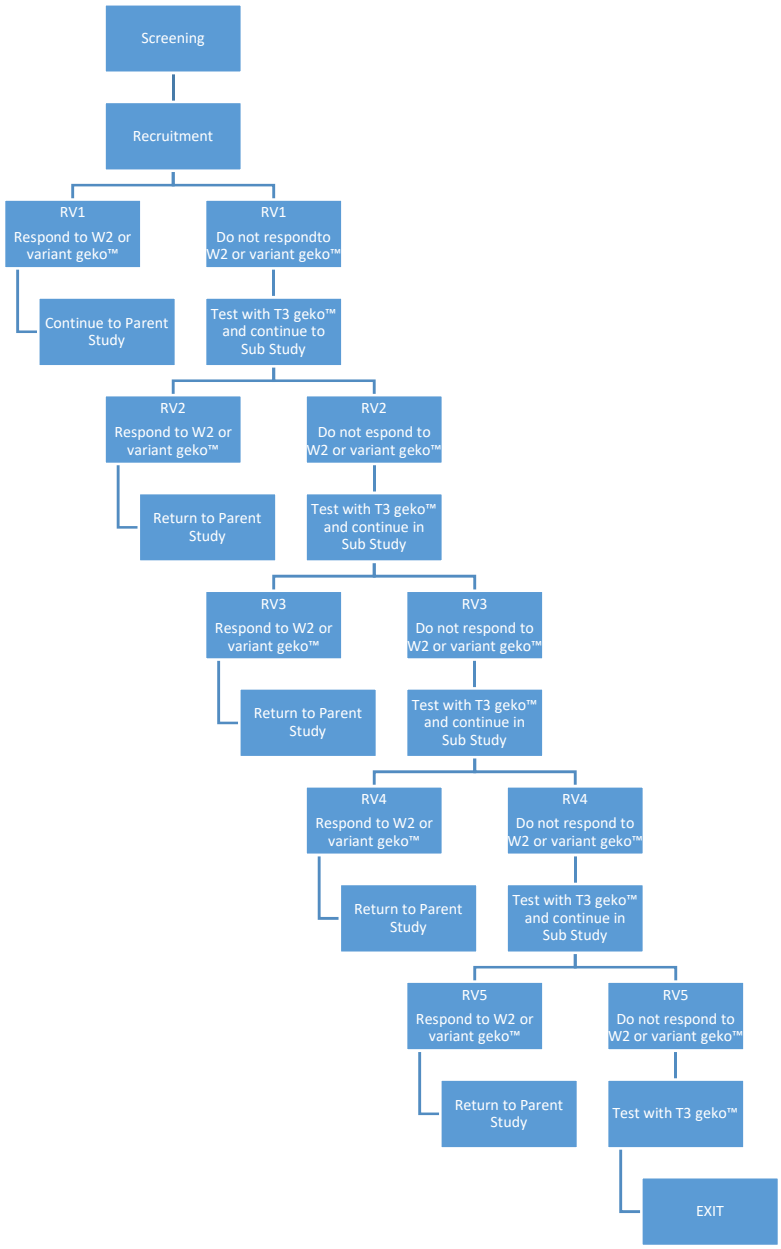
All sub-study visits will be conducted according to the same time frame outlined in the Study Schedule (Section 4) of the existing main protocol. A schematic picture of the sub-study flow is provided in Figure1.

Run-in Phase

During the Run-in Phase, subjects will be evaluated on a weekly basis and study assessments performed as follows, see also Table 1.

- Remove compression bandaging
- Confirm subject **does not** respond to the W-2 or variant geko™ device by absence of dorsiflexion an involuntary movement of muscles in the lower leg / foot at the maximum tolerable device setting If subject does not respond, test subject's response to the higher out-put T-3 device. Subject's **do not** need to exhibit a positive response to the T-3 geko™ device to continue in the sub-study (RV1 only). Note: It is important that the device is applied to clean dry skin. Prior to application of the device, skin should be washed with mild soapy water, rinsed and dried thoroughly. Do NOT apply moisturiser at the device fitting site
- Measure ABPI if a valid ABPI reading has not been taken within 8 weeks of RV1 (RV1only)
- Confirm eligibility (RV1 only). If the patient is eligible, continue with the following procedures.
  Note: qualified subjects who do not wish to participate in the sub-study are not eligible to continue in the main study and an early termination eCRF should be completed in EDC.
    - Record medical history and study ulcer history (RV1 only).
    - Administer the CWIS and EQ-5D-5L questionnaires in the participant's primary language (RV1 only).
    - Perform physical examination and assess Body Mass Index (RV1 only).
    - Assess concomitant medications (con-meds) and update con-med form in EDC as appropriate).
    - Assess compression bandaging (See Section 9.8).

Figure 1. Sub-study flow chart



- Assess leg oedema using a tape measure to determine leg circumference at the level of the geko™ device application site. Using an indelible surgical pen, mark a reference point on the leg, to ensure weekly measurements are taken at the same place on the leg.
- Record study ulcer location, history and duration (RV1 only).
  Note: 'Study ulcer location' is defined by the ulcer being on the left or right leg, by the location of the ulcer on the malleolus, low gaiter or high calf, and by the positioning of the ulcer as lateral, medial, anterior or posterior.
- Administer the study ulcer pain VAS assessment.
- Determine Venous Clinical Severity Score (RV1 only) Assess for AEs - Any AEs occurring during the Run-in Phase are to be recorded on an AE form in EDC.
- Cleanse the study ulcer.

- Obtain a digital image of the study ulcer (if debridement is planned, this is the Pre-debridement image). Note: all study ulcer measurements will be performed using the pre-debridement images.
- At the discretion of the Investigator, perform debridement of the study ulcer to obtain a clean, granulating ulcer base with minimal adherent slough.
- If applicable, obtain a post-debridement digital image of the study ulcer
- Apply standard care. A non-adherent (NA) wound contact dressing and/or an absorbent dressing may be used at Investigator's discretion if required in addition to the compression system.
- Record all dressing use
- Assess for any AEs since signing ICF
- Schedule next study visit in one week's time
-

The Run-in phase ends with RV5/TV1 which is also the first visit of the Treatment Phase.

Treatment Phase

At the first Treatment Phase (TV1), once compression bandaging has been removed, confirm subject's response to the W-2 or variant geko™ device by presence of involuntary movement of muscles (dorsiflexion) in the lower leg / foot at the maximum tolerable device setting. If the subject does not respond to the W-2 or variant device the subject should be exited from the study and an early termination eCRF completed in EDC.

Once a subject's continued eligibility has been confirmed, randomisation and assignment to study treatment will take place and the subject will re-join the Treatment Phase of the main protocol and assessments completed as per the main protocol from section 4.2 onwards. Statistical analysis will be carried out using the Student's t-test

Table 1. Run-in Phase: Schedule of Sub-Study Assessments (assessments in bold are sub-study specific)

Activity/Assessment	RV1	RV2	RV3	RV4	RV5/TV1
Informed consent	√				
Remove compression bandaging and assess response to W-2 or variant geko ™	√∞	√∞	√∞	√∞	√∞
Asses response to T-3 geko ™	√∞	√∞	√∞	√∞	√∞
Ankle-Brachial Index (ABPI) if a valid ABPI reading has not been taken within 8 weeks of RV1	√				
Confirmation of eligibility	√				
Assessment of leg oedema	√¥	√¥	√¥	√¥	√¥
Medical history	√				
CWIS, EQ-5D-5L and assessments	√				
Physical examination and BMI	√				
Concomitant medications	√	√	√	√	√
Assessment of compression bandaging	√	√	√	√	√
Study ulcer history	√				
Study ulcer pain (VAS) assessment	√	√	√	√	√
Venous Clinical Severity Score	√				√
Assess for AEs		√	√	√	√
Study ulcer cleaning	√	√	√	√	√
Study ulcer surrounding skin assessment	√				
Study ulcer image(s)	√⌘	√⌘	√⌘	√⌘	√⌘
Study ulcer debridement	√§	√§	√§	√§	√§
Application of compression	√¶	√¶	√¶	√¶	√¶
Assessment for AEs since signing ICF	√	√	√	√	√
Scheduling of next visit	√	√	√	√	√

∞ **Presence of involuntary movement (dorsiflexion) of muscles in the lower leg and dorsiflexion of the foot at the maximum tolerable device setting W-2 or variant and T-3 before addition of compression bandaging**

¥ **Assess leg oedema using a tape measure to determine leg circumference at the level of the geko™ device application site. .Using an indelible surgical pen, mark a reference point on the leg, to ensure weekly measurements are taken at the same place on the leg.**

§ Study ulcer debridement at Investigator's discretion. N.B All study ulcer measurements will be performed using the pre-debridement images.

⌘ If debridement is performed a pre-debridement and a post-debridement image is taken.

¶ A non adherent (NA) wound contact dressing and/or an absorbent dressing may be used at Investigator's discretion if required in addition to the compression system.