# Randomized Trial Comparing a Dual Action Pneumatic Compression System against Multi-Layer Bandaging Systems: A non-inferiority study

## Protocol# 6010

## 27 September 2016

## Protocol Version 2.0

**Investigator Signature**

Protocol Title: Randomized Trial Comparing a Dual Action Pneumatic Compression System against Multi-Layer Bandaging Systems: A non-inferiority study

Protocol Number: 6010
Version: 2.0; 27 September 2016

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practices (GCP), the International Conference on Harmonization Guidelines, Therapeutic Goods Act, institutional research policies, and procedures and other appropriate regulatory requirements.

_____
Site Principal Investigator Name (Print)

_____ _____
Site Principal Investigator Signature Date

SYNOPSIS

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|---|---|
| **Title of Study** | Randomized Trial Comparing A Dual Action Pneumatic Compression System against Multi-Layer Bandaging Systems: A non-inferiority study |
| **Protocol Date** | 27 September 2016 |
| **Protocol Version** | V 2.0 |
| **Name of Sponsor** | Tactile Medical™ |
| **Investigational Product** | ACTitouch Adaptive Compression System |
| **Primary Endpoint** | Percentage of ulcer area reduction at 16 weeks, comparable |
| **Secondary Endpoint** | HRQOL; outpatient cost per subject |
| **Objectives:**<br>Demonstrate the following when comparing ACTitouch Adaptive Compression to multi-layer bandaging:<br>• Comparable rate of healing<br>• Greater improvement in QOL<br>• Lower overall cost of care; lower resource utilization (in clinic time; clinic charges; patient treatment burden) | |
| **METHODOLOGY** | |
| **Study Design** | Open label, non-inferiority, two arm, prospective, stratified, multi-center, randomized controlled trial (RCT) |
| **Treatments** | Daily ACTitouch usage; at least 12 hours sustained mode; two hours of Intermittent Pneumatic Compression (IPC) mode<br>Multi-Layer Bandage (MLB): 24 hours except during clinic visits |
| **Treatment Duration** | Run-in – 2 Weeks<br>Study treatment duration – 16 Weeks<br>Follow Up – 3 months (Subjects in the ACTitouch arm who heal during the treatment period.) |
| **SUBJECT POPULATION** | |
| **Number Planned** | 204 randomized subjects; 102 in each study arm |
| **Major Inclusion/ Exclusion Criteria** | Inclusion:<br>• Subject must be ≥ 18 years of age or legal age at the time of enrollment.<br>• Chronic venous insufficiency confirmed by ultrasound within previous 12 months or prior to randomization.<br>• Must have at least one of the following within the past 6 months:<br>o Dorsalis Pedis (DP) systolic pressure ≥ 80mmHg for diabetic patients or ≥ 60mmHg for non-diabetic patients on study limb<br>o Posterior Tibial (PT) systolic pressure ≥ 80mmHg for diabetic patients or ≥ 60mmHg for non-diabetic patients on study limb<br>o Transcutaneous partial pressure oxygen (TcP02) > 30mmHg<br>o Great toe systolic pressure > 40mmHg<br>• Active ulceration (CEAP classification of C6).<br>• Ulcer duration: Non healing VLU ≥ 1 month but not greater than 24 months.<br>• Ulcer size ≥ 2cm$^2$ ≤ 50cm$^2$.<br>• Three or fewer separate full thickness ulcers on the study limb.<br>o Sum of the ulcer areas on the study limb must be ≤ 50cm$^2$ to participate in the study.<br>• Must be able and willing to provide informed consent prior to study |

| | |
|---|---|
| | participation.<br><br>Exclusion:<br>• Target ulcer or any other ulcer on the study limb involves exposure of tendon, muscle, or bone.<br>• Treatment of the target ulcer with living cellular therapy within 30 days of the time of projected randomization.<br>• Endovenous ablation or other venous surgery within two weeks of enrollment.<br>  o Venous ultrasound must be completed after procedure to determine whether there is still venous insufficiency at the time of enrollment.<br>• Acute deep vein thrombosis (DVT) or pulmonary embolism (PE) within the last 3 months.<br>• Acute thrombophlebitis within the last 6 weeks.<br>• History of pulmonary edema or decompensated congestive heart failure within 6 weeks of screening.<br>• Currently has an active infection of the skin on target limb such as cellulitis requiring antibiotics.<br>• History of target limb cancer within the last 2 years with the exception of treated non-melanoma skin cancer unless ulcer biopsy performed at screening is negative for neoplasia.<br>• Active cancer receiving chemotherapy and/or radiation therapy.<br>• Poorly controlled diabetes with an HbA1c value of > 12% within the past 3 months.<br>• Changes to medications that affect edema within the last 30 days.<br>• Use of systemic corticosteroids requiring daily administration at doses greater than 5 mg of Prednisone per day or equivalent for greater than 2 weeks.<br>• Currently pregnant or trying to become pregnant.<br>• Inability or unwillingness to participate in all aspects of study protocol.<br>Exclusions after a 2 week run-in:<br>• If ulcer area has decreased by greater than 30% compared to baseline area, the subject will be removed from the study.<br>• Ulcers measuring less than 1.5cm² after the run in.<br>• Ulcers increasing in size greater than 50% after run.<br>• Any ulcer appearing to have evidence of infection.<br>• If the sum of the ulcer areas on the study limb is > 50cm$^2$ the subject is not eligible to participate in the study. |
| **ASSESSMENTS** | |

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| **Efficacy *[If applicable]*** | Group 1: Multi-Layer Bandage<br>• Will be seen in clinic once per week for:<br>  o Wound assessment<br>  o wound dressing changes, debridement, if necessary, as determined by the treating study investigator<br>  o wound tracing; photo<br>  o limb volume measurements<br>• Subjects will be instructed to wear the MLB 24 hours daily, except upon removal and re-application during weekly clinic visits with debridement as determined necessary by PI<br>Group 2: ACTitouch Adaptive Compression System<br>• Will be seen in the clinic at weeks 1, 2, 4, 6, 9, 12, 16 during the treatment period. Subjects who experience complete healing of the study VLU will return to the investigational site 1, 2 and 3 months post heal.<br>  o wound assessment, as applicable<br>  o wound dressing changes, debridement, if necessary, as determined by the treating study investigator<br>  o wound tracing; photo, as applicable<br>  o limb volume measurements<br>• Subject will be instructed to wear the AT in sustained mode for a minimum of 12 hours per day plus 2 hours IPC mode. |
| **Safety** | Adverse event monitoring<br>Subject interview<br>Physical examination |

TABLE OF CONTENTS

## 1.0 Contact Information:

1.1 Sponsor Contact Information

Tactile Medical™

1.2 Study Principal Investigator Information

## 2.0 Abbreviations:

| | |
|---|---|
| ABI | Ankle Brachial Index |
| AE | Adverse Event |
| CEAP | Clinical-Etiology-Anatomy-Pathophysiology |
| CFR | Code of Federal Regulations |
| CRFs | Case Report Forms |
| CVD | Chronic Vascular Disease |
| CVI | Chronic Venous Insufficiency |
| DSMB | Data Safety Monitoring Board |
| DVT | Deep Vein Thrombosis |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practices |
| HRQOL | Health-Related Quality of Life |
| ICH | International Conference on Harmonization |
| IPC | Intermittent Pneumatic Compression |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| MLB | Multi-Layer Bandaging |
| MITT | Modified Intent-to-Treat |
| QOL | Quality of Life |
| RCT | Randomized Controlled Trial |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| U/S | Ultrasound |
| VLU | Venous Leg Ulcer |
| VSU | Venous Stasis Ulcer |
| IWRS | Web-Based Randomization Process |

*The term ulcer and wound are used interchangeably throughout this document.

## 3.0 Introduction:

### 3.1 1 Background and Rationale:

Up to 1% of the adult population in developed countries will suffer from leg ulceration during their lifetime.[1] The most severe form of CVI is when limb ulceration occurs due to chronic venous hypertension. It is estimated that the prevalence of venous leg ulceration (VLU) is between 1 and 1.5 million patients in the United States.

It is important to address the underlying hemodynamic problem associated with chronic venous insufficiency rather than focusing solely on wound healing.[2] Treatment for chronic venous disease relies on provision of adequate external compression therapy to diminish venous hypertension, as these therapies diminish progressive dilation of incompetent veins, may help close the damaged valves, and diminish the accumulation of extravascular fluid.[3] Compression is a key component of treatment guidelines for the management of VLU.

The current standard of care in the treatment of VLUs is wound management in conjunction with compression therapy to promote venous return and reduction in edema.[4,5] Options for limb compression treatment include compressive garments, use of multi-layer bandage systems, and paste bandage systems.[2,3,6] Despite the inclusion of high strength compression in numerous VLU treatment guidelines, it is estimated that as many as 50% of VLUs never receive this type of therapy. In part, the reason for poor utilization of compression therapy is that most patients find the therapy difficult to use, due to difficulties in applying compression garments and/or pain or discomfort associated with use of the garment itself. To date, compression bandaging remains the most commonly used therapy in the treatment of VLUs.[3,7]

Therefore, effective compression treatment must be easy to use (don and doff) and must be comfortable as key factors likely to increase patient compliance.[8,9] Intermittent pneumatic compression (IPC) treatment is one alternative.[8] IPC was introduced as an adjunct treatment for VLU in 1981 which led to growing support for IPC as a treatment modality for patients with VLUs.[10] IPC is a mechanical method of delivering compression that uses an air pump to periodically inflate/deflate bladders incorporated into sleeves which envelop the limb.[11,12]

Published studies have demonstrated significant hemodynamic and hematologic improvement with IPC, as well as increases in ulcer healing rates when IPCs are used with standard compression therapy.[8,13,14]

Harding et al. compared the efficacy and tolerability of the ACTitouch device to that of a conventional multi-layer bandaging system when treating VLUs.[15] In this trial, the ulcer healing rate between the ACTitouch group and the conventional four-layer system group was similar. However, the ACTitouch performed significantly better in several key areas related to patient quality of life including, exudate management, skin protection, removal ease, bathing, and sleep comfort.

This study provides evidence to suggest that the ACTitouch system is as effective as four layer bandaging systems in healing venous leg ulcers, but is better accepted and achieves higher patient-reported quality-of-life scores in these challenging patients.

3.2 2 Device Descriptions:

**ACTitouch** – ACT - Adaptive Compression Therapy Delivery System (Tactile

**PROFORE** (Smith & Nephew, Hull, United Kingdom) is a multi-layer compression bandaging system developed to apply sustained graduated compression for the management of venous leg ulcers and associated conditions. Four-layer compression bandaging is often the first choice in treatment for venous leg ulcers.[16]
The four-layer system consists of a single layer of orthopedic wool applied in a spiral from toe to knee, followed by a crepe bandage applied in a spiral, an elastic long stretch bandage applied by the figure of eight method and finally a cohesive bandage applied in a spiral (Appendix B). PROFORE provides approximately 40mmHg pressure at the ankle decreasing to 17mmHg at the knee.[17]

**Coban™ 2 Compression System** (3M Health Care, St. Paul, MN, USA) is composed of two latex free layers that combine to create an inelastic sleeve conforming to the limb contour to provide a consistent proper pressure profile to

reduce edema. The Coban 2 compression system is indicated for patients with venous leg ulcers, lymphedema, and other conditions where compression therapy is appropriate.

The two-layer system consists of an inner "comfort" layer made of a polyurethane foam and cohesive bandage. The outer layer is a cohesive bandage, designed to provide graduated compression. Inner and outer layer cohere to each other to reduce slippage. Application of the compression system should be done according to the manufactures instructions as outlined in the Instructions for Use (Appendix C).

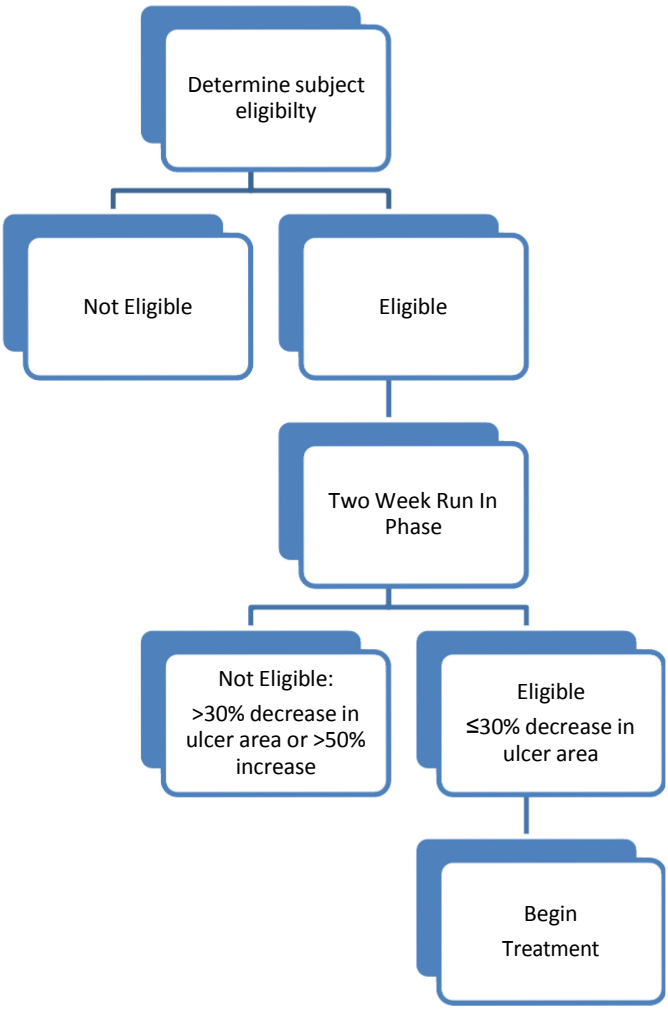
## 4.0 Study Objectives:

The primary study objectives:
Test non-inferiority of chronic VLU area reduction at 16 weeks with ACTitouch therapy compared to a standard regimen of multi-layer bandaging.
The secondary study objectives:
Assessment of the effect of the ACTitouch compared to a standard regimen of multi-layer bandaging at 16 weeks on health related quality of life (HRQOL) and outpatient costs.

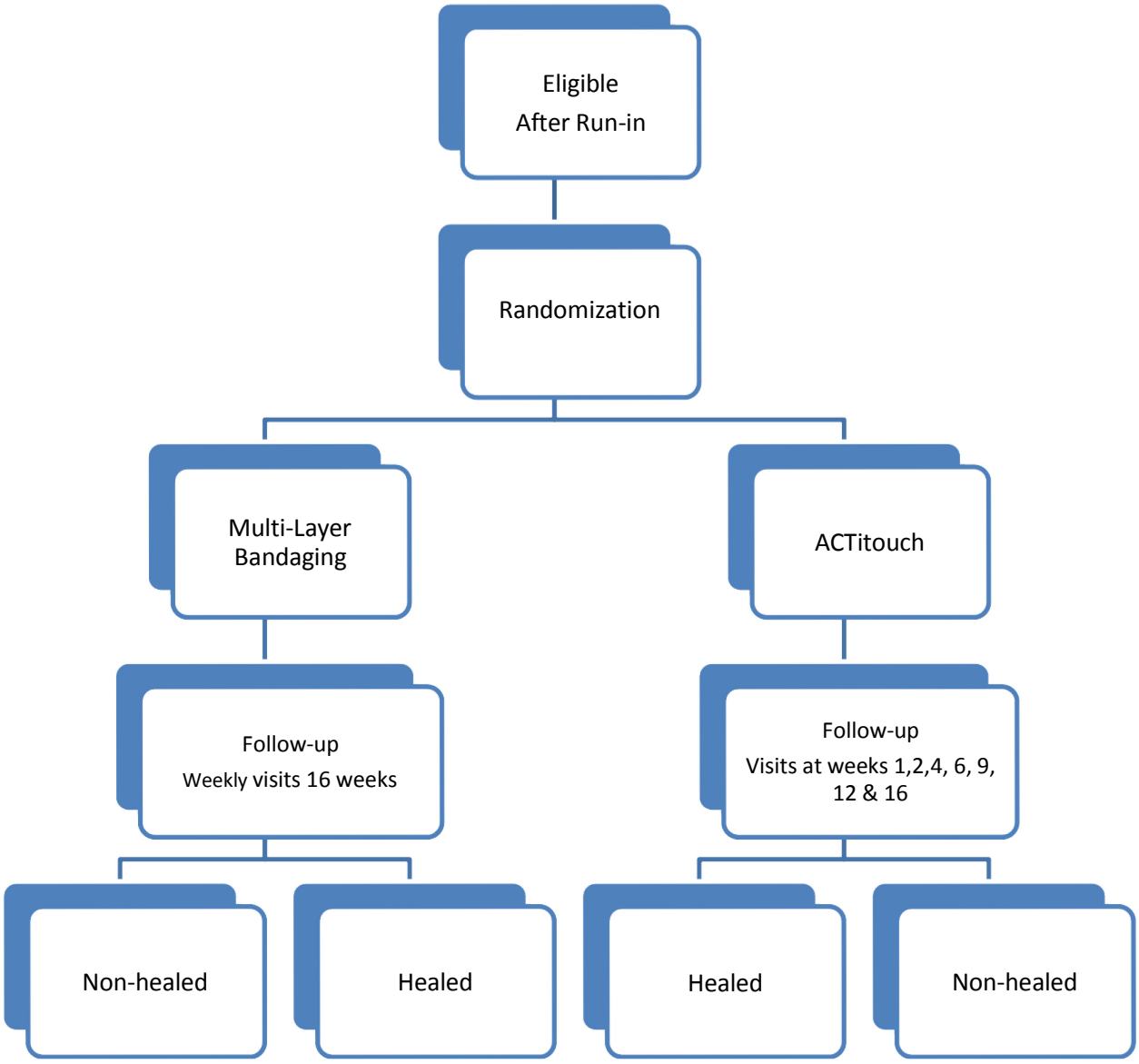
## 5.0 Study Design:

The study is a two arm, open label, non-inferiority, prospective, stratified, multi-center, RCT. As part of screening there will be a two week run in period measuring the VLU initial treatment response. The study is designed to evaluate percentage of ulcer area reduction in venous leg ulcer patients comparing ACTitouch to multi-layer bandaging during the 16 week treatment phase.

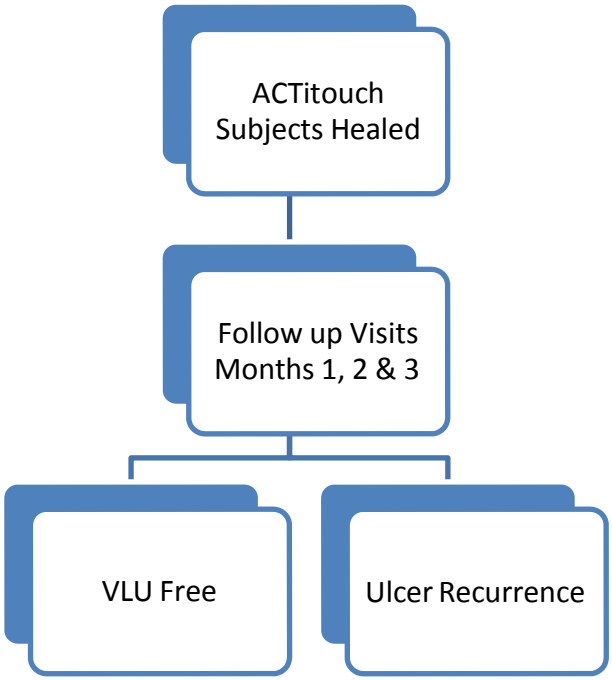
Run In Period – Two Week Treatment Response



Treatment Period (16 weeks)



Follow Up Period:




5.1 1 Study Endpoints:

5.1.1 Primary Endpoints:

The primary clinical endpoint:

- Percentage of ulcer area reduction at 16 weeks

5.1.2 Secondary Endpoints:

The secondary clinical endpoints will include the following:

- Improvement in HRQOL
- Outpatient costs per subject
- Complications

5.2 2 Subject Selection:

This is a community based trial. The study population will be drawn from patients who have chronic non-healed VLUs of at least one (1) month prior to the start of the study. Only patients who meet the criteria listed below will be considered for participation. A minimum of 204 subjects will be enrolled at approximately 30 centers in the United States.

5.2.1 Inclusion Criteria:

- Subject must be ≥ 18 years of age or legal age at the time of enrollment.

- Chronic venous insufficiency confirmed by ultrasound within previous 12 months or prior to randomization.
    - If a study subject has bilateral CVI, the limb that possess the largest ulcer meeting study criteria will be used as the study treatment limb for evaluation and documentation throughout the study. Non-study limbs will receive standard of care treatment as determined by the treating clinician.
- Must have at least one of the following within the past six
    - months:
        - Dorsalis Pedis (DP) systolic pressure ≥ 80mmHg for diabetic patients or ≥ 60mmHg for non-diabetic patients on study limb
        - Posterior Tibial (PT) systolic pressure ≥ 80mmHg for diabetic patients or ≥ 60mmHg for non-diabetic patients on study limb
        - Transcutaneous partial pressure oxygen (TcP02) > 30mmHg
        - Great toe systolic pressure > 40mmHg
- Active ulceration (CEAP classification of C6)
    - VLU is defined by open skin lesion of the leg or foot that occurs in an area affected by venous hypertension.
- Ulcer duration: Non healing VLU ≥ 1 month but not greater than 24 months.
- Ulcer size ≥ $2cm^2$ ≤ $50cm^2$
    - If there are multiple ulcers on the study limb, the largest ulcer will be used as the study treatment ulcer for evaluation and documentation throughout the study. If two ulcers are separated by no more than one centimeter of normal skin, their areas will be added together for study purposes.
- Three or fewer separate full thickness ulcers on the study limb.
    - Sum of the ulcer areas on the study limb must be ≤ $50cm^2$ to participate in the study.
- Leg circumferences within the following range:
  Ankle – 12 to 44cm
  Calf – 22 to 60cm
  Below knee – 22 to 68cm
- Must be able and willing to provide informed consent prior to study participation.

5.2.2 Exclusion Criteria: Subjects will be ineligible for this study if they meet any of the criteria described below:

- Target ulcer or any other ulcer on the study limb involves exposure of tendon, muscle, or bone.
- Target ulcer is of non-venous etiology (sickle cell anemia,

necrobiosis lipoidica diabeticorum, pyoderma, malignancy).

- Treatment of the target ulcer with living cellular therapy within 30 days of the time of projected randomization.
- Endovenous ablation or other venous surgery within two weeks of enrollment
    - Venous ultrasound must be completed after procedure to determine whether there is still venous insufficiency at the time of enrollment.
- History of skin sensitivity to any of the components of AT, multi-layer bandages or compression garments.
- History of an acute deep vein thrombosis (DVT) or pulmonary embolism (PE) within the last three (3) months.
- Acute thrombophlebitis within the last six (6) weeks.
- History of pulmonary edema or decompensated congestive heart failure within six (6) weeks of screening.
- Currently has an active infection of the skin on the target limb such as cellulitis requiring antibiotics.
- History of target limb cancer within the last two years with the exception of treated non-melanoma skin cancer unless ulcer biopsy performed at screening is negative for neoplasia.
- Active cancer receiving chemotherapy and/or radiation therapy.
- Poorly controlled diabetes with an HbA1c value of > 12% within the past three (3) months.
- Changes to medications that affect edema within the last 30 days prior to enrollment (e.g. diuretics, calcium channel blockers of the dihyropyridine class, pioglitazone, cox-1 inhibitors, pregabalin, and gabapentin, diltiazem or fluctuating doses of systemic steroids).
- Use of systemic corticosteroids requiring daily administration at doses greater than 5mg of Prednisone per day or equivalent for greater than two weeks.
    - Low dose steroid administration (Prednisone up to 5mg per day or equivalent) is allowable for an unlimited period of time. Topical steroid administration to peri-ulcer area or other skin is allowable but cannot be applied to the ulcer itself.
- Currently pregnant or trying to become pregnant.
- Inability or unwillingness to participate in all aspects of study protocol.
- Exhibit any condition which, according to the Investigator, justifies the subject's exclusion from the study, such as a medical condition where an increase in venous or lymphatic return is undesirable.
- Currently participating in another clinical trial.

5.2.3 Additional Exclusions after two week run-in: Subjects will exit the study if they meet any of the following criteria:

- Subject's target ulcer has decreased in size by greater than 30% compared to the baseline area.
- Subject's target ulcer has increased in size by greater than 50% compared to the baseline area.
- Subject's target ulcer measures less than 1.5cm² at the Randomization Visit.
- Subject appears to have evidence of infection in any ulcer.
- The sum of the ulcer areas on the subject's study limb is > 50cm$^2$.

5.2.4 Subject Withdrawal or Early Termination:
Subjects will exit the study if they meet any of the following criteria:

- Subject death
- Subject voluntarily withdraws or investigator's decision
- Subject experiences an adverse event that in the investigator's clinical judgment necessitates study discontinuation
- Ulcer recurrence during the 3 month follow up period
- Subject acquires any of the exclusion criteria, except
    - If subject acquires an infection, they may be treated for the infection and continue in the trial in the investigator's discretion. The investigator can instruct the subject to cease sustained or IPC treatment for up to two (2) consecutive weeks but no more than four (4) weeks total. If the subject is required to abstain from study treatment for greater than the amount described above, the subject will be removed from the study.

5.3 Dosage:

Run-in

All subjects will participate in a two week run-in phase. The treatment will include multi-layer compression bandaging which must be worn 24 hours a day except during clinic visits. The run-in phase is intended to assess the subject's initial response to standard of care treatment using multi-layer bandaging before receiving treatment with the investigational device.

VLU Treatment Period

All subjects enrolled will be randomized into either treatment using the ACTitouch system or multi-layer bandaging which consists of either PROFORE or Coban 2.

Investigational Group: Subjects assigned to the ACTitouch system must wear the device in sustained mode during all wakeful hours (at least 12 hours each day) and IPC mode for a minimum of 2 hours each day. Subjects will be instructed to remove the ACTitouch for bathing and when driving or operating machinery, and reapply immediately after these activities.

At each visit the subject's compliance will be evaluated via the compliance tracker on the ACTitouch device.

Subjects randomized to the ACTitouch arm of the study will also be contacted weekly between study visits by study personnel to support device compliance and answer questions as outlined in Section 7.16.

Control Group: Subjects assigned to multi-layer bandaging must wear the bandaging 24 hours a day except during clinic visits when the limb is being assessed by the study staff.

Follow Up Period

All subjects assigned to the ACTitouch arm who heal during the 16 week treatment period will be followed for 3 months post VLU healing. These subjects will be instructed to continue to use the ACTitouch device as outlined in the 16 week treatment period [sustained mode during all wakeful hours (12 hours each day) and IPC mode for 2 hours daily]. Subjects will be instructed to remove the ACTitouch for bathing and when driving or operating machinery, and reapplied immediately after these activities.

5.4 Study Timetable:

| Task | Months | | | | |
|---|---|---|---|---|---|
| | 1-6 | 7-12 | 13-18 | 19-24 | 24-30 |
| Identify Sites | X | | | | |
| IRB/Regulatory | X | | | | |
| Enrollment | | X | X | | |
| Treatment | | X | X | X | X |
| Data Entry | | X | X | X | X |
| Data Analysis | | | | | X |

## 6.0 Study Visit Summaries:

6.1 Screening Visit:

At this visit, the patient will be asked to provide written informed consent and inclusion and exclusion criteria will be evaluated to ensure that the patient meets all entrance criteria. See the Study Schedule of Activities section 7.17 for visit activities. After the informed consent process is complete, the subject will begin the run-in phase of the study.

Subjects may be enrolled if they are on a current Pentoxifylline regimen, but Investigators should not start patients on Pentoxifylline during the trial if the patient is not taking the drug at enrollment.

6.2 Run-in Visit:
There could be up to 4 visits during the run in phase, 3 visits if the Screening and Baseline visits occur on the same day. The visit schedule is as follows Screening/Baseline; Run-in Week 1 and Randomization (±2 days). The subjects will follow the treatment regimen outlined in section 7.17. At each visit the study staff will access the ulcer. If the subject meets any of the exclusion criteria listed in section 5.2.3 at the Randomization Visit the subject will be excluded from the study.

6.3 Randomization Visit:
At the randomization visit the subject will undergo procedures as outlined in the Study Schedule of Activities table in section 7.17.

The subject will leave the randomization visit with:

- Schedule for the next study visit (if possible, follow-up visits should be scheduled at the same time of day)
- Instructions on use and application of the assigned study apparatus, as applicable
- Diary and instructions to record daily activity
- Contact information and instructions to call if any problems arise

6.4 Treatment Visits (Weeks 1-16 or healed):
Investigational Group: Subjects will be seen in clinic at weeks 1, 2, 4, 6, 9, 12, 16 (±2 days) for 16 weeks or until the VLU is completely healed, as defined by complete closure with no open area or exudate. At the visits the subject will undergo the procedures as outlined in the Study Schedule of Activities table in section 7.17.

Control Group: Subjects will complete weekly visits for 16 weeks or until the VLU is completely healed, as defined by above. At the weekly visits the subject will undergo procedures as outlined in the Study Schedule of Activities table in section 7.17.

The study staff will review the subject diary with the subject during each visit to ensure that all entries are complete and understood by the study staff. Any corrections must be made by the subject, and initialed and dated by them.

6.5 Support Contact:
Subjects randomized to the ACTitouch arm of the study will be contacted by study personnel (via text or phone call). The first follow up contact will occur 3 days (±1 day) after the Randomization Visit and the second follow up contact will occur 3 days (±1 day) after the Treatment Week 1 Visit.

For the remainder of the VLU treatment period, follow up contact will occur on weeks that the subject is not returning to the clinic for a study visit. The subject will be contacted during treatment weeks 3, 5, 7, 8, 10, 11, 13, 14, and 15 (±2 days from optimal date). If an ACTitouch subject is seen for an unscheduled study visit

within one of these windows, this will take the place of the support contact for that week.

6.6 Follow Up Visits (Months 1, 2 &3):
Subjects who are assigned to the ACTitouch device and heal during the 16 week treatment period will continue to be seen monthly for 3 months (±7 days) post healed visit. At the visit the subject will undergo the procedures outline in the Study Schedule of Activities table in section 7.17.

The study staff will review the subject diary with the subject during each visit to ensure that all entries are complete and understood by the study staff. Any corrections must be made by the subject, and initialed and dated by them.

6.7 Unscheduled Study Visit:
The subject may return to the investigational site for unscheduled visits during the study. At this unscheduled study visit the subject will complete all study procedures as outlined in the Study Schedule of Events Section 7.17.

6.8 Recurrence Visit:
If the subject's VLU recurs during the 3 month follow up period the subject will be instructed to return to the investigational site to be assessed. At the visit the subject will undergo the procedures outlined in the Study Schedule of Activities table in section 7.17.

**7.0 Study Procedures:**

7.1 Pre-screening:
Pre-screening of potential subjects will be conducted by study staff either by phone or in person. Potential subjects who are interested in participating in the study will meet with study staff in-person for the consent process.

7.2 Informed Consent:
Informed consent must be obtained from all subjects prior to participation in clinical studies as mandated by Federal Regulations and/or the qualifying Institutional Review Board/Ethics Committee (IRB/EC). A blank copy of the IRB/EC-approved informed consent form must be kept on-site and by Tactile Medical. The signed original for each subject must be kept in the subject's medical records.

A copy of the consent will be given to the subject to read and take home to consider if they prefer. All questions must be answered prior to signing the informed consent form. Clinical study procedures cannot be performed until subject signs the consent. A signed copy of the consent should be provided to the subject.

7.3 Laboratory Testing:
After providing informed consent, women of child bearing potential will be tested for pregnancy at the site specific clinical laboratory according to site standard

procedures. If the pregnancy test is positive, subjects will be excluded from the study.

Subjects with diabetes must have a HbA1c value ≤ 12% within the past three (3) months. If the subject does not have a documented HbA1c at the time of consent then one must be completed after providing informed consent but before randomization. If the HbA1c is > 12% the subject will be excluded from the study.

All potential subjects must have a dorsalis pedis (DP), posterior tibial (PT), TcP02, or great toe pressure as outlined in the criteria within the last six months to meet study eligibility, unless approval is obtained from the Sponsor Chief Medical Officer. If the aforementioned tests are > 6 months or the subject hasn't undergone one of the required tests one will need to be completed to determine eligibility.

7.4 Randomization:

After completing the informed consent process, subjects who meet the entrance criteria will complete the Run-in Phase before being randomly assigned into either the multi-layer bandage or ACTitouch group. The scheme will be generated randomly, electronically by Clindex, and will be stratified based on ulcer size and duration at time of randomization.

For the purpose of this study, multi-layer bandages include PROFORE and Coban 2 only. The use of multi-layer bandaging other than the pre-specified bandages will be considered a deviation from the protocol and must be reported to the sponsor immediately. This deviation could result in termination of the study subject.

7.5 Leg Volume Measurements:

Circumferential measures of both legs will be taken at 4cm intervals starting at 10cm up from the bottom of the subject's heel, flexed at 90 degrees to the leg and continue to the knee at the popliteal fold (Appendix D). If possible, the same clinician will be asked to take the measurements for each patient visit.

7.6 Wound Assessment:

At each study visit (if applicable) the ulcer will be assessed by qualified study personnel. The ulcer features that will be assessed will include ulcer drainage, type and amount, ulcer bed features, wound margin, and periwound areas; and other aspects including but not limited to odor, pain, and debridement.

Ulcer closure/healing is defined by 100% epithelialization and no drainage.

7.7 Wound Debridement:

Ulcer debridement will be undertaken as needed per the investigator's clinical decision. The methods of debridement may include enzymatic, sharp, surgical, and mechanical debridement and/or pulse lavage.

7.8 Wound Dressings:
All subjects will undergo wound dressing changes, either in the clinic or at home. Wound dressing will be selected by the investigator. Generally, "dry ulcers" will require hydrocolloid dressings and "wet ulcers" will require foam or alginate.

7.9 Wound Photograph and Tracing:
At each study visit, (if applicable) the study ulcer will be photographed and the wound will be traced using the Silhouette™ system (Appendix E).

In addition, at the initial visits all ulcers on the study limb will be photographed and traced to ensure that the sum of the areas is not greater than $50cm^2$. Any ulcers that form on the study limb during the course of the study will also be photographed and traced for AE documentation.

The initial visit, enrollment visit, and healed visit image and tracing will be evaluated by a single independent adjudicator to increase integrity and to provide a blinded analysis. Ulcer surface areas that fall on or near the minimum or maximum ulcer surface area allowed for study inclusion will be adjudicated in a timely manner. Study staff will have access to the adjudication results by a time no later than the next scheduled subject visit.

7.10 Tissue/Skin Assessment:
The subject's legs will be examined for irritation, trauma and ulceration at each study visit. At any time during the study the investigator may determine that a tissue/skin change requires the subject to be withdrawn from the study.

7.11 Compression Application:
<u>Application of ACTitouch System:</u>
The ACTitouch system will be applied by the trained study staff. First the ACTitouch under-sock will be applied. The sock will be in direct contact with the skin and wound dressings and the ACTitouch sleeve will wrap around the pre-covered leg. The ACTitouch will be applied while the subject is seated, with the feet lightly resting on the floor.

<u>Application of Multi-Layer Bandaging:</u>
The trained study staff will apply the multi-layer bandaging according to manufacturer's instructions. The multi-layer bandaging will be in direct contact with the skin and the wound dressings.

7.12 Application Timing:
The time to apply compression by study personnel on the subject's limb in clinic will be recorded throughout the study as specified (section 7.16). Both treatment application methods will be timed and recorded. The study personnel will lay out all required materials to be applied. Immediately after the timing starts either the first contact layer in the multi-layer bandaging group or the under-sock of the

[redacted]

7.13 Compliance Assessment:
Subject compliance will be evaluated through the support call, subject diary, interview, and ACTitouch Compliance Tracker (for the subjects randomized to ACTitouch) at each study visit.

7.14 Cost: A sub-study evaluating economics will also be included in this study. The economic sub-protocol outlines the collection of essential health economic items concerning visits, procedures and lab tests, QOL and work productivity. (Appendix G).

7.15 Study Surveys/Questionnaires: Subjects and study clinicians will complete survey/questionnaires to assess symptoms, quality of life, acceptance/tolerability, and ease of use of their assigned device.

Charing Cross Venous Ulcer Questionnaire: Consists of 21 items for the assessment of patients' perception of their health when venous ulceration is present, to be used in conjunction with the SF-36. (Appendix H)

[redacted]

Venous Clinical Severity Score (VCSS): A disease severity measurement tool including clinical descriptors that have the ability to change over time which allows for improvements to be captured. (Appendix J)

[redacted]

7.16 Study Schedule of Activities

Run In / Treatment Periods:

Follow Up Period:

| Key:<br>*Active Ulcer | Follow Up Month 1 | Follow Up Month 2 | Follow Up Month 3 | VLU recurrence visit |
|---|---|---|---|---|
| [redacted] | | | | |

**8.0 Study Device Accountability:**

Site personnel must maintain device accountability log(s). Completion of these log(s) will ensure that all ACTitouch Control Units and Sleeves are properly tracked and accounted for throughout the study from the time they are received by the institution to the time they are returned to Tactile Medical. Device location, Subject ID assigned, date, and final disposition (e.g., returned to Tactile Medical, garments discarded, garments retained by subject) of all ACTitouch Control Units and Sleeves will be documented. Tactile Medical must also maintain device accountability documenting all shipments and returns of Control Units by serial number, date, and person completing the log. Storage locations for the Control Units and Sleeves will be secure (i.e., locked and away from other devices) with access restricted only to investigators and authorized research personnel.

Sanitation Procedure:

At the conclusion of the study, the subject must return the ACTitouch controller to the investigational site. The site personnel will disinfect the Control Unit by thoroughly cleaning it with a disinfectant before it can be reassigned to a subject or returned to the Tactile Medical. The subjects may keep the sleeve and under-socks. If sleeve and under-socks are returned to the site they **CANNOT** be reused on multiple subjects and should be appropriately discarded upon study return.

**9.0 Risk Analysis and Adverse Events:**

9.1 Risk Analysis:

The subjects enrolled in the study are not expected to be at any higher or additional risk than those who use non-study pneumatic compression devices. There is risk with using any IPC device. These may include, but are not limited to risk of explosion if the device is used in the presence of flammable gases, risk of electrical

shock if the device is immersed in water or if the housing is broken and subject attempts to service the unit.

IPC devices are contraindicated for use in the presence of pulmonary edema, acute thrombophlebitis, congestive heart failure, acute deep vein thrombosis, episodes of pulmonary embolisms, acute infection, and inflammation or other conditions where increased venous or lymphatic return in undesirable.

There are minimal side effects expected from either treatment subjects will receive in this study and the study uses only currently FDA cleared interventions. The expected risks are often a failure to respond to the treatment intervention and are not related to the treatment itself. In some cases, side effects due to CVI or VLUs can be serious, long lasting, or may be permanent. The risks listed below are symptoms of CVI and/or VLUs and may be experienced by all subjects:

- Pain or discomfort
- Swelling of the lower legs/ankles
- Aching or tiredness in the legs
- Leathery looking skin
- Flaking or itching of the skin
- Stasis ulcers

9.2 Adverse Event Definition:

An adverse event (AEs) includes any complication whose clinical significance is greater than anticipated, or which occurs with a frequency greater than that which is usually seen for this type of device. A serious adverse event (SAE) is defined as an event that,

- results in death
- is life-threatening (places the subject at immediate risk of death from the experience as it occurred)
- results in a persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions)
- results in medical or surgical intervention
- results in or prolongs an existing hospitalization (even if the hospitalization is a precautionary measure for observation)

An unanticipated adverse device effect (UADE) is any serious adverse effect related to the device that meets the definition above or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Investigators must report all SAE and/or UADE to Tactile Medical within 72 hours of first learning of the event. SAE and/or UADE will be reported in writing to the appropriate IRB in accordance with their policy.

9.3 Adverse Event Reporting:

Investigators will be responsible for reporting the following pre-defined adverse events regardless of severity, to Tactile Medical in a timely manner:

- New or worsening ulceration

- Clinically worsened or new onset heart failure
- Increase in leg swelling greater than 20%
- Skin irritation/blistering
- Infection of the study limb(s)
- Other – an AE that according to the investigator's opinion is significant and requires reporting to Tactile Medical but doesn't necessarily meet the definition of the pre-defined AEs or an SAE

**10.0 Deviation from Investigational Protocol:**

Any deviation from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to Tactile Medical and the respective IRB as soon as possible, but in no event later than five (5) working days after the emergency occurred. Anticipated deviations from the protocol in a non-emergency situation must be pre-approved by Tactile Medical via telephone, email, fax, or mail. It is preferred that deviations scheduled to be performed in a nonemergency situation not be conducted until authorized by Tactile Medical. All protocol deviations must be documented. Deviation that may affect the scientific soundness of the study, or the rights, safety or welfare of the subject must also be reported to the reviewing IRB according to their reporting requirements. Protocol deviations may necessitate the discontinuation of the subject or the investigational site from the study.

**11.0 Quality Assurance Procedures:**

This study will be conducted in accordance with Good Clinical Practice and International Conference on Harmonization (ICH) Guidelines, Code of Federal Regulations (CFR), institutional research policies and procedures and other appropriate regulatory requirements to ensure subject safety and quality of clinical procedures related to the conduct of the clinical trial. The investigators will permit regular monitoring, audits and site inspections by the IRB, the sponsor, government regulatory bodies and any institution compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspection of applicable study related facilities. Clinical trial monitoring may be conducted to ensure compliance to this protocol.

11.1 Site Qualifications:

Tactile Medical may conduct onsite visits or telephone qualification (pre-study audit) prior to study initiation to verify adequate resources, qualified staffing and a sufficient subject pool.

11.2 Data Collection Procedures:

Raw data will be collected on appropriate Source Document Worksheets, or site-specific appropriate forms which include but are not limited to, clinic charts and site-generated Source Document Worksheets. Data collected shall be entered into the validated and secure Clindex electronic data capture system.

11.3 Clinical Site Monitoring:

Clinical sites will be monitored for compliance with the clinical protocol, investigator agreement, and applicable regulatory requirements. Regular contact will be maintained to ensure:

- Subject safety
- That clinical site staff is well informed of regulations and sponsor requirements
- That the clinical protocol is followed
- That data is gathered in a complete and timely way
- That problems with data or data collection are addressed appropriately and in a timely manner
- That adverse events are properly reported in a timely manner

Investigator and Institution will permit trial related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data and documents as appropriate. Monitoring will be performed by study sponsor and/or designee. Monitoring will review subject source documentation and Case Report Forms (CRFs) for accuracy, completeness, and compliance with Good Clinical Practice procedures. In addition to site visits, a screening log will be submitted to Sponsor or designee by the sites as requested (by fax or e-mail). This screening log will be reviewed with the site for plan vs. actual recruitment purposes.

11.4 Data Safety Monitoring Board:

An independent data safety monitoring board (DSMB) will be established by the sponsor to review and monitor any serious adverse events, review safety data and may be called upon to review interim analysis data. The frequency of the review is expected to be quarterly but may be dependent on a number of parameters including but not limited to; the rate of enrollment, number of AEs and/or SAE, number of significant deviations from the protocol. At the conclusion of the review the DSMB may provide recommendations pertaining to study continuation, modification, or termination of the trial or a specific investigational site.

11.5 Investigator Reports and Records:

Records to be maintained by the investigator in a designated study file include:

- Investigational plan and all amendments
- Signed Investigator Agreement
- IRB approval letter, including a copy of the approved consent forms, progress reports, Adverse Event Report
- IRB roster or Assurance number, if applicable
- All correspondences relating to the conduct of this study between the site and sponsor, IRBs, and study monitor
- Curriculum Vitae and professional license for all study personnel, if applicable
- Site personnel signature and documentation regarding the Investigator's delegation of responsibility
- Clinical Site Visit log

- Protocol/device related training records for all applicable study personnel
- Investigational device inventory information including the date, quantity and serial number of all devices and received identification of all subjects who received treatment, and final disposition of the devices.
- Screening log
- Reports (see Table 3)

The following records must be maintained for each subject enrolled:

- Signed and dated informed consent form
- Completed CRFs, queries and source document worksheets (if applicable)
- Complete medical records including procedure reports, lab reports (if applicable), etc.

Investigators are required to prepare and submit to the sponsor or its designees complete accurate and timely reports on this investigation as required by regulations. The types of reports to be submitted are summarized in Table 3.

**Table 3: Investigator Reports**

| Reports | Submit To | Timeframe |
|---|---|---|
| Unanticipated Adverse Device Event | Sponsor and Reviewing IRB DSMB | As soon as possible but no later than 10 working days |
| Withdrawal of IRB Approval | Sponsor | Within 5 working days |
| Progress | Sponsor and Reviewing IRB | Annually, at a minimum |
| Final | Sponsor and Reviewing IRB | Within 3 months following the completion or termination of the Investigator's part |

Subject study records, correspondence files, all supporting study documentation, and reports must remain on file at the investigational site for a minimum of ten years after the conclusion of this study. All investigators must contact Tactile Medical prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

Additionally, Tactile Medical must be contacted if the Investigator plans to leave the investigational site to ensure that arrangements for a new Investigator or records transfer are made prior to the Investigator's departure.

11.6 Change to Study Plan:

Should changes in the study plan or protocol become necessary in the course of the clinical trial, those specific changes will be discussed and agreed upon by the Sponsor, its acting representative if appropriate, Investigator, and appropriate IRB

approval obtained before the changes are implemented. All changes must be documented.

## 12.0 Data Analysis and Statistical Considerations

12.1 Statistical Considerations:

This is a prospective, randomized, stratified, open label, parallel-group, multi-center trial designed to assess the clinical non-inferiority with respect to the percentage of wound area reduction at 16 weeks with the ACTitouch® Adaptive Compression System compared to the Multi-layer Bandaging system in subjects with venous leg ulcer (VLU). Secondary endpoints include health-related quality of life (HRQOL) and Cost of the ACTitouch® Adaptive Compression System compared to the Multi-layer Bandaging system in subjects with VLU. Two hundred and four (204) subjects will be randomized 1:1 into 2 arms, ACTitouch® and Multi-layer Bandaging Systems. Subjects will receive follow-up evaluations at regularly scheduled clinic visits during 16 weeks of follow-up. Subjects will be randomized to 4 strata based on ulcer size and duration (age):

- Size of Ulcer
  - 1.5cm<=size<=12cm
    12cm<size<= 50cm
- Age of Ulcer
  1<=age<=6 months
  6<age<= 24 months

Subjects will be randomized to treatment groups within strata using a web-based randomization process.

Unless otherwise specified, all safety data, efficacy data, demographic data, and other baseline characteristics will be summarized by treatment group. Continuous data will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum values. Categorical data will be described using frequency tables showing the number and percentage of subjects falling within a particular category.

Efficacy analysis and associated p-value calculation are described below and will be further elaborated in the Statistical Analysis Plan (SAP) issued prior to database lock. Statistical tests will be performed at a one-sided alpha of .025 for non-inferiority and two-sided alpha level of 0.05 for all other comparisons, unless otherwise specified. Between-group analyses will employ analysis of covariance (ANCOVA) with stratum and treatment group as covariates for continuous data, and chi-square or Cochran-Mantel Haenzel (CMH) methods for stratified categorical data. Kruskal-Wallis tests will be used to compare ordinal variables stratified by ulcer age, wound area and treatment group. If serious departures in the assumptions of normality and homogeneity of variance occur, nonparametric methods will be used for continuous data.

12.2 Objectives:

The primary efficacy objectives are:

- Assess the non-inferiority of chronic VLU closure at 16 weeks with ACTitouch® therapy compared to a standard regimen of multi-layer bandaging.

The secondary and exploratory efficacy objectives include assessment of the effect of ACTitouch® compared with multi-layer bandaging treated subjects on:

- HRQOL
- outpatient cost per patient
- incidence of 100% healed VLU
- ulcer free days
- outpatient cost per patient healed
- outpatient cost per patient not healed
- time-to-100% healed
- cumulative incidence of 100% healed
- total cost per patient (including inpatient costs)

The safety objective is to compare ACTitouch® treated subjects to multi-layer bandaging treated subjects at 16 weeks in terms of the incidence of ulcer-related adverse events including infections, maceration, allergic reaction to dressing, hospitalization for worsening VLU.

12.3 Endpoints:

12.3.1 Primary Endpoints

The percentage of ulcer area reduction at 16 weeks.

12.3.2 econdary Endpoints

The secondary endpoints in clinical order of prioritization are as follows:

- the difference in changes in HRQOL at 16 weeks using the overall score of the Charing Cross Venous Ulcer Questionnaire.
- outpatient cost per subject at 16 weeks

12.3.3 xploratory Endpoints

- the incidence of subjects with 100% healed VLUs at 16 weeks
- ulcer-free days at 16 weeks
- HRQOL at 16 weeks using the overall and physical scores of the SF-36.
- outpatient cost per subject for subjects with 100% healed VLU at 16 weeks
- outpatient cost per subject for subjects without 100% healed VLU at 16 weeks
- time-to-100% healed VLU
- cumulative incident of 100% healed
- total cost per patient (including inpatient costs)
- ease of use
- treatment satisfaction
- limb volume changes
- compliance

12.3.4 afety Endpoints

The safety endpoints are as follows:

- the incidence of ulcer-related adverse events at 16 weeks
- the incidence of ulcer infections at 16 weeks
- the incidence of hospitalization for worsening VLU at 16 weeks

12.4 Sample Size Assumptions:

12.5 Analysis Populations:

**Intent-to-Treat (ITT):** All randomized subjects.

**Modified-intent-to-treat (MITT):** All randomized subjects who received the investigational procedure per protocol. This is the primary analysis population.

**Per-Protocol (Completers):** All randomized subjects who have received the investigational procedure per protocol and who completed the 16 week follow-up visit.

The Primary and Secondary Efficacy analyses will be performed on the ITT, MITT and Completer populations. Safety analyses will be performed on the MITT population.

12.6 Analysis Plan:

12.6.1 eneral Analysis Issues:

Statistical analysis will be performed using SAS Version 9.4 or higher. Non-inferiority analyses will be considered statistically significant at the

one-sided α=.025 level. All other p-values presented will be two-sided and will be considered statistically significant at the two-sided α=.05 level of significance unless otherwise noted. Statistical testing of the primary and secondary endpoints (Stage I) will be performed in hierarchical fashion. The primary efficacy analysis will be performed at the one-sided α=.025 level. If the primary efficacy analysis is statistically significant then the first secondary end point will be analyzed at the two-sided α=.05 level. If this analysis is statistically significant, then the second secondary end point will be analyzed at the two-sided α=.05 level. Otherwise, testing on secondary endpoints will cease and the treatment will not be considered beneficial on either secondary endpoint. P-values for exploratory endpoints will not be adjusted for multiple comparisons.

Baseline demographic and background variables will be summarized by treatment group and strata. For categorical variables, frequencies and percentages will be presented. For continuous variables, descriptive statistics including: sample size, mean, standard deviation, minimum, and maximum, will be presented. Continuous variables will be compared between treatment and control groups using ANCOVA. Categorical variables will be compared between treatment and control groups using the Kruskal-Wallis tests.

12.6.2 Primary Endpoint Analysis:

The percentage of each subject's ulcer area reduction at 16 weeks will be assessed using a specialized ulcer camera and ulcer imaging system. Images will be centrally read by a qualified independent adjudicator. The percentage of ulcer area reduction for the ACTitouch® treated subjects will be compared with multi-layer bandaging treated subjects using analysis of covariance (ANOCOVA) with the following covariates: treatment group; duration of VLU ([1,6]; (6,24] months); baseline size of VLU, [1.5,12cm], (12,50cm]; history of diabetes; age. The analysis will be conducted on the ITT, MITT and Completer populations. The covariate adjusted one-sided lower bound 97.5% confidence interval of the treatment difference in mean percent ulcer area reduction (calculated as mean of ACTitouch® group minus mean of multi-layer bandaging treated group) is compared to the non-inferiority margin (-.125) . If the lower bound exceeds the margin, the null hypothesis is rejected, and ACTitouch® system is deemed non-inferior to multi-layer bandaging.

A treatment-by-study center interaction will be assessed at the 0.10 level of significance using analysis of covariance with effects for treatment, study center and treatment-by-study center interaction. A non-significant interaction or any significant interaction deemed only quantitative in nature will not preclude study centers from being pooled for the final analysis. A significant qualitative interaction will be further inspected to

assess the study centers causing the interaction. Study centers with less than 15 subjects will be pooled by geographic region prior to carrying out the analysis.

A qualitative interaction between center and treatment group is defined as directionally inconsistent estimated coefficients for the treatment group parameter in a subgroup analysis of treatment group by center – i.e., analysis of covariance model with stratification by center specified as subgroups. Any study center with a qualitatively different treatment group effect by subgroup will be compared with other centers in terms of a number of variables including: enrollment rate, adverse event rate, rate of data queries generated by clinical data management, confirmation of correct drug assignment and randomization at the site, number and seriousness of protocol deviations. If a center is deemed to be qualitatively different from the other centers in terms of their interaction with treatment group, then the primary efficacy analysis will be stratified by center (i.e., those centers with a qualitative a difference versus all others). If only one or two centers are qualitatively different, then analyses will be conducted with and without the centers, and the results will be compared.

Several imputation approaches will be used for missing data due to subjects prematurely withdrawing prior to the 16 week time point. The results will be descriptively compared across approaches to assess the sensitivity of results to the various techniques.

- Complete case analysis
- Multiple imputations via the linear regression technique, where the imputation model will include treatment group and all covariates discussed in the Analysis Plan.
- Available data analysis (include any available measurements) using the general linear mixed models.

12.6.3 econdary Endpoint Analysis

The following analyses will be carried out on all three analysis populations defined above. ACTitouch® treated subjects will be compared with multi-layer bandaging treated subjects in terms of:

- the difference in changes in HRQOL at 16 weeks assessed by the overall score of the Charing Cross Venous Ulcer Questionnaire using a similar ANCOVA model as used in similar to the Primary Endpoint Analysis. If the primary efficacy analysis was significant, then the difference will be tested at the two-sided $\alpha$=.05 level.
  the difference in VLU-related outpatient cost per subject at 16 weeks between ACTitouch® treated subjects with multi-layer bandaging treated subjects using non-parametric rank-order, Wilcoxon rank sum tests. If the prior secondary efficacy analysis was significant, then the difference will be tested at the $\alpha$=.05 level.

12.6.4 xploratory Endpoint Analysis

- To compare the difference in the incidence of subjects with 100% healed VLUs at 16 weeks between ACTitouch® treated subjects with multi-layer bandaging treated subjects based on logistic regression with the same covariates as used in the Primary Endpoint Analysis.
- To compare the difference in ulcer-free days at 16 weeks between ACTitouch® treated subjects with multi-layer bandaging treated subjects based on non-parametric analysis of covariance using the same covariates.
- To compare the difference in changes in HRQOL at 16 weeks compared to baseline between ACTitouch® treated subjects with multi-layer bandaging treated subjects using the physical component score of the SF-36 using the same method as the Primary Endpoint Analysis.
- To compare the difference in VLU-related outpatient cost per subject for subjects with 100% healed VLU at 16 weeks between ACTitouch® treated subjects with multi-layer bandaging treated subjects using non-parametric rank-order, Wilcoxon rank sum tests.
- To compare the difference in outpatient cost per subject for subjects without 100% healed VLU at 16 weeks between ACTitouch® treated subjects with multi-layer bandaging treated subjects using non-parametric rank-order, Wilcoxon rank sum tests.
- To compare the difference in the time-to-100% healed VLU between ACTitouch® treated subjects with multi-layer bandages treated subjects using a Cox Proportional Hazard model with the same covariates as above.
- To compare the cumulative incidence graphs of subjects with 100% percent healed VLU between ACTitouch® treated subjects with multi-layer bandaging treated subjects using Kaplan-Meier product-moment estimates.
- To compare total VLU-related cost per subject (including cost of scheduled VLU-related study visits, VLU-related inpatient admissions, non-study ACTitouch® treated subjects with multi-layer bandaging treated subjects using non-parametric rank-order, Wilcoxon rank sum tests.
- Subjects who are assigned to the ACTitouch device and heal during the 16 week treatment period will continue to be seen monthly for each of 3 months (±7 days) post healed visit. At the visit the subject will undergo the procedures outline in the Study Schedule of Activities table in section 7.17. For such subjects, the recurrence rate (percent of subjects who are no longer 100% healed) at months 1, 2 and 3 will be tabulated. Descriptive statistics of the percentage of wound area reduction will be tabulated at each of the 3 monthly

visits. The percentage of non-compliant patients will also be presented at each month.

12.6.5 afety Endpoint Analysis

The following analyses will be carried out on the Safety Populations. ACTitouch® treated subjects will be compared with multi-layer bandaging treated subjects in terms of:

- the difference in the incidence of ulcer-related adverse events (defined as ulcer infections, maceration, allergic reaction to dressing, or hospitalization for worsening VLU) at 16 weeks using the Kruskal-Wallis test.
- the difference in the incidence of ulcer infections at 16 weeks using the Kruskal-Wallis test.
- the difference in the incidence of ulcer maceration at 16 weeks using the Kruskal-Wallis test.
- the difference in the incidence of allergic reactions to dressing at 16 weeks using the Kruskal-Wallis test.
- the difference in the incidence of hospitalization for worsening VLU at 16 weeks using the Kruskal-Wallis test.

12.7 Interim Analysis:

There will be a formal interim analysis of the primary endpoint when 50% of the subjects have completed the 16 week treatment phase, defined as completing all 16 weeks, healed or withdrew prior to the 16 week visit or healing. At this interim visit, comparison of the percentage ulcer area reduction between ACTitouch® treated subjects with multi-layer bandaging treated subjects will be made using the same ANOCOVA model as above. The DSMB will not recommend stopping the study for overwhelming efficacy based on the comparison of the ACTitouch® doses versus control (multi-layer bandaging). Nevertheless, due to the interim look, an O'Brien-Fleming-type alpha-penalty for the final analysis will be taken; and the final one-sided alpha will be 0.0249

The DSMB will be provided with conditional power of obtaining non-inferiority of ACTitouch to control with respect to mean percent ulcer healing by the end of the study. This conditional power is calculated according to the following formula:

$$CP_{\delta}(n_2, z_{\alpha}|z_1) = 1 - \emptyset\left[\frac{Z_{\alpha}\sqrt{2(n_1+n_2} - Z_1\sqrt{2n_1} - n_2(\delta-\delta_{\Delta})}{\sqrt{2n_2}}\right]$$

where:

$n_1$ – sample size per arm at interim;

$n_2$ – sample size per arm in second stage (from interim to final analysis) as originally planned;

$\Delta$ – non-inferiority margin;

$\delta_{\Delta} = \Delta/\sigma$ ;

$\sigma^2$ – assumption of true variance of treatment effects pooled across arms (estimated from the interim data);
$\delta$ – assumption of true effect size=$(\mu_C - \mu_T)/\sigma$ (this will be set to 0);
$z_1$ – non-inferiority test statistic calculated at the interim analysis;
$z_\alpha$ – $\alpha$ percentile of the standard normal distribution ($\alpha$ = one-sided 0.0249);
$z_\beta$ – $\beta$ percentile of the standard normal distribution;
$\Phi[]$ – the standard normal cumulative distribution function.

The Data Safety Monitoring Board (DSMB) and Statistical Analysis Plan (SAP) will outline the various recommendations the DSMB may make regarding the continuation of the study based on the conditional power calculated at the interim analysis. Each recommendation depends on the pattern of conditional power calculated under the assumption that the true population treatment difference is the original point estimate in excess of the non-inferiority margin. The following table, which will be included in the DSMB Charter, outlines the various recommendations the DSMB may make regarding the continuation of the study based on the conditional power calculated at the interim analysis.

| Conditional Power | Possible DSMB Recommendations |
|---|---|
| < 10% | Stop study for futility[20] |
| 10%-30% | Continue randomization into ACTitouch and multi-layer bandaging arms. |
| 30%-80% | Continue randomization into ACTitouch and multi-layer bandaging DSMB may recommend an increase in randomized sample size in order to achieve conditional power of 80% for a significant non-inferiority effect |
| > 80% | Continue randomization into ACTitouch and multi-layer bandaging arms using the originally planned sample size. |

In the event the DSMB recommends a sample size increase for the final analysis to achieve 80% conditional power, the critical value to be used for the final analysis will be:

$C_2$ - new final critical value (maintaining the overall 0.025 level of significance) to be used when sample size is increased from $n_1$ to $n_2$

$$C_2 = \frac{(Z_{\square} + Z_1)Z_{\square} + \sqrt{\frac{n_1}{2}}\left(\sqrt{\frac{2Z^2}{1}}\right)}{\frac{n_1 - \delta_{\Delta})Z_1}{2}}$$

$$\sqrt{n_1}\left[\sqrt{n_1} - \delta_{\Delta}\right] + (Z_{\square} + Z_{\square})^2$$

Computer simulations show that this approach to sample size increase maintains Type I error at the desired nominal level.

There is no stopping the study for overwhelming efficacy of the experimental arm. However, note that the DSMB can recommend stopping the study for safety issues at any time, regardless of interim results.

## 13.0 Compensation:

Study subjects may be compensated for their time and travel associated with participation in this study.

## 14.0 Publication Plan:

All information obtained during the conduct of the study will be considered to be confidential and is property of Tactile Medical. Written permission from the Sponsor is required before disclosing any information related to this study. All publications (e.g. manuscripts, abstracts, and presentations) based on this study must be submitted to the Sponsor for review and approval before submission or according to the individual site clinical trial agreement.

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## 16.0 Appendices

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