DE NOVO CLASSIFICATION REQUEST FOR dermaPACE SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Extracorporeal shock wave device for treatment of chronic wounds. An extracorporeal shock wave device for treatment of chronic wounds is a prescription device that focuses acoustic shock waves onto the dermal tissue. The shock waves are generated inside the device and transferred to the body using an acoustic interface.

NEW REGULATION NUMBER: 21 CFR 878.4685

CLASSIFICATION: II

PRODUCT CODE: PZL

BACKGROUND

DEVICE NAME: dermaPACE System

SUBMISSION NUMBER: DEN160037

DATE OF DE NOVO: July 25, 2016

CONTACT: SANUWAVE Health, Inc.
11475 Great Oaks Way #150
Alpharetta, GA 30022

INDICATIONS FOR USE

The SANUWAVE dermaPACE System is indicated to provide acoustic pressure shockwaves in the treatment of chronic, full-thickness diabetic foot ulcers with wound areas measuring no larger than 16 cm^2, which extend through the epidermis, dermis, tendon, or capsule, but without bone exposure. The dermaPACE System is indicated for adult (22 years and older), diabetic patients presenting with diabetic foot ulcers greater than 30 days in duration and is indicated for use in conjunction with standard diabetic ulcer care.

LIMITATIONS

Prescription use only: Federal (USA) law restricts this device to sale by or on the order of a physician.

Limitations on device use are also achieved through the following statements included in the instructions for use:

Warnings:

The dermaPACE System is not indicated for pediatric use.

The noise emitted during a dermaPACE procedure may lead to a risk of hearing impairment. All persons in the treatment area should wear hearing protection in the form of foam ear plugs or ear muffs specified by the manufacturer with a noise reduction rating of at least 20dB.

Do not use the dermaPACE in oxygen enriched environments, near flammable anesthetic gas mixtures or other potentially explosive/flammable environments.

Ensure that cleaning agents and disinfectants have evaporated completely before turning the dermaPACE Console into the ON position. Some cleaning agents and disinfectants can produce explosive gases.

When the dermaPACE device is considered for use in treatment of unresponsive wounds the patient and practitioner should carefully monitor for osteomyelitis There may be an increased risk of developing osteomyelitis when more than 7 treatments are given.

Due to the treatment with the dermaPACE, patients can experience discomfort, but the discomfort normally y resolves without intervention directly after the treatment or in the following days.

Reddening of the skin and petechiae in the treatment area has been observed in individual cases and usually resolves without intervention shortly after treatment.

Hematomas have been reported in rare cases.

It may be possible that migraine, nausea, and syncope can be induced in rare cases.

Effects on subsequent graft success are unknown and have not been evaluated.

Employing more than 4 treatments may increase risks of developing Treatment Emergent Serious Adverse Events in patients.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

The dermaPACE System has not been evaluated in:
- a foot ulcer which involves osteomyelitis diagnosed prior to initial treatment
- active cellulitis either at the site of, or in the surrounding area of, the target ulcer;
- patients who had a target ulcer that has visually purulent exudates or that has malodorous exudates on examination;
- active Charcot foot;

- patients who had a surgical procedure to correct biomechanical abnormities (e.g., lengthening of the Achilles tendon, correction of hammer toe, correction of Charcot foot) within eight weeks of initiation of treatment;
- patients with clinical evidence of lymphedema;
- patients who had chemotherapy within 60 days prior to initiation of treatment.

DEVICE DESCRIPTION

The dermaPACE System consists of a bench-top Control Console and the PACE Applicator (Figure 1). The PACE Applicator is connected to the Control Console via a six-feet-long cable. The Control Console and PACE Applicator are intended to be reusable. Single use, disposable, sterile sleeves are used to cover the applicator during use. Sterile ultrasound coupling gel ensures proper transfer of the acoustical waves to the treatment area. Both the sterile sleeves and the coupling gel are provided with the device.

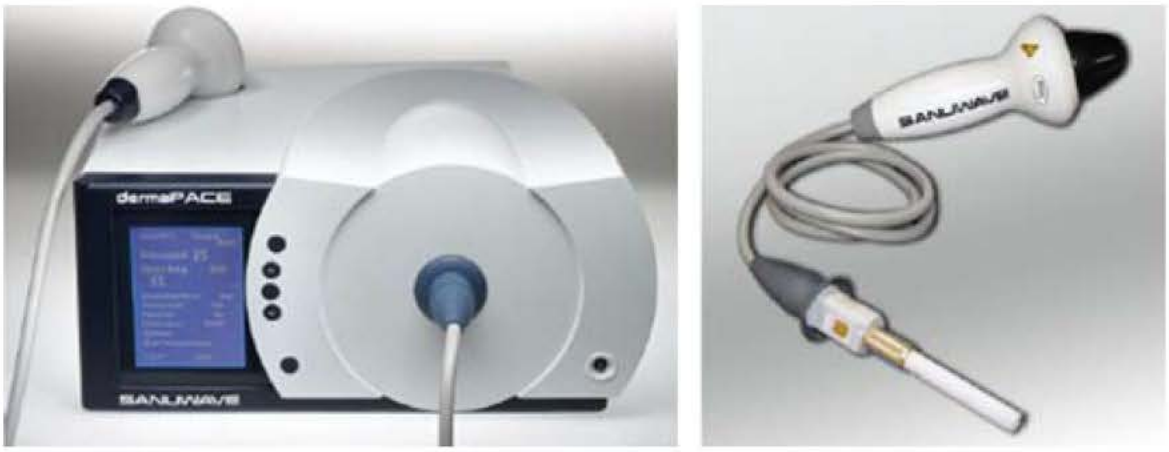

Figure 1: dermaPACE Control Console (left) and PACE Applicator (right).

The PACE Applicator generates shock waves by the electrohydraulic method. A high voltage current (18,000-23,000 Volts) (b) (4) . (b) (4) the applicator at its tip which contacts the patient (Figure 2a and b).

Figure 2a: Applicator

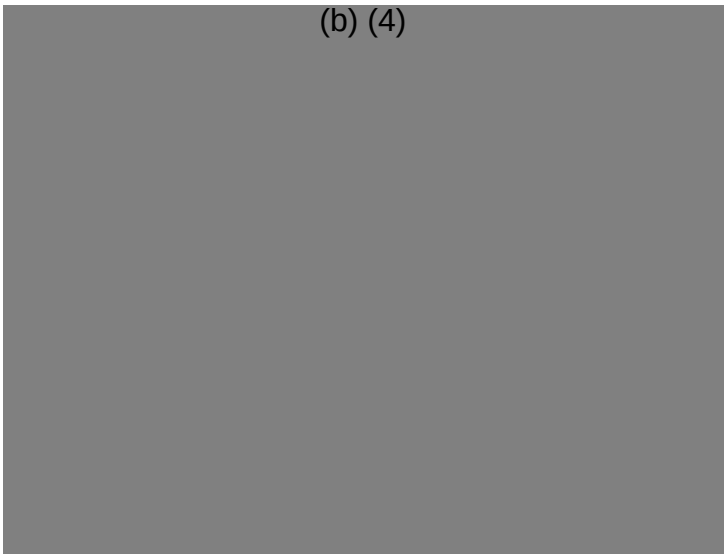

Figure 2b: Schematic representation of the focusing of shockwaves F1 (b) (4) and F2 (focus point of the shockwaves)

The acoustic pressure shock waves generated by the device consist of a dominant compressive pressure pulse, low negative pressures, and the tensile wave (Figure 3).

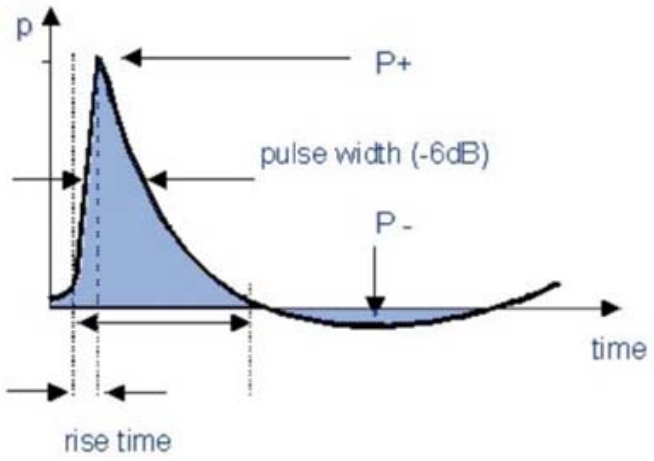

Figure 3: Pressure changes in the tissue during each pulse delivered by the device.

The device has multiple output settings, but the software will default to a standard setting of 500 pulses and a frequency of 4 pulses per second.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The dermaPACE Control Console, PACE Applicator housing, and cable are not patient contacting. No biocompatibility testing was conducted on these components of the device system.

The PACE Applicator coupling membrane was evaluated per the FDA guidance, "Use of

International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process'" (June 16, 2016). The PACE Applicator is covered with a sterile sleeve during treatment application. The PACE Applicator coupling membrane, while not patient contacting, may come into contact with the patient if there is an unintended breach in the sterile sleeve during treatment application. The coupling membrane has undergone a biocompatibility assessment, including intracutaneous toxicity, muscle implantation, systemic toxicity, and sensitization testing. **Table 1** below summarizes the biocompatibility testing that was conducted on the coupling membrane.

Table 1: Biocompatibility testing conducted on PACE Applicator membrane

Biocompatibility Test	Acceptance Criteria	Results
Cytotoxicity (Neutral Red Uptake Test)	Test system suitability conditions must be met; viability % level is (b) (4) % or greater	Pass
Cytotoxicity (MTT Test)	Test system suitability conditions must be met; viability % level is (b) (4) % or greater	Pass
USP Intracutaneous	The cumulative average erythema and edema score for each test extract and corresponding control is calculated. For each extract, a difference in average scores (test minus control) of (b) (4) or less is considered acceptable.	Acceptable
Sensitization (Kligman Maximization)	Use of Magnusson and Kligman Scale and USP Sensitization Classification	The material is classified as a non-sensitizer
USP Muscle Implant	The requirements were met if the difference between test and control score averages was not greater than (b) (4)	Pass
USP Systemic Toxicity	The test mice must not show a significantly greater reaction than the control mice	Pass

The biocompatibility of single-use, sterile probe sleeves was demonstrated in K980210 and for the transmission gel in K802146.

USE LIFE/STERILITY

The dermaPACE system is provided non-sterile. To prevent cross-contamination to both user and patients, a sterile sleeve is placed over the PACE Applicator and cable prior to treatment. Upon completion of treatment, the sleeve is removed and discarded.

Both the Control Console and PACE applicator are reusable. The use life of the Control Console is indefinite with proper maintenance and repair. The PACE applicator was shown to deliver (b) (4) repeatable shock wave pulses with bench testing. The PACE applicator is software deactivated and needs to be replaced after delivering (b) (4) pulses.

CLEANING/REPROCESSING

The dermaPACE configuration consists of the Control Console and the PACE Applicator. The PACE Applicator is connected to the Control Console via a six-feet-long cable. The PACE Applicator is covered by a single-use sterile sleeve and does not make contact with the patient. The sterile sleeve provided to the user is 120 cm long and covers the entire applicator head and most of the attached cable. No uncovered part of the device should contact the patient during normal use.

Both cleaning and low level disinfection validations of the PACE applicator were conducted in accordance with the guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff". A cleaning validation was conducted following artificial soiling with clinically relevant test soil. Two clinically relevant soil markers (protein and hemoglobin) were quantified to show removal of residual soil following cleaning using the worst case cleaning instructions provided to the end user. Following this, a disinfection validation was conducted following the worst case disinfection instructions provided to the end user. Based on the risk of the device and its potential patient contact, it was determined low level disinfection is adequate. A low level disinfection validation was conducted showing a minimum 3 log reduction of clinically relevant bacteria. Also, a reusability study confirmed that the PACE applicator can deliver its pre-programmed (b) (4) shock waves following multiple rounds of reprocessing. In this study, The PACE applicator was used to deliver shock wave pulses at a continuous rate to simulate use and the pulses were monitored to ensure regularity. Applicators were made to deliver pulses until a missed discharge or misfire was recorded at which point the total number of pulses was recorded. This test was repeated on (b) (4) applicators, and an average value for maximum number of pulses that can successfully be delivered was found. To incorporate a safety factor, the maximum number of allowed pulses was set as (b) (4) % of total number of successful pulses, resulting in a final use life expectancy of (b) (4) pulses for the applicator.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The dermaPACE system was tested in accordance with the following consensus standards and passed the following electromagnetic compatibility (EMC), electrical, mechanical, and thermal safety tests:

Table 2: EMC and electrical, mechanical and thermal safety testing

Standard	Test/Function	Results
ANSI/AAMI ES60601-1:2005/(R2012) + A1:2012	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance (IEC 60601-1:2005, MOD)	Complies
IEC 60601-1-2: 2007	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests	Complies

SOFTWARE

Software documentation was provided based on the software documentation requirement at a MAJOR software level of concern per FDA guidance: "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices", as follows:

- Software Requirements Specification
- Software and architecture design specification
- Requirements to validation traceability analysis
- Software Configuration Description
- Fault insertion and white box verification testing
- Software validation testing
- Revision Level History
- Unresolved Anomalies report
- Usability validation per IEC 60601-1-6

Adequate documentation describing the software development program as required per the guidance document was provided and deemed adequate. Verification and Validation (V&V) testing was conducted to address the potential hazards with satisfactory results. The software development procedures provide the foundation that the software will operate in a manner as described in the specifications.

The software documentation is in sufficient detail to provide reasonable assurance that the software performs as intended and all software-related risks have been adequately mitigated.

PERFORMANCE TESTING – BENCH

Additional bench testing was performed to characterize the acoustic shock waves delivered by the dermaPACE system and to ensure that the shock waves were consistent and repeatable. Technical parameters of the device that may affect the treatment were measured. These parameters included but were not limited to: volume of the pressure field, focal volume, peak compression and rarefaction acoustic pressures, energy flux density, energy per pulse, acoustic energy (audible noise). The performance testing represented normal clinical use conditions. As the dermaPACE device included a flexible membrane applicator that can be pressed against the patient's skin, the characterization of the pressure shockwaves was repeated for no compression, typical compression during normal use, and at maximum compression of the membrane. The following FDA recognized consensus standards were used:

Table 3: Engineering/Bench Tests for dermaPACE

Specification or Applied Standard	Test/Function	Results
IEC 61846 : 1998	Pressure field characterization testing	Complies
IEC 60601-2-36: 2014	Focal volume, peak compression and rarefaction acoustic pressures, energy flux density, and energy per pulse, and acoustic energy measurements	Complies

SUMMARY OF CLINICAL INFORMATION

The dermaPACE system was evaluated using two studies. The studies were designed as prospective, randomized, double-blind, parallel-group, sham-controlled, multi-center 24-week studies at 39 centers. There were 206 subjects enrolled in Study 1 and 130 subjects in Study 2 for a total of 336 subjects enrolled and treated with dermaPACE plus standard of care or standard of care alone. Standard of care included, but was not limited to, debridement, saline-moistened gauze, and pressure reducing footwear. The objective of the studies was to compare the safety and effectiveness of the dermaPACE device to sham-control application, when administered with standard of care.

Study subjects were enrolled using pre-determined inclusion/exclusion criteria to obtain a homogenous study population with chronic diabetes who had a diabetic foot ulcer that persisted for a minimum of 30 days with an area between 1cm^2 and 16cm^2, inclusive. Subjects were enrolled at Visit 1 and followed for a run-in period of two weeks. At two weeks (Visit 2 – Day 0), the first treatment was applied (either dermaPACE or sham control application) if subjects met inclusion/exclusion criteria. Applications with either dermaPACE or sham control were then made at Day 3 (Visit 3), Day 6 (Visit 4), and Day 9 (Visit 5) with the potential for 4 additional treatments in Study 2 which were administered every other week (patients with unhealed wounds were eligible for additional treatments). Subject progress including wound size was observed on a bi-weekly basis for up to 24 weeks, at a total of 12 visits (Weeks 2-24; Visits 6-17).

Study Protocols Description

The dermaPACE Diabetic Foot Ulcer study has been conducted under two separate studies using two near-identical protocols.

The first subject for Study 1 was randomized and treated in October 2007. A total of 206 subjects were enrolled in the first dermaPACE Study at 22 centers in US, 1 in England, and 1 in Germany. The last subject completed the study in September 2010.

The first subject for Study 2 was randomized and treated in June 2013. A total of 130 subjects were enrolled in the second dermaPACE Study at 18 participating centers in the United States and 1 site in Canada. The last subject completed Study 2 in May 2015.

Study Procedures

Each subject assigned to active application in Study 1 and 2 was to undergo a dermaPACE application with a total of 500 pulses (shock waves), with a pulse frequency of 4.0Hz (i.e., 4 pulses per second, 240 pulses per minute), and delivered at a power setting of E2. The minimum active application time was 2 minutes. For subjects randomized to sham application, a dummy treatment head (non-energized treatment applicator that was not connected to the generator) was applied to the subject's wound area. All subjects, in both the treatment and control groups, were positioned such that the application was not visible. While the non-energized applicator was passed across the wound area in a simulated application, 500 pulses were discharged on a second, separate applicator that was connected to the generator. The energized applicator did not contact the subject and was used only to provide the sound-effect of dermaPACE delivery.

For subjects with 2 qualifying ulcers, the oldest, largest volume or deepest ulcer was chosen (in that order). For subjects with 3 or more qualifying ulcers, the ulcer that was the median (in age, volume and depth) was chosen.

The difference between the two study designs was the number of treatment applications of the dermaPACE device. Study 1 (DERM01; n=206) prescribed four (4) device applications/treatments over a two-week period (non-responders did not receive more than 4 treatments), whereas, Study 2 (DERM02; n=130) prescribed up to eight (8) device applications (4 within the first two weeks of randomization, and 1 treatment every two weeks thereafter up to a total of 8 treatments over a 10-week period). Therefore, the length of follow-up between the last treatment and the 12 week analyses was shorter for subjects who received more than 4 treatments in Study 2. Furthermore, subjects who had non-responsive wounds by treatment 4 received as many as 8 treatments in Study 2. If the wound was determined closed by the primary investigator (PI) during the treatment regimen, additional planned applications were not performed.

Subject Selection

In both studies, subjects were required to meet all inclusion criteria and none of the exclusion criteria to be considered eligible for study participation. Prior to being randomized, all subjects' wounds were traced (Study 1) or imaged (Study 2) and were assessed for response to standard of care during the 2-week run-in period. Any subject with > 50% reduction in wound volume were removed from the study.

Overall, the inclusion and exclusion criteria were similar across both studies. The minimum age was 18 years for Study 1 and 22 years for Study 2. This did not have an impact on the overall mean age as a similar mean age was seen in both studies. Similar target ulcer criteria (i.e., wound size, duration, and penetration) and severity of diabetes were utilized in the two studies. The inclusion and exclusion criteria across studies are shown below in Tables 4 and 5.

Table 4: Inclusion Criteria for Study 1 and Study 2

Inclusion Criteria	
Study 1	**Study 2**
Is male or female ≥ 18 years of age;	Is male or female ≥ 22 years of age at Visit 1;
If female of child-bearing potential, the subject must: • Practice one of the following methods of contraception (administered for at least one month prior to the start of initial application and maintained per prescribed schedule) and continues through the duration of the study: hormonal contraceptives, intrauterine device (IUD), spermicide and barrier or implantable device, and • Have a negative urine qualitative β-HCG pregnancy test within two weeks of Visit 2;	If female of child-bearing potential, both of the following must be met at Visit 1: • Practices one of the following methods of contraception (administered for at least one month prior to the start of initial application and maintained per prescribed schedule) and continues through the duration of the study: hormonal contraceptives, intrauterine device (IUD), spermicide and barrier or implantable device, and • Has a negative urine qualitative β-HCG pregnancy test;
If female and post-menopausal, the subject must: Have had a complete hysterectomy, bilateral	If female and post-menopausal one of the following must be met at Visit 1:

Inclusion Criteria	
Study 1	**Study 2**
salpingo-oophorectomy or tubal ligation or otherwise be incapable of pregnancy, or Be postmenopausal for at least one year (absence of menses for 12 consecutive months, including spotting);	Has had a complete hysterectomy, bilateral salpingo-oophorectomy or tubal ligation or otherwise be incapable of pregnancy, or is postmenopausal for at least one year (absence of menses for 12 consecutive months, including spotting);
Has at least one diabetic foot ulcer that is located in the ankle area or below that has persisted a minimum of 30 days prior to the study Screening visit. Subjects may have more than one diabetic foot ulcer, but only one will be treated in this study. The target ulcer will be determined via utilization of a flow chart in Section 4.1 of the study protocol. **Note: Target Ulcer on Toe(s)** *For a target ulcer located on the toe(s), the tip of the dermaPACE applicator must be able to be held perpendicular to the target ulcer **and** must be able to be applied to the entire surface of the target ulcer including the area 1 cm beyond the surface of the ulcer in each direction at Visit 2.*	Has at least one diabetic foot ulcer that is located in the ankle area or below that has persisted a minimum of 30 days prior to Visit 1. Subjects may have more than one diabetic foot ulcer, but only one, the target ulcer, will be treated in this study. The target ulcer will be determined via utilization of a flow chart in Section 3 of the study protocol. **NOTE: Target Ulcer on Toe(s)** *For a target ulcer located on the toe(s), the tip of the PACE Applicator must be able to be held perpendicular to the target ulcer **and** must be able to be applied to the entire surface of the target ulcer including the area 1 cm beyond the surface of the ulcer in each direction at Visit 2.*
Is diabetic (Diabetes Mellitus) with a $Hb_{A1c} \leq 12\%$;	Has Type I or Type II Diabetes Mellitus with a $HbA_{1c} \leq 12\%$ at Visit 1;
Is capable of wound care at home;	Is capable of wound care at home;
Has a target ulcer ≥ 1.0 cm^2 and ≤ 16 cm^2;	Has a target ulcer ≥ 1.0 cm^2 and ≤ 16 cm^2 at Visits 1 and 2;
Has a target ulcer which has an Ulcer Grade 1 or 2, Stage A according to the University of Texas Diabetic Wound Classification system: Grade 1: Superficial wounds through the epidermis or epidermis and dermis that have not penetrated to tendon, capsule or bone Grade 2: Wounds that penetrate to tendon or capsule (but not to bone or into the joint) Stage A: Clean wounds (non-infected, non-ischemic);	Has a target ulcer that is Grade 1 or 2, Stage A according to the University of Texas Diabetic Wound Classification system, at Visits 1 and 2): Grade 1: Superficial wounds through the epidermis or epidermis and dermis that have not penetrated to tendon, capsule or bone Grade 2: Wounds that penetrate to tendon or capsule (but not to bone or into the joint) Stage A: Clean wounds (non-infected, non-ischemic);
Has an Ankle Brachial Index (ABI) ≥ 0.7 and ≤ 1.2, OR toe pressure > 50 mmHg, OR $tcPo_2 > 40$ mmHg;	In the leg with the target ulcer has an ABI ≥ 0.7 and ≤ 1.2 OR if the ABI is >1.20 has a toe pressure > 50 mmHg OR $tcpO_2 > 40$ mmHg at Visit 1;
Subject agrees, or if applicable the subject's legal representative agrees for the subject, to participate in the study, including all study related procedures and evaluations and documents this agreement by signing the IRB/EC-approved informed consent form.	Subject agrees, or if applicable, the subject's legal representative agrees that the subject can participate in the study, including all study related procedures and evaluation and documents this agreement by signing the IRB/EC-approved informed consent form at Visit 1 and prior to any study specific procedures.

Table 5: Exclusion Criteria for Study 1 and Study 2

Exclusion Criteria	
Study 1	**Study 2**
Female subjects who are currently pregnant or plans to become pregnant during the study; Female subjects who are nursing or actively lactating;	Is female and is currently pregnant or plans to become pregnant during the study; Is nursing or actively lactating;
Is morbidly obese (Body Mass Index ≥ 40);	Is morbidly obese (Body Mass Index ≥ 40) at Visit 1;
Is on dialysis;	Has clinically significant renal disease and/or impaired renal function defined as having an estimated creatinine clearance of ≤ 40mL/min at Visit 1;
Has either a foot ulcer which involves osteomyelitis or has osteomyelitis (Note: In order to rule out osteomyelitis on the foot, an x-ray of the foot in 3 views should be performed);	Has osteomyelitis in the foot or ankle on which the target ulcer is located at Visit 1 or 2 *Note: For a prior episode of osteomyelitis in the foot or ankle on which the target ulcer is located, the subject must have completed systemic antimicrobial therapy 60 or more days prior to the screening visit to be eligible for this study. If any portion of the systemic antimicrobial regimen for osteomyelitis is given within 60 days prior to the screening visit, the subject is excluded from this study.
Has evidence of prior ulcer in the same area as the target ulcer;	Has evidence of a prior ulcer in the same anatomic location as the target ulcer, and it has healed and re-opened within the previous 60 days;
Has a target ulcer that has decreased in volume by 50% or more (based on Canfield's web-based system) at the end of the two-week Run-in period (wound tracing at the time of randomization) as compared to the Screening visit;	Has a target ulcer that has decreased in volume by 50% or more at Visit 2 as compared to the volume at Visit 1* *Note: If volume of target ulcer is zero or not measurable at Visit 1 or Visit 2, then a decrease in *area* by 50% or more at Visit 2, as compared to the *area* at Visit 1, will exclude the subject from the study.
Has multiple foot ulcers that are connected by fistulas or has an ulcer(s) that are within 5 cm of the target ulcer;	Has multiple foot ulcers that are connected by fistulas or has an ulcer(s) that are within 5 cm of the target ulcer at Visit 1 or 2;
Has a target ulcer that tunnels into wound tracks which cannot be fully visualized from the wound surface;	Has a target ulcer that tunnels into wound tracks which cannot be fully visualized from the wound surface at Visit 1 or 2;
Has active cellulitis either at the site of, or in the surrounding area of, the target ulcer;	Has active cellulitis either at the site of, or in the surrounding area of, the target ulcer at Visit 1 or 2;
Has a target ulcer that has visually purulent exudates or that has malodorous exudates on examination;	Has a target ulcer that has visually purulent exudates or that has malodorous exudates on examination at Visit 1 or 2;

Exclusion Criteria	
Study 1	**Study 2**
Has peripheral vascular disease, per Doppler Ultrasound, requiring vascular surgery intervention;	Has peripheral vascular disease (PVD), per Doppler Ultrasound, requiring vascular surgery intervention at Visit 1 or 2;
Requires off-loading for the foot intended for study application for a reason other than for a target ulcer on the plantar surface of the foot;	Requires use of off-loading Diabetic Walker device for the foot intended for study application for a reason other than for a target ulcer on the plantar surface of the foot at Visit 1 or 2;
Has had a lower extremity revascularization procedure (e.g., percutaneous transthoracic angioplasty, vein graft bypass, etc.) within eight weeks of the study Screening visit (Visit 1);	Has had a lower extremity revascularization procedure (e.g., percutaneous transluminal angioplasty, vein graft bypass, etc.) of the index lower extremity within eight weeks prior to Visit 1;
Has active Charcot foot;	Has active Charcot foot of the index foot at Visit 1 or 2;
Has had a surgical procedure to correct biomechanical abnormities (e.g., lengthening of the Achilles tendon, correction of hammer toe, correction of Charcot foot) within eight weeks of the study Screening visit (Visit 1);	Has had a surgical procedure to correct biomechanical abnormities of the index foot (e.g., lengthening of the Achilles tendon, correction of hammer toe, correction of Charcot foot) within eight weeks prior to Visit 1;
Has had a deep vein thrombosis within six months of study Screening visit (Visit 1);	Has had a deep vein thrombosis (DVT) of the index lower extremity within six months prior to Visit 1;
Has clinical evidence of lymphedema;	Has clinical evidence of lymphedema of the index lower extremity at Visit 1;
Has had chemotherapy within 60 days prior to the study screening visit;	Has had chemotherapy within 60 days prior to Visit 1;
Has a life expectancy $\leq$ 2 years;	Has a life expectancy $\leq$ 2 years;
	Has previously participated in a dermaPACE diabetic foot ulcer study;
Has had treatment of the target ulcer with growth factors, prostaglandin therapy, negative pressure or vasodilator therapy within two weeks of the study Screening visit (Visit 1);	Has had treatment of the target ulcer with growth factors, prostaglandin therapy, negative pressure or vasodilator therapy within two weeks of Visit 1;
Is receiving $\geq$ 10 mg of steroid therapy per day (includes topicals, inhalers, etc.);	Is receiving $\geq$10 mg/day of steroid therapy;
Has sickle cell anemia;	Has sickle cell anemia;
Has a known immunodeficiency disorder to include, but not be limited to, Acquired Immunodeficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV), etc.;	Has a known immunodeficiency disorder to include, but not be limited to: Acquired Immunodeficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV), etc. at Visit 1 or 2;
Has received radiation treatment within 120 days of the study Screening visit (Visit 1);	Has received radiation treatment within 120 days prior to Visit 1;
Has received treatment with immunosuppressants, or biologically active cellular products, e.g.	Has received treatment with immunosuppressants within sixty days prior to Visit 1;

Exclusion Criteria	
Study 1	**Study 2**
Apligraf, Dermagraft, etc. within sixty (60) days of the study Screening visit (Visit 1);	
Has received treatment with acellular (collagen-based) products, e.g. Alloderm, Integra, etc. within 30 days of the study Screening visit (Visit 1);	Has received treatment with biologically active cellular products on the target ulcer, e.g. Apligraf, Dermagraft, etc. within sixty days prior to Visit 1; Has received treatment with acellular (collagen-based) products on the target ulcer, e.g. Alloderm, Integra, etc. within 30 days prior to Visit 1;
Has a current history of substance abuse (current is defined as within 120 days of the study Screening visit (Visit 1);	Has a current history of substance abuse (current is defined as within 120 days prior to Visit 1);
Has a history of major systemic infections requiring hospitalization within three months of the study Screening visit (Visit 1);	Has a history of major systemic infections requiring hospitalization within three months prior to Visit 1;
Has a current malignancy or a history of malignancy within the past five years, except for basal cell carcinoma that has been treated with local excision and is no longer present;	Has a current malignancy or a history of malignancy within five years, of Visit 1 except for basal cell carcinoma that has been treated with local excision and is no longer present;
Has a physical or mental disability or geographical concerns (e.g., residence not within reasonable travel distance) that would inhibit compliance with required study visits;	Has a physical or mental disability or geographical concerns (e.g., residence not within reasonable travel distance) that would inhibit compliance with required study visits;
Is planning to undergo an exclusionary treatment or procedure during the study;	Is planning to undergo an exclusionary treatment or procedure during the study;
Is an employee of the Investigator or study site with direct involvement in the proposed study or other studies under the direction of that Investigator or study site;	Is an employee of the Investigator or study site with direct involvement in the proposed study or other studies under the direction of that Investigator or study site;
Has participated in another clinical investigation within 30 days prior to study Screening visit (Visit 1); or	Has participated in another clinical investigation within 30 days of Visit 1; or
Is believed by the Investigator to be unwilling or unable to comply with study protocol requirements, including the application of dermaPACE or sham procedure, standard-of-care requirements, and all study-related follow up visit requirements.	Is believed by the Investigator to be unwilling or unable to comply with study protocol requirements, including the application of dermaPACE or sham treatment, standard-of-care requirements, and all study-related follow up visit requirements.

Analysis Populations

Modified Intent-to-Treat (MITT) Population: All subjects who were randomized and who provided at least one post-treatment assessment.

Per-protocol (PP) Population: All randomized subjects who follow the protocol without significant protocol deviation.

Safety Population: All randomized subjects.

In both Study 1 and Study 2 all effectiveness analyses were performed on the MITT Population and all safety variables were analyzed on the Safety Population.

Because of the difference between studies in the maximum number of treatment applications and some baseline patient characteristics such as target ulcer age (see Demographics Section), some of the results are presented separately by study.

Post Hoc analysis revealed different trends related to subject outcomes which resulted in the need to separate the analysis by number of treatments received. Therefore, the data will be separated by Study, and then the Post-Hoc analysis will discuss the safety issues which resulted in device use restrictions in number of treatments.

Study Endpoints

The following endpoints were evaluated in all subjects who had at least one dermaPACE application. The primary objective of these clinical studies was to demonstrate superiority of wound closure of the dermaPACE device to sham-control at 12 weeks post-application, when administered in conjunction with the standard of care, in the treatment of diabetic foot ulcers. A 10% difference in the point estimate for wound closure rate at 12 weeks in favor of the dermaPACE device would be considered to represent study success. Primary and secondary endpoints were evaluated for both safety and effectiveness as described below in **Table 6**.

Table 6: Overview of Primary and Secondary Endpoints

Primary Endpoints	
Study 1	**Study 2**
Complete target ulcer (wound) closure at 12 Weeks	Complete target ulcer (wound) closure at 12 weeks
Determine Rate of adverse events (AEs) at 24 weeks post initial application.	
Secondary Endpoints	
Study 1	**Study 2**
• Wound area, volume, depth and perimeter	• Wound area, perimeter, depth and volume
• Rate of wound closure	• Rate of wound closure
• Mean wound area reduction	• Mean wound area reduction
• Percentage of subjects with increase in wound area	• Percentage of subjects with increase in wound area
• Rate of Treatment Emergent Adverse Events, Treatment Emergent Serious Adverse Events, and Device-Related Treatment Emergent Adverse Events	• Rate of Treatment Emergent Adverse Events, Treatment Emergent Serious Adverse Events, and Device-Related Treatment Emergent Adverse Events
• Recurrence and Amputation Rate	• Recurrence and Amputation Rate
• Rate of dermaPACE malfunctions	
• Changes in baseline values in wound pain assessed by the Visual Analog Scale (VAS)	

The prospectively defined primary effectiveness endpoint for the dermaPACE studies was the incidence of complete wound closure at 12 weeks post-initial application of the dermaPACE

system (active or sham). Complete wound closure was defined as skin re-epithelialization without drainage or dressing requirements, confirmed over two consecutive visits within 12-weeks (as determined by blinded evaluator). If the wound was considered closed for the first time at the 12 week visit, then the next visit was used to confirm closure. Investigators continued to follow subjects and evaluate wound closure through 24 weeks.

Primary safety endpoint was evaluated by assessing the rate of adverse events of the dermaPACE and sham control through 24 weeks post initial application, including serious adverse events, device-related adverse events, and dermaPACE malfunctions throughout the application, treatment, and follow-up periods. Other secondary effectiveness endpoints included: time to achieve complete wound closure and comparison of the mean wound reduction in area, volume, depth and perimeter.

Study Results for Study 1

Demographics

The total number of subjects screened in the dermaPACE trial at the 24 clinical sites was 293 with 87 screen failures resulting in a total randomized population of 206 subjects; 107 randomized to dermaPACE and 99 randomized to sham-controls.

A comparison across these cohorts was completed for each demographic (**Table 7**). Notable differences were that the average age for all subjects treated with dermaPACE was higher than subjects treated with sham-control, 60.4 ±10.4 years versus 56.2 ±9.4 years (p=0.0050) with a median age of 62.0 and 57.0, respectively. Target ulcers treated with dermaPACE were larger in average area than those in sham-control subjects, 3.5 ± 3.2 cm^2 versus 2.8 ± 1.8 cm^2, respectively (p=0.1151). While the difference in target ulcer age is not statistically significant this finding is clinically significant.

Table 7: Summary of Subject Demographics

	Study 1	
Demographic	**dermaPACE**	**Sham Control**
Age (years)	60.4±10.4	56.2±9.4
Gender (% Male)	77.6%	83.8%
Height (inches)	70.0±4.1	70.0±3.8
Weight (pounds)	222.0±42.2	221.5±44.7
BMI (kg/m^2)	31.8±5.1	31.6±5.2
Smokers	13.1%	22.2%
Target Ulcer Size (cm^2)	3.46±3.21	2.79±2.23
Target Ulcer Age (weeks)	48.7±66.6	69.5±107.5
HbA1c<7	30.8%	33.3%
HbA1c ≥7	69.2%	66.7%

Subject Accountability

A summary of the subject accounting for Study 1 is provided below (**Table 8**). Early terminations are those subjects that were discontinued due to adverse event or consent voluntarily/involuntarily withdrawn. Subjects discontinued due to an adverse event were considered failures for all following visits.

The Intent-to-Treat (ITT) population included those subjects who satisfied all entry criteria to be randomized, although may or may not have received a device application, resulting in a total ITT population of 206 subjects.

The Modified Intent-to-Treat (MITT) population was defined as any subject receiving at least one Active or sham-control treatment resulting in a total MITT of 206 subjects since all subjects who were randomized received at least one application. By this definition in the dermaPACE protocol, the MITT population is the ITT population.

Table 8: Subject Accountability

Study 1 Patient Accountability For All Subjects		
Event	**dermaPACE (N=107)**	**Control (N=99)**
Subjects Screened	293	
Subjects Randomized	206	
Subjects not randomized	87 (29.7%)	
Subjects completing treatment phase (i.e. completed 12 weeks)	88 (82.2%)	76 (76.8%)
Withdrawn during treatment	19	23
Subjects completing follow-up phase (i.e. completed 24 weeks)	78 (72.9%)	71 (71.7%)
Withdrawn during follow-up	10	5

Table 9: Study 1 Reasons for Subject Withdrawal from Study

Study 1 Reasons for Subject Withdrawal From Study						
Premature Termination Reason	**dermaPACE (N=107)**		**Control (N=99)**		**Total (N=206)**	
	Treatment	**Follow-up**	**Treatment**	**Follow-up**	**Treatment**	**Follow-up**
Adverse Event	9 (8.4%)	4 (3.7%)	6 (6.0%)	4 (4.0%)	15 (7.3%)	8 (3.9%)
Death	1 (0.9%)	1 (0.9%)	1 (1.0%)	0	2 (1.0%)	1 (0.5%)
Subject Withdrew Consent	5 (4.7%)	2 (1.9%)	7 (7.1%)	1 (1.0%)	12 (5.8%)	3 (1.5%)
Lost to Follow-up	3 (2.8%)	0	4 (4.0%)	0	7 (3.4%)	0
Investigator's Decision	1 (0.9%)	2 (1.9%)	1 (1.0%)	0	2 (1.0%)	2 (1.0%)
Other	0	1 (0.9%)	4 (4.0%)	0	4 (1.9%)	1 (0.5%)
Total	19 (17.8%)	10 (9.3%)	23 (23.3%)	5 (5.1%)	42 (20.4%)	15 (7.3%)

Fifty-seven (57) subjects, 29 dermaPACE, and 28 sham-control prematurely discontinued throughout the course of the study. These subjects prematurely discontinued for the following reasons: adverse events (23), withdrawal of consent (15), lost-to-follow (7), Investigator or Sponsor's decision (4), death (3), and other (5). A total of 164 subjects at 12 weeks and 149 subjects at 24 weeks remained in the ITT (MITT) populations for analysis.
The follow-up rate at 24 weeks was 73% and 72% for the dermaPACE and control cohorts, respectively.

Effectiveness Results

The treatment group received wound care consistent with the standard of care, in addition to device application.

Primary Endpoint of Complete Wound Closure (Table 10)

Study 1: At the 12-week endpoint, 20.6% dermaPACE subjects had complete wound closure, compared to 15.2% in the control group (p = 0.363). At the 24-week endpoint, the rate of wound closure in the dermaPACE cohort was 39.3% compared to 26.3% for the control group (p = 0.054).

Table 10: Primary Endpoint of Complete Wound Closure Study 1

Complete Wound Closure								
Study	Visit	dermaPACE			Sham			χ^2 p-value
		Total Enrolled N[1]	Actual N[2]	n (%)[3]	Total Enrolled N[1]	Actual N[2]	n (%)[3]	
Study 1	Week 12	107	90	22 (20.6%)	99	81	15 (15.2%)	0.363
	Week 24	107	82	42 (39.3%)	99	74	26 (26.3%)	0.054

[1] Total number of randomized subjects per study and pooled

[2] Total number of subjects who completed the 12 or 24 weeks in each study

[3] Wound closure percentage and χ^2 p-value calculated using all enrolled subjects

Secondary Endpoints

Rate of Wound Closure Study 1

The time to reach complete wound closure was analyzed over the full 24 weeks of the study. Figure 4 presents Kaplan-Meier estimates by treatment group for the MITT population. The difference in time to wound closure between groups was not statistically significant at the 0.05 level (p=0.102) but there appears to be a clinically significant difference among wound closure rates showing continuing improvement in the dermaPACE treatment group from 12 weeks to 24 weeks after treatment as well as improved wound closure rates in the dermaPACE treatment group compared to sham.

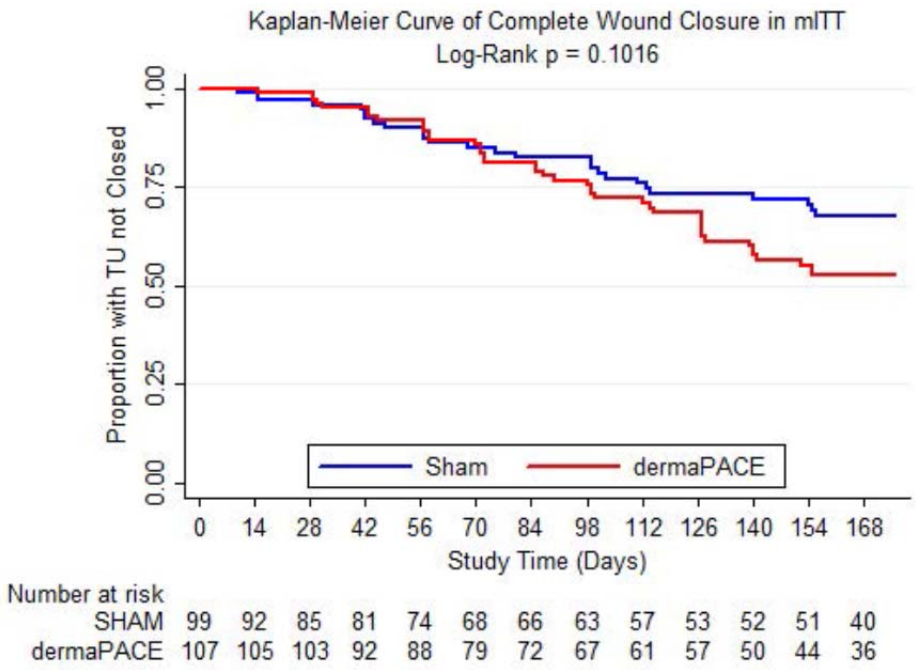

Figure 4: Kaplan-Meier Curve of Complete Wound Closure; Study 1

Demographic Stratification of Wound Closure Rates

Wound closure rates in dermaPACE treated subjects were higher for male subjects and smokers through 24 weeks. A trend of higher rates of wound closure in dermaPACE treated subjects with lower BMI at 12 weeks seemed to continue to trend towards higher rates of wound closure regardless of BMI by 24 weeks. This may indicate that the dermaPACE treatment has improved rates of wound closure when compared to sham treatment by 24 weeks regardless of BMI when receiving 1-4 treatments. Wounds that were less than 12 months of age also demonstrated better wound closure than older wounds at 12 and 24 weeks. These differences will be discussed further in the Post Hoc analyses later in the document.

Table 11a: Study 1 Results Stratified by Demographic Characteristics at 12 Weeks
(% Wound Closure by 12 weeks)

Demographic		dermaPACE			Control		
		N[1]	n[2]	%	N[1]	n[2]	%
Age (years)	< 65	70	15	21.5%	81	13	16.1%
	≥ 65	37	7	18.9%	18	2	11.2%
Gender	Male	83	20	24.1%	83	11	13.3%
	Female	24	2	8.4%	16	4	25.0%
Smoking Status	Non-Users	93	19	20.4%	77	13	16.8%
	Users	14	3	21.4%	22	2	9.1%
BMI (kg/m^2)	< 32	53	14	26.5%	50	8	16.0%
	≥ 32	54	8	14.8%	49	7	14.3%
Weight (pounds)	< 220	49	12	24.5%	47	9	19.1%
	≥ 220	58	10	17.3%	52	6	11.4%
Height (inches)	< 70	44	3	6.8%	42	8	19.0%
	≥ 70	63	19	30.2%	57	7	12.2%
Ulcer Age (months)	< 12	80	19	23.8%	66	14	21.2%
	≥ 12	27	3	11.1%	33	1	3.0%
HbA1c	<7	33	8	24.2%	33	5	15.1%
	≥7	74	14	18.9%	66	10	15.1%

[1]The total number of subjects in each demographic cohort
[2]The number of subjects with wound closure in each cohort

Table 11b: Study Results Stratified by Demographic Characteristics at 24 Weeks
(% Wound Closure by 24 weeks)

Demographic		dermaPACE			Sham Control		
		N[1]	n[2]	%	N[1]	n[2]	%
Age (years)	< 65	70	28	40.0%	81	22	27.2%
	≥ 65	37	14	37.9%	18	4	22.2%
Gender	Male	83	36	43.3%	83	20	24.1%
	Female	24	6	25.0%	16	6	37.6%
Smoking Status	Non-Users	93	36	38.7%	77	20	25.9%
	Users	14	6	42.8%	22	6	27.3%
BMI (kg/m^2)	< 32	53	22	41.4%	50	14	28.0%
	≥ 32	54	20	37.1%	49	12	24.5%
Weight (pounds)	< 220	49	21	42.9%	47	15	31.9%
	≥ 220	58	21	36.2%	52	11	21.2%
Height (inches)	< 70	44	13	29.6%	42	14	33.3%
	≥ 70	63	29	46.0%	57	12	21.1%
Ulcer Age (months)	<12	80	35	43.8%	66	22	33.3%
	≥ 12	27	7	25.9%	33	4	12.1%
HbA1c	<7	33	14	42.4%	33	9	27.3%
	≥7	74	28	37.8%	66	19	28.8%

[1]The total number of subjects in each demographic cohort
[2]The number of subjects with wound closure in each cohort

Mean Wound Area Reduction

The mean wound area reduction for both cohorts in Study 1 is presented below in Table 12. As the table demonstrates, the mean wound reduction for dermaPACE subjects at 24 weeks was $1.92cm^2$ compared to 0.16 cm^2 in the control group (p=0.047). Because means can be influenced by outliers in the data, the median wound reduction was also reported and favored dermaPACE.

Table 12: Mean Wound Area Reduction

Study Visit	Wound Area Reduction from Baseline						T-test p-value
	dermaPACE			Sham Control			
	N	Mean (cm^2)	Med. (cm^2)	N	Mean (cm^2)	Med. (cm^2)	
Week 12	86	1.90	1.36	73	0.16	1.14	0.0046
Week 24	72	1.92	1.47	67	0.16	1.28	0.0471

Additional descriptive analyses related to wound closure rate association with these variables will be discussed in the Post HOC analyses section to follow.

Safety Results Study 1

Adverse event rates between the dermaPACE and control subjects were reported through 24 weeks follow-up. The primary safety endpoint was all adverse events. A total of 80.4% (86 out of 107) of dermaPACE and 78.8% (78 out of 99) of control subjects experienced an adverse event (p = 0.725). Secondary safety endpoints included treatment emergent adverse events (TEAE), serious adverse events, and device-related adverse events. The dermaPACE device demonstrated comparable AE rates overall with lower rates of SAE and treatment emergent SAE (TESAE). Also, the device group appeared to have lower rates of recurrence, partial amputation rates and target foot amputation rates (see Table 13).

Table 13: Safety Endpoints of Study 1 (All subjects received 1-4 treatments)

Safety Endpoints	dermaPACE (n=107)	Sham-Control (n=99)	p-value
Primary Endpoint	n (%)	n (%)	
All Adverse Events (24-Weeks)	86 (80.4%)	78 (78.8%)	0.725
Secondary Endpoints			
Treatment-Emergent AEs	58 (54.2%)	50 (50.5%)	0.545
Serious AEs	34 (31.8%)	37 (37.4%)	0.384
Treatment-Emergent Serious AEs	12 (11.2%)	20 (20.2%)	0.069
Device-Related Treatment-Emergent AEs	7 (6.5%)	2 (2.0%)	0.117
Additional Safety Analyses			
Recurrence Rate[2]	3 (7.1%)	4 (15.4%)	0.415
Partial Amputation Rate	2 (1.9%)	5 (5.1%)	0.265
Target Foot Amputation Rate	4 (3.7%)	11 (11.1%)	0.059

Note:
[1] Fisher's Exact test (2-sided)
[2] Recurrence rates determined as 3/42 (7.1%) and 4/26 (15.4%), respectively.
Serious AEs were defined as AEs which required medical intervention and were disruptive to the daily activities of the subject.
Device related Treatment-Emergent AEs were defined as AEs which were determined by the Investigators to be possibly or probably related to the treatment.

Changes in Baseline Values in Wound Pain Assessed by Visual Analog Scale (VAS)
The Visual Analog Scale (VAS) was used to assess target ulcer pain at each visit throughout the trial. The VAS was used to assess target ulcer pain only, not related to neuropathic pain. The VAS scale was a 10-cm line with no pain beginning at 0-cm to worst pain at 10-cm. The final results showed there was no significant change in target ulcer pain from baseline and there was no significant difference in target ulcer pain between the dermaPACE and Sham-control groups throughout the application, treatment and follow-up periods of the study.

There was no significant difference in pain between the dermaPACE and Sham-control groups, at 12 weeks, 53.1% of dermaPACE subjects experienced a 30 % decrease in pain vs. 54.1% in the Sham-Control. By 24 weeks, 76.2% of the dermaPACE subjects showed a 30% decrease in pain compared to 54.3% of control.

DermaPACE Device Malfunctions
There were twelve instances where replacement of the initial console was required. Reasons for the twelve replacements included Console to Applicator contact errors, high voltage system time-outs, and hard shut-down anomalies. The clinical sites that had control consoles due for routine electrical safety checks or experienced a console related error message that required attention by SANUWAVE were sent another console immediately. The sites were instructed to discontinue using the console until they received a replacement console. None of the device malfunctions resulted in any safety related issues with the study subjects.

Treatment-Emergent Adverse Events (TEAEs)
A treatment-emergent adverse event (TEAE) was defined as an event that started or worsened in severity during or after the initial application with the study device through 30 days after the last device application. Subjects who reported more than one event for a System Organ Class or Preferred Term were only counted once for each category.

The overall rate of treatment-emergent adverse events did not differ significantly between the two treatment groups. There were 58 out of 107 (54.2%, 95% CI: [44.3, 63.9]) dermaPACE subjects that experienced at least one TEAE. Likewise, there were 50 out of 99 (50.5%, 95% CI: [40.3, 60.7]) sham-control subjects that experienced at least one TEAE. The rate of treatment-emergent adverse events between dermaPACE and sham-control was not statistically different at the 0.05 level (p=0.5452).

Table 14: Treatment Emergent AEs
(Treatment Emergent Serious Adverse Events (TESAE) and TEAE); Study 1

		Study 1	
Safety Endpoints		**dermaPACE**	**Control**
Identified Safety Risk	**Related Adverse Event**	**(N=107) n (%)**	**(N=99) n (%)**
Adverse Tissue Reaction	Wound Complication	0 (0.0%)	1 (1.0%)
	Wound Drainage Procedure	0 (0.0%)	0 (0.0%)
	Excoriation	2 (1.9%)	1 (1.0%)
	Post Procedural Hematoma	1 (0.9%)	0 (0.0%)

		Study 1	
Safety Endpoints		**dermaPACE**	**Control**
	Application Site Complication*	3 (2.8%)	2 (2.0%)
	Inflammation	0 (0.0%)	0 (0.0%)
Infection	Bacterial Infection***	1 (0.9%)	0 (0.0%)
	Infected Skin Ulcer**	0 (0.0%)	0 (0.0%)
	Localized Infection	0 (0.0%)	0 (0%)
	Osteomyelitis	0 (0.0%)	2 (2.0%)
	Paronychia	0 (0.0%)	0 (0.0%)
	Any Abscess Bacterial	0 (0.0%)	2 (2.0%)
	Cellulitis	10 (9.4%)	7 (7.0%)
	Application Site Infection/Cellulitis	14 (13.1%)	15 (15.1%)
	Any Wound Infection	3 (2.8%)	2 (2.0%)
	Sepsis	0 (0.0%)	0 (0.0%)
	Septic Shock	0 (0.0%)	0 (0.0%)
	Tinea Pedis	0 (0.0%)	1 (1.0%)
	Gangrene	0 (0.0%)	0 (0.0%)
	Other	16 (15%)	4 (4.0%)
	Percentage of subjects with at least 1 Infection	30 (28%)	25 (25.3%)
Application Site Pain	Procedural Pain at application site	2 (1.1%)	0 (0%)
	Application Site Pain	5 (4.7%)	12 (12.1%)
	Extremity Pain	3 (2.8%)	0 (0.0%)

*Necrosis, Erythema, Irritation
**Includes Diabetic Foot Infection
***Includes AE classified as Infection other than ulcer infection, cellulitis or osteomyelitis

Table 15: Investigator Assessed Device Related Treatment Emergent Adverse Events Study 1

Study No.	Subject Number	Treatment Assignment	Event Verbatim Term	Study Device Causality
1	16015	dermaPACE	Burning Sensation Left Foot Secondary to dermaPACE Treatment	Probable
1	16015	dermaPACE	Enlargement Left Target Ulcer	Possible
1	16015	dermaPACE	Left Foot Bacterial Infection – Target Ulcer	Possible
1	23007	dermaPACE	Burning of the Right Foot at the Target Ulcer After the First Application	Possible
1	26001	dermaPACE	Headache	Probable
1	26001	dermaPACE	Headache	Probable
1	28004	dermaPACE	Target Wound with Light Staphylococcus, Klebsiella/ Enterobacter-Like Diptheroids Infection	Possible
1	06009	Sham-control	Increased Sensation More Feeling Not Pain Target Ulcer Left Foot	Possible
1	23005	Sham-control	Burning in Left Foot After Application of the Foot in General	Possible

Serious Adverse Events (SAEs)

The overall rate of serious adverse events after randomization was slightly higher in the sham-control group but did not differ in a clinically significant manner between the two treatment groups. There were 34 out of 107 (31.8%, 95% CI: [23.1, 41.5]) dermaPACE subjects that experienced at least one SAE. Likewise, there were 37 out of 99 (37.4%, 95% CI: [27.9, 47.7]) sham-control subjects that experienced at least one SAE. The rate of serious adverse events between dermaPACE and sham-control was not statistically different at the 0.05 level (p=0.3835).

Treatment-Emergent Serious Adverse Events (TESAEs)

The overall rate of treatment-emergent serious adverse events (TESAEs) was lower in the dermaPACE group. There were 12 out of 107 (11.2%, 95% CI: [5.9, 18.8]) dermaPACE subjects that experienced at least one TESAE. Likewise, there were 20 out of 99 (20.2%, 95% CI: [12.8, 29.5]) sham-control subjects that experienced at least one TESAE. The rate of TESAEs between dermaPACE and sham control was not statistically significant at the 0.05 level (p=0.0688).

Table 16: Infections and Infestations Study 1 referenced in Table 14 TESAE

Adverse Event	Trial 1	
	dermaPACE	Sham-Control
	N=107	N=99
Infections and infestations	**7 (6.5%)**	**15 (15.2%)**
Abscess	0 (0.0%)	2 (2%)
Abscess limb	0 (0.0%)	1 (1%)
Cellulitis	1 (0.9%)	1 (1%)
Gangrene	0 (0.0%)	0 (0.0%)
Application Site Infection	4 (3.7%)	7 (7.1%)
Infected skin ulcer	0 (0.0%)	0 (0.0%)
Localized infection	0 (0.0%)	0 (0.0%)
Pneumonia	1 (0.9%)	0 (0.0%)
Osteomyelitis	0 (0.0%)	3 (3%)
Scrotal abscess	0 (0.0%)	0 (0.0%)
Sepsis	0 (0.0%)	0 (0.0%)
Septic shock	0 (0.0%)	0 (0.0%)
Urinary Tract Infection	0 (0.0%)	1 (1%)
Wound infection	1 (0.9%)	0 (0.0%)

As seen in Table 16, the largest contributor to the overall TESAE adverse event rate was the system organ class of Infections and Infestations. Within this system organ class, specific to subjects with TESAEs, 7 of the 107 (6.5%) dermaPACE subjects had a TESAE in the System Organ Class of Infections and Infestations. However, 15 of the 99 (15.2%) sham-control subjects

had a TESAE in this System Organ Class with 7 of the 15 subjects having an application site-related TESAE.

Related to investigator assessed AE which were related to the device, there were 7 out of 107 (6.5%) dermaPACE subjects that experienced at least one related TEAE. and 2 out of 99 (2.0%) sham-control subjects that experienced at least one related TEAE (p=0.117) see table 15.

STUDY 2

Demographics

The total number of subjects screened in the dermaPACE trial at the 18 clinical sites was 261with 87 screen failures resulting in a total randomized population of 130 subjects; 65 randomized to dermaPACE and 65 randomized to sham-controls.

A comparison across these cohorts was completed for each demographic (**Table 17**). The average age for all subjects treated with dermaPACE was higher than subjects treated with sham-control, 59.1±9.4 years versus 56.8±10.7 years (p=0.195) with a median age of 59 and 57, respectively. Target ulcers treated with dermaPACE were not as old as than those in sham-control subjects, there were more smokers in the dermaPACE treatment group compared to sham, and the sham treatment group had about 15% more subjects with poor glycemic control.

Table 17: Summary of Subject Demographics

	Study 2	
Demographic	**dermaPACE**	**Sham Control**
Age (years)	59.1±9.4	56.8±10.7
Gender (% Male)	83.1%	75.4%
Height (inches)	69.6±3.9	70.7±4.8
Weight (pounds)	217.2±45.0	225.5±49.0
BMI (kg/m^2)	31.4±5.6	31.6±5.5
Smokers	18.5%	13.9%
Target Ulcer Size (cm^2)	3.71±2.83	3.73±2.82
Target Ulcer Age (weeks)	44.6±53.4	49.7±59.2
HbA1c<7	34.9%	20.6%
HbA1c ≥7	65.1%	79.4%

Subject Accountability

A summary of the subject accounting for Study 2 is provided below (**Table 18**). Early terminations are those subjects that were discontinued due to adverse event or consent voluntarily/involuntarily withdrawn. Subjects discontinued due to an adverse event were considered failures for all following visits.

The Intent-to-Treat (ITT) population included those subjects who satisfied all entry criteria to be randomized, although may or may not have received a device application, resulting in a total ITT population of 130 subjects.

The Modified Intent-to-Treat (MITT) population was defined as any subject receiving at least one Active or sham-control treatment resulting in a total MITT of 130 subjects since all subjects who were randomized received at least one application. By this definition in the dermaPACE protocol, the MITT population is the ITT population.

Table 18: Study 2 Subject Accountability

Study 2 Patient Accountability For All Subjects		
Event	**dermaPACE (N=65)**	**Control (N=65)**
Subjects Screened	261	
Subjects Randomized	130	
Subjects not randomized	131 (50.2%)	
Subjects completing treatment phase (i.e. completed 12 weeks)	50 (76.9%)	55 (84.6%)
Withdrawn during treatment	15	10
Subjects completing follow-up phase (i.e. completed 24 weeks)	43 (66.2%)	50 (76.9%)
Withdrawn during follow-up	7	5

Table 19: Study 2 Reasons for Subject Withdrawal from Study

Study 2 Reasons for Subject Withdrawal From Study						
Premature Termination Reason	**dermaPACE (N=65)**		**Control (N=65)**		**Total (N=130)**	
	Treatment	**Follow-up**	**Treatment**	**Follow-up**	**Treatment**	**Follow-up**
Adverse Event	6 (9.2%)	4 (6.2%)	4 (1.9%)	2 (1.0%)	10 (7.7%)	6 (4.6%)
Death	0	0	0	0	0	0
Subject Withdrew Consent	4 (6.2%)	0	3 (1.5%)	1 (0.5%)	7 (5.4%)	1 (0.8%)
Lost to Follow-up	3 (4.6%)	1 (1.5%)	2 (1.0%)	1 (0.5%)	5 (3.8%)	2 (1.5%)
Investigator's Decision	2 (3.1%)	2 (3.1%)	0	0	2 (1.5%)	2 (1.5%)
Other	0	0	1 (0.5%)	1 (0.5%)	1 (0.8%)	1 (0.8%)
Total	15 (23.1%)	7 (10.8%)	10 (15.4%)	5 (7.7%)	25 (19.2%)	12 (9.2%)

Thirty-seven (37) subjects, 25 dermaPACE, and 12 sham-control prematurely discontinued throughout the course of the study. These subjects prematurely discontinued for the following reasons: adverse events (16), withdrawal of consent (8), lost-to-follow (7), Investigator or Sponsor's decision (4), death (0), and other (2). A total of 105 subjects at 12 weeks and 93 subjects at 24 weeks remained in the ITT (MITT) populations for analysis.

The follow-up rate at 24 weeks was 66.2% and 76.9% for the dermaPACE and sham cohorts, respectively.

In Study 1 where subjects received 4 or fewer treatments, the loss to follow up rates at 24 weeks were 27% for the dermaPACE cohort and 28% for the control group. In Study 2 where subjects received 4 or as many as 8 treatments, the loss to follow up rates at 24 weeks were 33.8% in the dermaPACE cohort and 23.1% in the control.

Effectiveness Results

The treatment group received wound care consistent with the standard of care, in addition to device application.

Primary Endpoint of Complete Wound Closure

At the 12-week endpoint, 26.2% dermaPACE subjects had complete wound closure, compared to 23.1% in the control group (p = 0.684). At the 24-week endpoint, the rate of wound closure in the dermaPACE cohort was 35.4% compared to 26.2% for the control group (p = 0.254).

Table 20: Primary Endpoint of Complete Wound Closure Study 2

Complete Wound Closure								
Study	Visit	dermaPACE			Sham			χ^2 p-value
		Total Enrolled N[1]	Actual N[2]	n (%)[3]	Total Enrolled N[1]	Actual N[2]	n (%)[3]	
Study 2	Week 12	65	54	17 (26.2%)	65	59	15 (23.1%)	0.684
	Week 24	65	40	23 (35.4%)	65	39	17 (26.2%)	0.254

[1] Total number of randomized subjects per study and pooled

[2] Total number of subjects who completed the 12 or 24 weeks in each study

[3] Wound closure percentage and χ^2 p-value calculated using all enrolled subjects

Secondary Endpoints

Rate of Wound Closure

The time to reach complete wound closure was analyzed over the full 24 weeks of the study. Figure 5 presents Kaplan-Meier estimates by treatment group for the ITT population. The difference in time to wound closure between groups was not statistically significant at the 0.05 level (p=0.188).

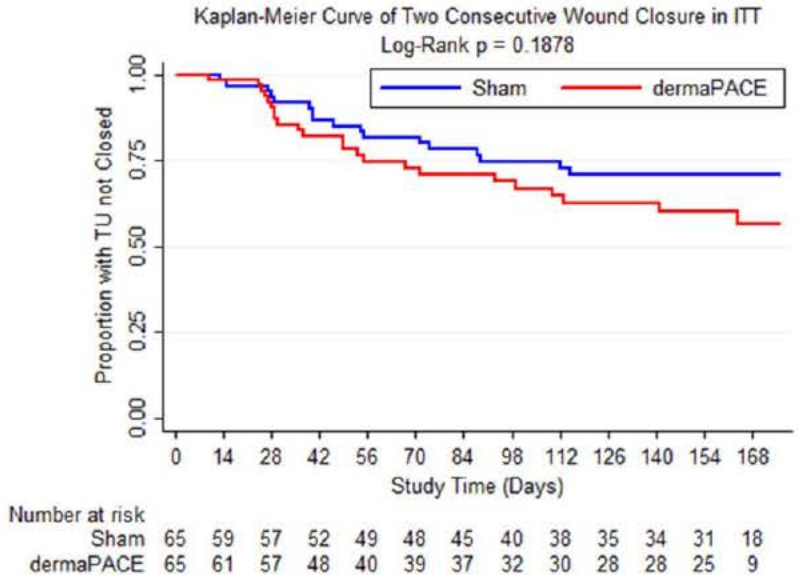

Figure 5: Kaplan-Meier Curve of Complete Wound Closure; Study 2

Demographic Stratification of Wound Closure Rates

The success results for Study 2 at 12 and 24 weeks have been stratified by demographic characteristics to determine if any notable differences in dermaPACE performance were identified when each characteristic is compared. Of note, wound closure rates (through 24 weeks) in subjects with BMI< 32 who received dermaPACE were 52% compared to wound closure rates in dermaPACE subjects whose BMI was ≥ 32 which were 21%. A similar trend is observed in subjects with ulcers <12 months (see Table 21 and 22 below). This may indicate that dermaPACE treatment has poorer performance in subjects (who mostly received 8 treatments) in patients who are obese in patients with older ulcers. Wound closure rates were also observed to be better through 24 weeks in subjects with uncontrolled diabetes as evidence by reported HgbA1c. There were no statistically significant differences observed between the two groups at 12 weeks although a trend of greater wound closure in patients with uncontrolled diabetes was observed. These variations in wound closure will also be evaluated in the Post Hoc analyses later in this document.

Table 21: Results Stratified by Demographic Characteristics at 12 Weeks (% Wound Closure)

Demographic		dermaPACE			Control			p-value
		N	n	%	N	n	%	
Age (years)	< 65	50	11	22.0	48	9	18.8	0.690
	≥ 65	15	6	40.0	17	6	35.3	0.784
Gender	Male	54	14	25.93	49	11	22.45	0.6810
	Female	11	3	27.27	16	4	25.00	0.8947
Smoking Status	Non-Users	53	13	24.53	56	13	23.21	0.8722
	Users	12	4	33.33	9	2	22.22	0.5770
BMI (kg/m^2)	< 32	31	11	35.48	37	8	21.62	0.2045
	≥ 32	34	6	17.65	28	7	25.00	0.4791
Weight (pounds)	< 220	37	10	27.03	31	6	19.35	0.4576
	≥ 220	28	7	25.00	34	9	26.47	0.8952
Height (inches)	< 70	28	6	21.43	30	9	30.00	0.4563
	≥ 70	37	11	29.73	35	6	17.14	0.2088
Ulcer Age (months)	< 12	33	11	33.33	32	11	34.38	0.9293
	≥ 12	32	6	18.75	33	4	12.12	0.4590

[N]The total number of subjects in each demographic cohort
[n]The number of subjects with wound closure in each cohort

Table 22: Results Stratified by Demographic Characteristics at 24 Weeks (% Wound Closure)

Demographic		dermaPACE			Sham Control			p-value
		N	n	%	N	n	%	
Age (years)	< 65	50	17	34.00	48	11	22.92	0.2247
	≥ 65	15	6	40.00	17	6	35.29	0.7838
Gender	Male	54	19	35.19	49	13	26.53	0.3432
	Female	11	4	36.36	16	4	25.00	0.5252
Smoking Status	Non-Users	53	18	33.96	56	15	26.79	0.4150
	Users	12	5	41.67	9	2	22.22	0.3496
BMI (kg/m^2)	< 32	31	16	51.61	37	8	21.62	0.0100
	≥ 32	34	7	20.59	28	9	32.14	0.3008
Weight (pounds)	< 220	37	14	37.84	31	6	19.35	0.0957
	≥ 220	28	9	32.14	34	11	32.35	0.9859
Height (inches)	< 70	28	7	25.00	30	11	36.67	0.3372
	≥ 70	37	16	43.24	35	6	17.14	0.0163

Demographic		dermaPACE			Sham Control			p-value
		N	n	%	N	n	%	
Ulcer Age (months)	< 12	33	16	48.48	32	11	34.38	0.2485
	≥ 12	32	7	21.88	33	6	18.18	0.7098

[N]The total number of subjects in each demographic cohort
[n]The number of subjects with wound closure in each cohort

Mean Wound Area Reduction

The mean wound area reduction for both cohorts in Study 2 is presented below in Table 23. As the table demonstrates, the mean wound reduction for dermaPACE subjects at 24 weeks was 2.43cm^2 compared to 1.73cm^2 in the control group. The median wound area reduction values for dermaPACE at 24 weeks were 1.04 cm^2 compared to 2.04 cm^2 for the sham treatment at 24 weeks which makes the median dermaPACE wound area reduction lower than the mean wound area reduction. Additional descriptive analyses related to the wound closure rate association with these variables are discussed in the Post HOC analyses section to follow. These data indicate that subjects who received 1-4 sham treatments had better wound closure rates than subjects who received 8 dermaPACE treatments. This difference in wound closure rates, is a likely contributor to the higher median wound reduction observed in the sham treatment group when compared to the dermaPACE treatment group.

Table 23: Mean Wound Area Reduction

Study Visit	Wound Area Reduction from Baseline						T-test p-value
	dermaPACE			Sham Control			
	N	Mean (cm^2)	Med. (cm^2)	N	Mean (cm^2)	Med. (cm^2)	
Week 12	53	2.07	1.40	56	1.43	1.25	0.2440
Week 24	41	2.43	1.40	50	1.73	2.05	0.4474

Safety Results

Adverse event rates between the dermaPACE and control subjects were reported through 24 weeks follow-up. The primary safety endpoint was all adverse events. A total of 61.54% of dermaPACE and 52.3% of control subjects experienced an adverse event. Secondary safety endpoints included treatment emergent adverse events, serious adverse events, and device-related adverse events. This table indicates an increase rate of SAE and TESAE in the dermaPACE cohort compared to sham.

Table 24: Safety Endpoints

Safety Endpoints	dermaPACE (N=65)	Control (N=65)
Primary Endpoint	***n (%)***	***n (%)***
All Adverse Events (24 Weeks)	40 (61.5%)	34 (52.3%)
Secondary Endpoints		
Treatment-Emergent AEs	38 (58.5%)	34 (52.3%)
Serious AEs	21 (32.3%)	14 (21.5%)

Safety Endpoints	dermaPACE (N=65)	Control (N=65)
Treatment-Emergent Serious AEs	21 (32.3%)	14 (21.5%)
Device-Related Treatment-Emergent AEs	2 (3.1%)	2 (3.1%)
Additional Safety Analyses		
Recurrence Rate[2]	2/23 (8.7%)	1/17 (5.9%)
Partial Amputation Rate	2 (3.1%)	0
Target Foot Amputation Rate	0	0

Treatment-Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event (TEAE) was defined as an event that started or worsened in severity during or after the initial application with the study device through 30 days after the last device application. Subjects who reported more than one event for a System Organ Class or Preferred Term were only counted once for each category.

The overall rate of treatment-emergent adverse events differed significantly between the two treatment groups. The dermaPACE cohort had 11% higher rates of TESAE and SAE (See Table 24. Most of these were due to the emergence of osteomyelitis in the dermaPACE cohort which was not observed to occur in the dermaPACE treatment cohort in Study 1(see Table 25 below).

Table 25: Treatment Emergent AEs (TESAE and TEAE); Study 2

		Study 2	
Safety Endpoints		**dermaPACE**	**Control**
Identified Safety Risk	**Related Adverse Event**	**(N=65) n (%)**	**(N=65) n (%)**
Adverse Tissue Reaction	Wound Complication	0 (0.0%)	0 (0%)
	Wound Drainage Procedure	0 (0.0%)	2 (3.1%)
	Excoriation	3 (4.6%)	3 (4.6%)
	Post Procedural Hematoma	0 (0.0%)	0 (0.0%)
	Application Site Complication*	2 (3.1%)	3 (4.6%)
	Inflammation	0 (0.0%)	1 (1.5%)
Infection	Bacterial Infection***	0 (0.0%)	0 (0.0%)
	Infected Skin Ulcer**	5 (7.7%)	6 (9.2%)
	Localized Infection	3 (4.6%)	2 (3.1%)
	Osteomyelitis	9 (13.8%)^	5 (7.7%)
	Paronychia	0 (0.0%)	1 (1.5%)
	Any Abscess Bacterial	0 (0.0%)	3 (4.6%)
	Cellulitis	5 (7.7%)	5 (7.7%)

		Study 2	
Safety Endpoints		**dermaPACE**	**Control**
	Application Site Infection/Cellulitis	5 (7.7%)	5 (7.7%)
	Any Wound Infection	1 (1.5%)	1 (1.5%)
	Sepsis	1 (1.5%)	0 (0.0%)
	Septic Shock	1 (1.5%)	0 (0.0%)
	Tinea Pedis	0 (0.0%)	0 (0.0%)
	Gangrene	0 (0.0%)	1 (1.5%)
	Other	5 (7.7%)	3 (4.6%)
	Percentage of subjects with at least 1 infection	24 (38.5%)	23 (35.4%)
Application Site Pain	Procedural Pain at application site	1 (1.54%)	1 (1.54%)
	Application Site Pain	0 (0.0%)	0 (0.0%)
	Extremity Pain	4 (6.2%)	4 (6.2%)

*Necrosis, Erythema, Irritation
**Includes Diabetic Infection
***Includes AE classified as Infection other than ulcer infection, cellulitis or osteomyelitis
^ 10 cases of osteomyelitis in 9 patients

With respect to device-related treatment emergent adverse events, Table 26 describes investigator assessments of whether TEAE were related to the dermaPACE or sham treatment. While osteomyelitis was a new emergent AE, the investigators did not seem to attribute the atypical incidence of osteomyelitis as being related to the study device (See Table 26 below).

Table 26: Investigator Assessment of Device Related Treatment Emergent Adverse Events Study 2

Study No.	Subject Number	Treatment Assignment	Event Verbatim Term	Study Device Causality
2	08016	dermaPACE	Pain in extremity, pain at ulcer site	Possible
2	08024	dermaPACE	Pain in extremity; pain B/L feet	Possible
2	08019	Sham-control	Cardiac disorder; atrial flutter	Possible
2	19001	Sham-control	Diabetic foot ulcer infection	Possible

The persistent rate of elevated TEAE and the new emergence of osteomyelitis in the dermaPACE treatment group lead to a Post Hoc evaluation of the risks of developing osteomyelitis and any associated variations between Study 1 and 2. Because the major difference between the two study designs is the number of treatments received, the focus of the Post Hoc analysis was to evaluate the benefit/risk profile related to subject outcomes and increasing number of treatments with the dermaPACE device.

Variation in wound healing outcomes was also observed related to differences in BMI and ulcer age. This was also evaluated in the Post Hoc analyses.

POST HOC ANALYSES
Pooled Effectiveness Outcomes

The effectiveness results demonstrate superiority in wound closure of dermaPACE compared to the control (sham plus standard wound care) at 24 weeks. In addition, supporting analysis of the pooled data across the two studies showed:

- dermaPACE demonstrated comparable wound closure at 12 weeks compared to the control (22.67% vs. 18.29%; p=0.320, respectively)
- dermaPACE trend towards clinically and statistically better wound closure at 24 weeks compared to the control (37.79% vs. 26.22%; p=0.023, respectively)

Subgroup Analysis of Wound Closure Rates
In the post-hoc analysis, data are analyzed which compare outcomes in subjects who received no more than 4 treatments in study 1 and study 2 to assess whether there were differences in clinical outcomes when more than 4 treatments were received.

BMI and Target Ulcer Age influence on Wound Closure rates tabulated by study
The success results at 12 and 24 weeks were stratified for the demographics BMI and Target Ulcer Age, by study due to notable differences found across studies **(Table 27 - 30).** Because the two studies used different numbers of maximum treatment applications, there could be implications for various subject subgroups.

In Tables 27-30 data compare study 1 (no more than 4 treatments) outcomes related to BMI and ulcer size to study 2 (the majority of subjects received more than 4 treatments). Subjects with BMI ≥32 seemed to have lower rates of wound closure when they received more than 4 treatments compared to subjects with BMI< 32 who received more than 4 dermaPACE treatments. The same trend appears to be true related to older ulcers which are greater than or equal to one year old.

Table 27: Study 1 Results Stratified by Demographic Characteristics at 12 Weeks (% Wound Closure)

Demographic		dermaPACE		Control	
		N	%	N	%
BMI (kg/m^2)	< 32	53	26.42	50	16.0
	≥ 32	54	14.81	49	14.29
Ulcer Age (months)	< 12	19	23.8	66	21.2
	≥ 12	27	11.1	33	3.0
HbA1c	<7	33	24.2	33	15.1
	≥7	74	18.9	66	15.1

Table 28: Study 1 Results Stratified by Demographic Characteristics at 24 Weeks (% Wound Closure)

Demographic		dermaPACE		Control	
		N	%	N	%
BMI (kg/m^2)	< 32	53	41.5	50	28.00
	≥ 32	54	37.0	49	24.5
Ulcer Age (months)	< 12	80	43.8	66	33.3
	≥ 12	27	25.9	33	12.1
HbA1c	<7	33	42.4	33	27.3
	≥7	74	37.8	66	28.8

Table 29: Study 2 Results Stratified by Demographic Characteristics at 12 Weeks (% Wound Closure)

Demographic		dermaPACE		Control	
		N	%	N	%
BMI (kg/m^2)	< 32	31	35.5	37	21.6
	≥ 32	34	17.7	28	25.00
Ulcer Age (months)	< 12	45	33.3	44	29.5
	≥ 12	20	10.0	21	9.5
HbA1c*	<7	22	13.6	13	23.1
	≥7	41	34.1	50	24.0

*2 subjects did not have HbA1c values recorded at screening

Table 30: Study 2 Results Stratified by Demographic Characteristics at 24 Weeks (% Wound Closure)

Demographic		dermaPACE		Control	
		N	%	N	%
BMI (kg/m^2)	< 32	16	51.6	8	21.6
	≥ 32	34	20.6	28	32.1
Ulcer Age (months)	< 12	45	46.7	44	31.8
	≥ 12	20	10.0	21	14.3
HbA1c*	<7	22	27.3	13	38.5
	≥7	41	41.5	50	24.0

*2 subjects from each cohort did not have HbA1c values recorded at screening

Incidence of Osteomyelitis and Association with Number of Treatments

Further evaluation into the rates in Infections and infestations lead to the following analysis which indicated that unlike the trend observed in Study 1 that rates of infection and infestations were higher in the sham treatment cohort, in Study 2 the incidence of infections was higher in the dermaPACE treatment cohort. Furthermore, the rate of infections appeared to have been 3 times higher in the dermaPACE treatment group in Study 2 than in the dermaPACE arm of Study 1 (See Table 31 below). When considering both studies combined, the majority of the issues related to infection were related to cellulitis and osteomyelitis as evidenced in Table 31.

To assess benefit/risk related to the potential risk related to development of osteomyelitis the sponsor compiled the following table which compares incidence of osteomyelitis with number of treatments subjects received in Study 1 and 2 (Table 32).

Table 31: Rates of TEAE infections by subject Separated by Study

Adverse Event	dermaPACE N=107 Study 1	Sham N=99 Study 1	dermaPACE N=65 Study 2	Sham N=65 Study 2
Infection and infestation	**7 (6.5%)**	**15 (15.2%)**	**15 (23.1%)**	**13 (20.0%)**
Cellulitis	1 (0.9%)	1 (1%)	5 (7.7%)	5 (7.7%)
Osteomyelitis	0 (0%)	3 (3%)	9 (13.8%)	5 (7.7%)

The difference between the two study designs was the number of treatment applications of the dermaPACE device. Study 1 (DERM01; n=206) prescribed four (4) device applications/treatments over a two-week period (non-responders did not receive more than 4 treatments), whereas, Study 2 (DERM02; n=130) prescribed up to eight (8) device applications (4 within the first two weeks of randomization, and 1 treatment every two weeks thereafter up to a total of 8 treatments over a 10-week period). Subjects in Study 2 received additional treatments beyond the initial 4 for persistent ulcers that were not healed during follow-up assessment. Therefore, the length of follow-up between the last treatment and the 12 week analyses was shorter for subjects who received more than 4 treatments in Study 2. Furthermore, subjects who had non-responsive wounds by treatment 4 received as many as 8 treatments in Study 2. The most significant difference between these studies was the number of treatments given to subjects.

Table 32: Rates of Various AE's by subject and LTFU Compared to Number of dermaPACE Treatments Applied – By Number of Treatments

	dermaPACE 1 - 4 treatments N=118	Sham 1 - 4 treatments N=111	dermaPACE 1-7 treatments N= 134	Sham 1-7 treatments N=119	dermaPACE 8 treatments N=38	Sham 8 treatments N=45
Overall AE	94 (80%)	86 (77%)	101 (75%)	88 (74%)	22 (58%)	24 (53%)
Occurrence of Osteomyelitis	0 (0%)	3 (3%)	4 (3%)	4 (3.3%)	5 (13.2%)	4 (9%)
Occurrence of Cellulitis	2 (2%)	2 (2%)	3 (2.2%)	2 (1.6%)	3 (8%)	4 (9%)
Loss to Follow-up Rate	36 (32%)	33 (30%)	41 (31%)	33 (28%)	10 (26%)	10 (22%)
Wound Closure Rate	49 (44%)	30 (27%)	59 (44%)	36 (30%)	6 (16%)	6 (13%)
Amputation (Partial/ulcer or foot)	2 (2%)	4 (4%)	3 (2%)	4 (3.3%)	1(3%)	1 (2%)

These data show higher percentage (13.2%) of reported osteomyelitis in subjects receiving more than 7 treatments than dermaPACE treatment cohorts receiving 7 or fewer treatments and all sham treated patients. (Table 32).

In both Studies 1 and 2, the majority of subjects did not achieve complete wound closure after 4 dermaPACE treatments (in Study 1, at 24 weeks, 60% of the dermaPACE treated subjects did not achieve wound closure and 74% of the sham did not achieve wound closure. In Study 2, these were 64% and 74%, respectively). Subjects in Study 1 who did not respond with complete wound closure to dermaPACE treatment did not receive more than 4 treatments unlike subjects in Study 2 who continued to receive treatments.

In subjects requiring 8 dermaPACE treatments, there was minimal effect on wound closure rates compared to sham. This difference in wound closure rates, is a likely contributor to the higher median wound reduction observed in the overall sham treatment group when compared to the overall dermaPACE treatment group (see Table 23).

These data appear to indicate that continued wound treatment to unresponsive wounds after 7 treatments may have more risk than benefit and is, therefore, not advised.

Post Hoc analyses also demonstrated:

- Recurrence rates are lower when subjects received 1-4 treatments compared to the sham cohort, 2 (4.8%) and 4 (15.4%) respectively.
- Partial Amputation/Target Foot Amputation rates are lower when subjects received 1-4 treatments compared to the sham cohort, 2 (2%) and 4 (4%) respectively.

The dermaPACE device should be used with caution in unresponsive wounds with careful monitoring for osteomyelitis when considering more than 4 treatments. The data also indicate that there may be an association with risk of developing osteomyelitis as well as observed reduced wound closure rates when more than 7 treatments are given.

Study Limitations

The two studies had moderate rates of loss to follow up of subjects; however, the LTFU rate was higher in Study 2. Although device treatment showed superiority at 24 weeks (when data were pooled), device performance did not achieve the pre-defined established primary endpoint of complete wound closure at 12 weeks. In Study 2, the majority of the subjects (58%) received 8 treatments while in Study 1 the majority of the subjects received 4 treatments. When comparing outcomes between 5-7 treatments and 8 treatments, data analyses were limited.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric subject population.

LABELING

Labeling has been provided which includes the instructions for use and an appropriate prescription statement as required by 21 CFR 801.109.

Device-specific risks addressed in the labeling include:

- The noise emitted during a dermaPACE procedure may lead to a risk of hearing impairment. All persons in the treatment area should wear hearing protection in the form of foam ear plugs or ear muffs specified by the manufacturer with a noise reduction rating of at least 20dB.

- dermaPACE device is intended to be used on open chronic wounds. The high risk of infection is mitigated by validated reprocessing instructions which include cleaning, disinfection, and the use of sterile wrap to cover any subject contacting components of the device. However, this risk does not mitigate risk of wound infection which may occur due to natural progression of chronic wounds.

RISKS TO HEALTH

Table 33 identifies the risks to health that may be associated with use of the extracorporeal shock wave device for treatment of chronic wounds and the measures necessary to mitigate these risks.

Table 33: Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation
Infection	Reprocessing validation Labeling
Inadequate healing	Labeling
Device failure / malfunction leading to application site injury	Non-clinical performance testing Electrical safety testing Electromagnetic compatibility (EMC) testing Use life testing Software verification, validation, and hazard analysis Labeling
Hearing loss	Non-clinical performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the extracorporeal shock wave device for treatment of chronic wounds is subject to the following special controls:

1. Non-clinical performance testing must be conducted to demonstrate that the system produces anticipated and reproducible acoustic pressure shock waves.

2. The patient-contacting components of the device must be demonstrated to be biocompatible.

3. Performance data must demonstrate that the reusable components of the device can be reprocessed for subsequent use.

4. Performance data must be provided to demonstrate the electromagnetic compatibility and electrical safety of the device.

5. Software verification, validation and hazard analysis must be performed.

6. Performance data must support the use life of the system by demonstrating continued system functionality over the labeled use life.

7. Physician labeling must include:
    a. Information on how the device operates and the typical course of treatment;
    b. A detailed summary of the device's technical parameters;
    c. Validated methods and instructions for reprocessing of any reusable components; and
    d. Instructions for preventing hearing loss by use of hearing protection.

8. Patient labeling must include:
    a. Relevant contraindications, warnings, precautions, adverse effects, and complications;
    b. Information on how the device operates and the typical course of treatment;
    c. The probable risks and benefits associated with the use of the device;
    d. Post-procedure care instructions; and
    e. Alternative treatments.

BENEFIT/RISK DETERMINATION

The clinical data demonstrate that dermaPACE provides a reasonable assurance of safety and effectiveness in the treatment of diabetic foot ulcers when combined with routine wound care. When combining data across both studies, the effectiveness results demonstrate superiority in wound closure of dermaPACE compared to the control (sham plus standard wound care) at 24 weeks. In addition, supporting analysis of the pooled data across the two studies showed:

- dermaPACE demonstrated comparable results in wound closure at 12 weeks compared to the control (22.67% vs. 18.29%; p=0.320, respectively)
- dermaPACE demonstrated superior results in wound closure at 24 weeks compared to the control (37.79% vs. 26.22%; p=0.023, respectively)
- While there are some differences in the success outcomes of certain demographic sub-populations, all statistically significant differences are in favor of dermaPACE. The wound closure rates at 24 weeks seem to indicate clinically relevant higher rates for the dermaPACE group compared to sham treatment.
- The overall percentage of adverse events was comparable between both study groups with the exception of osteomyelitis rates.

The risks of the device are based on nonclinical laboratory studies as well as data collected in the clinical studies described above. The probable risks associated with dermaPACE include: adverse tissue reaction, infection, inadequate healing, application site injury (including pain), and hearing loss. There appeared to be a correlation between the incidence of osteomyelitis and receiving greater than 7 treatments. Therefore, users are advised to not exceed 7 treatments with the dermaPACE device. Caution is advised in treating non-responsive wounds with more than 4 treatments. Users are advised to monitor closely for osteomyelitis when considering 5-7 treatments.

The risks related to dermaPACE are acceptable as demonstrated by the clinical data, and are similar in most cases to those for the sham control group (when patients receive no more than 7 treatments). These risks can be mitigated primarily by labeling and testing, including biocompatibility testing, reprocessing testing, use life validation, software testing, electrical safety and EMC testing, and non-clinical performance testing.

Additional factors to be considered in determining probable risks and benefits for dermaPACE System include existing alternative therapies:

- pharmacologic agents
- dermal grafts
- skin equivalents
- dermal substitutes
- negative pressure wound therapy

Patient Perspectives
This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion
In conclusion, given the available information above, the data support that for the following indications for use:

> The SANUWAVE dermaPACE System is indicated to provide acoustic pressure shockwaves in the treatment of chronic, full-thickness diabetic foot ulcers with wound areas measuring no larger than 16 cm^2, which extend through the epidermis, dermis, tendon, or capsule, but without bone exposure. The dermaPACE System is indicated for adult (22 years and older), diabetic patients presenting with diabetic foot ulcers greater than 30 days in duration and is indicated for use in conjunction with standard diabetic ulcer care.

the probable benefits outweigh the probable risks for the dermaPACE System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the dermaPACE System is granted and the device is classified under the following:

> Product Code: PZL
> Device Type: Extracorporeal shock wave device for treatment of chronic wounds
> Class: II
> Regulation: 21 CFR 878.4685