Clinical Study Report

Dedicated Computerized Clinical system for Decubitus Direct Current Treatment (DDCT)

March 2007

Harrison Clinical Research Medistat Ltd

LifeWave Ltd.

1. TITLE PAGE

STUDY TITLE: Dedicated Computerized Clinical system for Decubitus Direct Current Treatment (DDCT)

Device: DDCT Device

INDICATION: Patients with pressure ulcers

DESIGN: This was a multi-center, randomized, double blind placebo controlled study with two groups of patients. The control group received the standard passive treatment and the treatment group received the standard passive treatment plus the DDCT treatment. All were treated for 8 weeks.

Twenty minutes treatment sessions were to be performed 3 times a day during the first 14 days followed by twice daily up to the 56th day. The pressure ulcer assessments were to be performed at ten time points (days 1, 7, 14, 21, 30, 45, 57, 90, 120 and 147). The efficacy evaluation was originally planned to be based on the results observed on day 120. The revised protocol bases the efficacy evaluation on the results observed during and at the end of the treatment, i.e. - till day 57. This change naturally increases the number of the Per Protocol patients, to include patients who passed the whole 56 days treatment, but failed to qualify for the protocol on day 120.

SPONSOR: LifeWave Ltd.
1 Azrieli center, Round Tower
Tel-Aviv 67021

PROTOCOL CODE: P-720

PHASE: II

INITIATION: First patient was treated on March 2002.

COMPLETION: Final treatment was performed during April 2003.

The study was completed according to protocol. All data was collected and analyzed. . After study completion, a revised model for assessment of the wound size-change and healing was used. The new model is described in the report and the analysis of the efficacy parameters according to this model is used in this report. The analysis of the data according to the model described in the original protocol, is not included in this report. The rational for the change is explained in section 7.

PRINCIPAL INVESTIGATOR:

Thirteen centers were involved in the study. In each center the chief investigator acted as a principal investigator. There was no single country wide principal investigator.

GCP STATEMENT: This study was performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.

DATE OF REPORT: March 2007

STATEMENT OF RESPONSIBILITY

We the undersigned declare that this report fully and accurately reflects the data generated in this trial:-

March 18, 2007
Date

Ohad Goren, LifeWave Ltd
CEO

.....
Date

.....
Gill Harari, Medistat
Statistician and CEO of Medistat

.....
Date

.....
Prof. Adunsky, Country Principal Investigator
Sheba Medical Center

18 MAR 07
Date

Nira Garty, Ph.D., Author of the report
Harrison Clinical Research, Israel

2 SYNOPSIS

LifeWave	Name of Sponsor/company:
DDCT Device	Name of Device:

Title of the study:
A multicenter, double blind, placebo control, randomized study to evaluate the safety and efficacy of the DDCT device treatment in patients with pressure ulcers

Investigators:
There were thirteen centers involved in the study. Each center had it's principal investigator. Prof. Adunsky from Sheba Medical Center wasthe country PI. The list of the centers and the names of the investigators can be found in section 16.2.

Study centre(s):
Study centers were: Sheba Medical center (2 separate sites), Reuth Medical Center, Herzog Hospital, Assaf Harofeh Medical center, Harzfeld Hospital, Migdaley Hazahv Hospital, Rambam Medical Center, Geriatric Center Shoham, Beit Loewenstein Rehabilitation Center, Shaare Zedek Medical Center, Shmuel Harofe and Hopital Francias Saint Louis. A more detailed list can be found in section 16.2

Phase of Development:	**Study period:**
Phase II	First enrollment was on 7 Mar 02 Last treatment was on 10th of April 2003. Last follow-up July 2003.

Objectives:
Primary objectives:

- To compare between standard passive treatment alone and standard passive treatment with DDCT adjunction therapy with respect to the incidence of complete wound closure.
- To evaluate the safety profile of the treatment with the device.

Secondary objectives

- To compare rates of partial wound closure between the group receiving only the standard treatment and the group receiving the standard treatment with DDCT.

Methodology:
This was a multicenter, double blind, placebo control, randomized study. The patients were divided into two groups, the control group which received the standard passive treatment and the treatment group which received the passive standard plus the DDCT treatment. The patients were treated for 8 weeks. Follow-up period lasted 90 days following the termination of treatment. Patients were assessed during screening, baseline and on days 7, 14, 21, 30, 45, 57, 90, 120 and 147.

Number of subjects:
Planned: 62 total, 31 per treatment group.
Analyzed: 63 in the ITT group (28 placebo and 35 treatment) and 38 in the original PP

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group (19 placebo and 19 active) also analysis for the revised PP group (43 patients - 21 placebo and 22 active).

Diagnosis and main criteria for inclusion:

Hospitalized or institutionalized patients with chronic non healing stage III pressure ulcers (≥ 30 days of opening) whose ulcer duration was shorter than 24 months. The treated ulcer could not be on the head, upper back or chest area with dimensions of > 1cm square and < 50 cm square.

Exclusion:

Patients who had one of the following diabetic ulcers, a pacemaker, history of autoimmune disease, or who had a significant illness which might have interfered with the study.

Pregnant or lactating women. Patients that suffered from renal or liver failure, severe anemia or sepsis.

Patients who within 2 months prior to enrolment received steroids, chemotherapy or other immune-compromising drugs.

Test product: DDCT Device

Duration of treatment:

Eight weeks of treatment with a follow-up period of 90 days following the last treatment.

Criteria for evaluation:

Efficacy:

Measurement of complete wound closure and epithelia progression. Wound area relative reduction was originally planned to be a criterion, thus will be presented in the study.

Safety:

- Adverse event
- Haematology & Biochemistry
- Urinalysis
- Vital signs

Statistical methods:

The primary efficacy endpoint of this study is: Wound Closure Rate (Yes/No) at day 57.

Wound Closure was also analyzed using a logistic regression model, while controlling for the wound average critical path (the average distance that needs to be covered by epithelia) at baseline, and for the wound location (above/below knees).

Secondary Endpoint was defined as the epithelia progression (progression of new skin into the ulcers area). The total epithelia progression is the accumulation of the incremental progression during each period. Epithelia progression per period: the

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difference in the measured area between 2 sequential time points adjusted to the mean circumference of the same 2 time points.
Tertiary Endpoint was defined as the average relative reduction in ulcer area during the study.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Rate of wound closure, (especially when taking into account the critical path length), area reduction of wound and rate of epithelia progression all had better results in the treatment group when compared to placebo. The percent of patients with complete ulcer closure during the study period was 27.3% in the active group and 9.5% in the placebo group (p value 0.044). The Mean Progression of Epithelia (new skin) from day 1 to day 45 was 0.46 CM in the active group and 0.23 CM in the placebo group (p value 0.033).

SAFETY RESULTS:

Treatment with the DDCT device in this population of patients was found safe and tolerable. There were no serious adverse events related to the device. It is important to keep in mind that the patients that participated in this study and are planned to become the target population of this device, are elderly patients with sever health problems and are mostly bed-ridden.

CONCLUSION:

The DDCT device is a non invasive device used on the elderly and health challenged population with stage III pressure wounds. The device is safe for use both from the electrical point of view and the usage aspect. Significant treatment efficacy was observed, with even higher results in the treatment of pressure wounds above the knees. This significance was observed in both parameters that define wound healing – complete closure (primary) and epithelial progression (secondary, standing for partial closure).

The epithelial progression efficacy of DDCT depicted to have higher significance after 45 days, in comparison with the 57 days results.

Another observation was the significant negative impact of the ulcer average critical path at baseline (representing the average distance that needs to be covered by epithelia). A longer average critical path reduces the possibility of an ulcer to be closed within 57 days time-frame, for both treatment and placebo patients. That is not directly related to the efficacy of the treatment, but is quite significant.

Date of the report: March 2007

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

2.1 ABBREVIATIONS

AE Adverse Event
CRF Case Report Form
DDCT Dedicated Computerized Clinical System
EC Ethics Committee
Hb Hemoglobin
I.V. intra venous
MOH Ministry of Health

3 ETHICS

3.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The study protocol and any amendments were reviewed by the local Helsinki committees at each site and by the Ministry of Health. A list of all EC committees that participated is given in appendix 16.1.3.

3.2 ETHICAL CONDUCT OF THE STUDY

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

3.3 PATIENT INFORMATION AND CONSENT

Informed consent in Hebrew was approved by the various Helsinki committees. There were two forms of the informed consent, one for the signature of the patient and another version (MOH form # 3) for patients who are mentally incapable where the legal guardian of the patient signed as well. Patients had signed the informed consent prior to any procedure which was study related. All consents were obtained in writing. The master informed consent with the patient information sheet was modified in some sites according to the requirements of the relevant local Helsinki committee.

Representative written information for the subject and a sample consent form are provided in section 16.1.

3.4 INVESTIGATIONS AND STUDY ADMINISTRATIVE STRUCTURE

Study was performed in thirteen centers in Israel. Two of these centers were located in the same medical center (Sheba Medical Center) in two different departments. In most centers the departments involved were either the geriatric department of the rehabilitation department. One medical center was a rehabilitation center, two centers were hospitals for elderly people that need medical care. Prof. Adunsky of Sheba Medical center was the country PI. The sponsor employed a medical director (Dr. Yves Bitton) who reviewed the patients' wound characteristics and medical records, prior to approving them to the study. The sponsor also employed a contact person with the sites that demonstrated how to use the device and supervised the activities of the nurses and physicians involved in the study (Mr. Rami Zafrir). Randomization assignment was sent by cellular phone from the randomization center, directly to the device. The operator of the device could not know what treatment was assigned to the patient

A detailed list of persons and institutions involved in this study is provided in section 16.2.

4 INTRODUCTION

Pressure ulcers are usually created by lying motionless for prolonged periods, as in cases of older bed-ridden or comatose patients. A pressure ulcer is defined as a localized area of tissue necrosis, which develops when soft tissue is compressed between a bony prominence and an external surface for a prolonged duration of time. It is commonly accepted that continues pressure above 32 mmHg (average capillary pressure) is enough to cause ischemia, which can, in a matter of a few hours, develop into tissue necrosis. There are systemic conditions, such as malnutrition or anemia, which increase patient susceptibility to the development of pressure ulcers. In addition, certain conditions such as shear forces, friction and moisture influence the formation of pressure ulcers. Due to the large number of conditions that can lead to pressure ulcers, much attention and prophylactic treatment is given to ensure the prevention of pressure ulcers.

Pressure ulcers are a common complication among (28% of) hospitalized patients, who are confined to bed or wheel chair for long periods of time. Of all resident nursing homes, 3%-11% suffer from pressure ulcers.

According to studies, it has been found that the average length of hospitalization for patients who acquire pressure ulcers is double that of those patients who were under high risk of contracting pressure ulcers but did not, because of quality care. In addition, it has been found that the cost of treating patients with pressure ulcers is much higher than the cost of an average hospitalization.

In order to treat pressure ulcer, all the negative conditions preceding its appearance must be eliminated. That is, off-load of pressure, prevention of shear forces, improvement of nutrition etc.

The most effective method of managing tissue load, and preventing pressure ulcers is to frequently elevate and change position of the patient. In order to accomplish this, a large staff is necessary.

The Decubitus Direct Current Treatment (DDCT) device has been developed in order to provide a method that is more effective than the passive methods of treatment currently available for pressure ulcers. The DDCT device is a non-invasive system, developed to treat pressure ulcers through the use of sophisticated electrical wave stimulation, which was measured around self-healing wounds.

The DDCT treatment comprises transferring electrical currents to the healthy skin surrounding the necrotic area through the use of soft, external electrodes, placed on the healthy surrounding skin. The treatment is based on the research of LIFE-WAVE which found that chronic wounds emit abnormally weak electrical signals during the healing process. The DDCT device provides to the wounds sessions of signals that induce a normal healing process.

5 STUDY OBJECTIVES

The primary objectives of the study were:

- To compare between standard passive treatment alone and standard passive treatment with DDCT adjunctive therapy with respect to the incidence of complete wound closure.
- To evaluate the safety of the DDCT.

The Secondary objective was:

- To compare rates of wound partial closure between the group receiving only standard passive treatment and the group receiving the standard passive treatment with DDCT. The non-biased parameter that was chosen to represent the partial healing was the progression of epithelia during the study.

Efficacy was to be evaluated as the incidences of responders. A patient was defined as a responder if the ulcer has closed fully.

The safety was evaluated by determining the incidences of adverse reactions.

6 INVESTIGATIONAL PLAN

6.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

This was a multi center, double blind (masked), placebo controlled, randomized study. The two groups, treatment and control, were to be compared with respect to adverse events and incidence of responders.

Pre-study evaluation

This evaluation could be performed up to 6 days prior to the protocol commencement day. Eligible patients were screened and enrolled according to the inclusion exclusion criteria. Following the signing of the informed consent the following procedures were performed: Collection of demographics data, including age and gender, medical history, physical examination, complete blood count, blood chemistry, nutritional state, rectal examination and wound assessment that included (wound fluids were collected as well) measurement of surface area and wound photography.

Evaluation during study

Patients were assessed during the treatment period on the 7th, 14th, 21st, 30th, and 45th days.
The following assessments were performed:
Recording of adverse events, blood tests on day 30, wound fluids on days 14 and 30, measurement of wound area and wound photography were performed during all visits.

Post treatment evaluation

Following end of treatment patients were evaluated on the 57th, 90, 120th, and 147th days.
The following assessments were performed:
Recording of adverse events, wound assessment, physical examination on days 57 and 90

6.2 DISCUSSION OF STUDY DESIGN AND THE CHOICE OF CONTROL GROUPS

The purpose of the present clinical investigation was to evaluate the safety and effectiveness of the DDCT device as compared to standard methods commonly used in treating pressure ulcers. The trial entails two groups of patients: The **Treatment** group and the **Control (Placebo)** group. The Treatment Group was provided with the DDCT device in its active mode (i.e. emitting electrical wave stimulation), and the Control Group was provided with the device in its inactive mode (i.e. no electrical emission). The patients, the medical staff and the investigators were blinded to the mode of the device.

6.3 SELECTION OF STUDY POPULATION

6.3.1 INCLUSION CRITERIA

The study population included hospitalized patients with stage III pressure ulcers who met the following criteria:

1. Subjects $\geq$ 18 years, either male or female, of any race.
2. Patients with chronic non healing stage III pressure ulcers ($\geq$ 30 days of opening).
3. Hospitalized or institutionalized patients only.
4. Patients who were willing to participate, as evidenced by signing the written informed consent.
5. Women of childbearing potential who used medically acceptable methods of birth control.
6. Patients whose ulcer duration was shorter than 24 months.
7. Patients that had ulcer wound larger than 1 cm square, and smaller than 50 cm square.
8. The treated pressure ulcer was not on the head, upper back or chest area.

6.3.2 EXCLUSION CRITERIA

Subjects who met any of the following criteria were to be excluded from study participation.

1. Patients suffering from diabetic ulcers.
2. Patients that suffered from at least one of the following: renal failure (creatinine $\geq$ 2.0 mg/dl), liver failure (liver function enzymes with higher than x2 of upper limit of normal value), severe anemia (Hb < 10g/dl) or bilirubin < 1.1 mg/dl, Albumin < 2.6 gr/l, or sepsis.
3. Patients who had a pacemaker.
4. Patients who had a significant medical illness or disorder which, in the judgment of the investigator might have interfered with the study.
5. Patient who had any medical illness or limitation that might cause the patient to become noncompliant with the study protocol or could confound the interpretation of the data (patients that received radiation therapy or chemotherapy).

6. Patients that was previously randomized to this study.
7. Pregnant or lactating women.
8. Patients who had a history of autoimmune diseases.
9. Patients who received within 2 months prior to enrolment steroids (refers to chronic steroid use per os or IV of > 1 mg/kg), chemotherapy or other immune-compromising drugs, except for spinal cord injury patients who received a single 24 hours treatment of steroids (within 1 month prior to enrolment) or single treatment to treat allergic reactions.

6.3.3 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

The investigator had the right to terminate participation of any subject at any time. The following were justifiable reasons for premature withdrawal:

- Intolerable adverse event
- Relevant non-compliance with the protocol
- If the investigator deemed it was in the subject's best interest
- Deterioration of target wounds condition such as erythema, pain, discharge, infection, tissue necrosis, requirement for repeat debridement or other surgical intervention such as amputation and/or increase in ulcer surface area size.
- Patients who did not receive treatments for 3 or more complete days throughout the 8 weeks treatment or patients who experienced an interval of less than 1 week between two missed treatment days.

Participation in the study was strictly voluntary. A subject had the right to withdraw his consent at any moment for any reason or without giving reason. If he chose to withdraw, the investigator had to be informed immediately.

Any subject who was withdrawn or withdrew his consent and who had received treatment with the investigational device had to undergo a final, post-study examination. The reason and circumstances for premature discontinuation had to be documented in the Case Report Forms.

Patients that dropped out during the first two weeks with no serious side effects or patients that were not evaluated before day 30^{th} of the trial could be replaced by other patients. The replacement patients were to be assigned the same treatment as the patients that were replaced.

6.4 TREATMENTS

6.4.1 TREATMENTS ADMINISTERED

The treatment schedule and procedure were identical for both treatment and control groups.

The two electrodes of the DDCT device were placed around the pressure ulcer on the surrounding healthy skin 1-2 cm from the wound edge. The electrodes were placed at two opposing sides of the wound to assure reproducible stimulation.
The skin surface was cleaned and dried prior to the placement of the electrodes in order to ensure effective current passage.

The treatment of the first 14 days consisted three daily sessions of 20 minutes each.
The first treatment of the day was given in the morning. There was to be a minimum of five hours between the three daily treatments.
From day 15 to day 56, two 20 minutes, daily sessions were performed. The first daily session was performed in the morning and the second one was performed about 8 hours later.

Patients were monitored for 3 months following the termination of the treatment, regardless to the wound condition. Patients were monitored on days 57, 90 and 120. During that period a photograph of the wound was taken every one to two weeks. These photographs were used to assess the dimensions of the wounds. Final evaluation of the wound and patient status was performed on day 147 (last follow-up visit).

Missing of up to 2 non consecutive days of treatment were not considered as breach of protocol.

The treatment was discontinued prior to day 56 if the wound has fully closed during the treatment period.

6.4.2 DEVICE DESCRIPTION

The DDCT is a stand-alone device connected via electrodes to the patient's body. The DDCT device used for the study was connected to a computer (via a safe connection). The computer software contains archiving elements, such as patient database and photographs of the ulcer at different time points. In addition, it provides measurement and recording features (type and amount of body voltage surrounding the treated ulcer before and after each treatment), which are being collected for the purpose of future research. All are hidden from the investigators and part of the consent form. Each treatment session begins with the attachment of the two electrodes onto the patient's healthy skin surrounding the wound, at a distance ranging from 1 to 2 cm off the ulcer's contours, at opposite sides of the ulcer. Electrical stimulation lasts 20 minutes in every session.
The device is programmed to display an error message should there occur a disruption of current between the two electrodes.

6.4.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Eligible patients were allocated to the control or treatment group by randomization. Each department at each of the twelve centers received block numbers for groups of four consecutive

enrolled patients, according to the last digit of the random number drawn by a computer software. Each assigned block allocated two patients to the control group and 2 patients to the treatment group.

Allocation of patients to either of the two groups was determined randomly by the software function.

The complete randomization list with patient identifiers and assigned treatment is provided in section 15 of tables and listings.

6.4.4 BLINDING

The double blind was achieved by using the same DDCT for treating the treatment group and control groups.
To start the treatment the nurse recorded the patient's serial number. The allocation of patients to either of the groups was determined by the software function keeping the operating person blinded to the mode of the device.

Preliminary studies demonstrated that patients did not sense the electrical stimulations and therefore were also blinded to the treatment.

The study was performed under complete double-blind condition. Knowledge of the randomization list was limited to the persons responsible for creation of the randomization list, preparation of the random code envelopes and responsible for the device software until treatment of the last patient (i.e. final examination of the last patient), quality control and verification of the case report forms were completed. Copies of the complete randomization list were kept or dispensed in sealed envelopes.

Together with the study device the investigator received a sealed random code envelope for each individual patient number. Within this envelope the treatment group to which the patient number was assigned was documented. The sealed random code envelope was to be opened only in case of emergency when knowledge of the actual treatment became medically necessary. The clinical monitor and the sponsor were to be informed immediately regardless of whether the emergency was related to the study medication or not.

All unopened random code envelopes were returned to the sponsor at the end of the study.

6.4.5 CONCOMITANT THERAPY

Both groups were treated by standard medical treatment. The treatment included the following:

Stage III – one surgical debridement followed by daily application of hydrocolloid dressing or similar, first dressing soaked in Saline covered by dry dressing changed every day.

Stage II – after the wound decreased to stage 2 size- saline wash & Silverol cream, or similar, protected by a dry dressing changed every day.

Stage I – after the wound decreased to stage 1 size- Granuflex cream, or similar, with a dry dressing changed every 2-3 days.

Patients started the study with stage III and not less.

6.4.6 TREATMENT COMPLIANCE

All treatments were recorded. The date and duration of each treatment was recorded separately in tabulated form in the CRFs.

6.5 EFFICACY AND SAFETY VARIABLES

The efficacy parameters of this study are:

- The percent of patients with complete ulcer closure during the study
- The mean progression of Epithelia (new skin) in cm
- The mean relative reduction of ulcer area in percent

The safety parameters are:

- Adverse events and serious adverse events
- Blood test measurements
- Vital signs and physical examination

6.5.1 EFFICACY AND SAFETY MEASUREMENTS ASSESSED

A list of adverse events and their frequency was to be recorded through the trial period. The analysis of the safety aspects was based on the comparison between the two groups of treatment with respect to the incidence of individuals with one or more serious adverse events up to day 120.

The “average critical path” is the average distance in the ulcer, needed to be covered by the progression of epithelia, in order to achieve complete closure. The quantitative expression of this parameter is the formula “twice the ulcer area divided by circumference” (2*A/C), all at baseline measurements.

Wound location: Since there is a substantially weaker blood-flow below the knees, compared to the blood-flow above the knees, we added the wound location, with two options: above knees and below knees, to the efficacy analysis of both treatment and placebo.
The efficacy of the treatment was evaluated:

- Complete closure (primary endpoint): the rate of complete closure, taking into account the impact of wound area and shape, as reflected in the “average critical path length” at baseline, as well as wound location.

- Any advance towards closure (secondary endpoint): the progression of epithelium around the ulcer, measured by CM. A comparison of this parameter was made between baseline and each visit for each of the groups (control and treatment). This parameter was also analyzed controlled by ulcer location.

6.5.2 APPROPRIATENESS OF MEASUREMENTS

A case report form was developed to collect the required safety and efficacy data and was used for this study.

The data analysis originated from two sources, the CRF data which was collected into SAS files and wound photos taken for each patient at each of the assessment visits.
Database management system included edit check programming by Smith & Nephew. Pre-entry and post entry quality control of the clinical data has been performed at the data entry center. Queries were issued by the data entry center.
The photographs were measured by two assessors, blinded to the assigned treatment. The area and circumference of the wounds were measured using Trace V2.3 Software, acquired from Cardiff University, and were documented in excel files.
The measurement data was checked for consistency by Medistat Ltd. Data was then used to calculate the parametric variables underlying the study: average baseline, critical path (for complete closure) and epithelia progression (for all ulcers).

Measurement of wound area: As wounds not only differ in size but also may have a very complex shape, their area could not be a simple assumption of circular or oval shapes. A tracing software, Tracer version 2.3 (updated for this study) designed by the Medical Computing Research Group of the University of Glamorgan, Wales, UK, to accompany the MAVIS-II Project was used in these analysis. Photographs of the wounds were traced manually on the circumference of the wound and recorded in an imaging – tracing software that calculated the area and circumference of the wound.

6.6 DATA QUALITY ASSURANCE

The sites were monitored in order to ensure that the investigators conducted the trial in compliance with the protocol and applicable regulatory requirements.
Data entry was done by Smith and Nephew Inc and repeated with new data of wound photography assessments, by two independent assessors who sent their output to Medistat. Data in this report is based on the analysis performed by Medistat.

6.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

6.7.1 STATISTICAL AND ANALYSIS PLAN

The null hypothesis was that the number of patients with complete ulcer closure in the two groups will be equal.
The Mantel-Haenszel logrank procedure was used as the test of significance (at %5 level). The analysis was applied to the results observed at each of the nine examinations performed until day 120. Recurrence of wounds did not affect the statistical analysis of the trial.
The Paired T-test and Non-parametric Sign Rank Test were applied for testing differences between the time points. The T-test and Non-parametric Sign Rank Test were applied for testing differences between study groups.
The Logistic Regression was applied to predict the probability of the wound closure by study group (Treatment or Placebo) and baseline wound area.
Fisher's Exact Test was applied for testing the differences in the rate of wound closure between the study groups (Treatment or Placebo).
All tests applied were two-tailed, and p value of 5% or less was considered statistically significant.

6.7.2 DETERMINATION OF SAMPLE SIZE

The sample size was calculated for one-sided significance level at $\alpha=0.05$, with statistical power of 0.95. A sample size of 31 patients at each group was based on the assumption of 10% of responders in the control group and 50% of responders in the experimental at day 120.
This sample size was calculated for chi-square test with continuity correction.

7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Following the first preliminary analysis after study had ended, it was evident that due to the complexity and diversity of the wounds, (area, shape, depth and healing process) the planned wound measurement model used was not accurate and did not represent the true healing process. A different approach, based on new technologies and insight, was needed for assessment and analysis. The paragraphs below describe the method used to depict the results in this report with a different model.

Change in the efficacy evaluation

Initially the size of the wounds was measured by the investigators separately at each site. Wounds were traced on paper and area was calculated with an approximation to a round or oval shape. This data was collected and entered to the CRFs. In addition, the wounds were documented by photographs.

In order to evaluate the data more accurately and in a more unified form, an imaging calculator software (Tracer v2.3) was used. The measurement and evaluation of wound area and circumference were done according to the wound photos that were taken during the study for each patient at each visit. Two independent assessors traced the surfaces of the wounds electronically and results were processed by the software. Calculations of the wounds' area and amount of epithelial progression were made with properly designed software. The exact formula used is detailed in section 9.3.1.4.

Change in the statistical method

The following statistical tests were used in the analyses of the data presented in this study: The Paired T-test and Non-parametric Sign Rank Test were applied for testing differences between the time points. The T-test and Non-parametric Sign Rank Test were applied for testing differences between study groups.

The Logistic Regression was applied to predict the probability of the wound closure by study group (Treatment or Placebo) and baseline wound average critical path.

Fisher's Exact Test was applied for testing the differences in the rate of wound closure between the study groups (Treatment or Placebo).

All tests applied were one-tailed and p value of 5% or less was considered statistically significant.

The data was analyzed using the SAS software (SAS Institute, Cary North Carolina). ***References:***

SAS/STAT User's Guide, SAS Institute Inc

Hosmer, D.W., Jr. and Lemeshow S. (1989), Applied Logistic Regression, New York: John Wiley & Sons, Inc.

8. STUDY PATIENTS

8.1 DISPOSITION OF PATIENTS

All patients that were enrolled in the study were included in the intent to treat population (ITT) and evaluated for safety. The ITT group included 28 patients in the placebo group and 35 patients in the active group Total of 63 patients). The per-protocol (PP) population included only the patients who completed the study according to the protocol including follow-up to day 120. (38 patients, 19 in the placebo group and 19 in the active group). In this report, PP was redefined for time to day 57 when last treatment was administered. This decision increased the number of patients in the PP population to 44. There are 44 patients who completed the treatment at day 57. It should also be noted that as wound healing was reached at day 45 with most healed patients, some of the wound healing assessments were calculated to day 45.
Table 1 below describes the overall disposition of patients per site.

Table 1 Disposition of Patients per Site

Active		Placebo		Hospital Code
%	N	%	N	
17.1	6	21.4	6	101
2.9	1	3.6	1	102
11.4	4	10.7	3	103
2.9	1	3.6	1	104
31.4	11	32.1	9	105
17.1	6	14.3	4	107
2.9	1	3.6	1	108
0	0	3.6	1	109
2.9	1	3.6	1	110
2.9	1	0	0	111
8.6	3	3.6	1	112
100.0	**35**	**100.0**	**28**	**All**

As can be seen from the table, patients were not evenly distributed between the sites, however, within the sites, with the exclusion of sites 111 and 109, which recruited one patient each only) there was even distribution between the two treatment arms in most sites. Thirty eight patients completed the study (evenly from both groups). Fifteen patients terminated participation due to adverse event or medical complications, two discontinued due to

worsening condition and two had withdrawn consent. Sites 106 and 113 did not recruit patients at all.

Table 2 Disposition of Patients

Reason for Ending Study	Placebo		Active	
	N	**%**	**N**	**%**
Study completed through follow-up	19	67.9	19	54.3
Patient consent withdrawn	1	3.6	1	2.9
Condition worsened	1	3.6	1	2.9
Adverse event/ Complication	5	17.9	10	28.6
Other	2	7.1	4	11.4
All	**28**	**100.0**	**35**	**100.0**

8.2 PROTOCOL DEVIATIONS

Protocol deviations were recorded and are listed according to categories:

8.2.1 DEVIATIONS FROM INCLUSION / EXCLUSION CRITERIA.

There were 9 deviations recorded: Three patients were included with background medical history which was not permitted, two have had recent steroid intake, one patient had wound area which exceeded the required by protocol (by 2%) and three patients exceeded the baseline wound duration as required by protocol.

8.2.2 DEVIATIONS OF MISSING TREATMENTS - :

Twenty Six (26) placebo treatments and 10 active treatments were not performed at all during the study (there are three treatments per study visit) In some cases (patients 1002 and 10008 – both placebo) whole sessions were not performed. These two patients were not included in the PP analysis.

9. EFFICACY EVALUATION

9.1 DATA SETS ANALYSED

9.1.1 INTENT-TO-TREAT POPULATION

The intent to treat population (ITT) included all the patients who were randomized into the study (N=63)

9.1.2 PER-PROTOCOL POPULATION

The per protocol (PP) group consisted of 38 patients who completed the treatment according to the protocol. Assessments were done up to day 57.

9.1.3 PP^2 POPULATION – ALL PATIENTS WITH VALID DATA UP TO DAY 57 (N=43)

9.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics

Sixty three patients were enrolled in the study, 26 men (13 in the placebo group and 13 in the treatment group) and 37 women (15 in the placebo group and 22 in the treatment group). All patients were Caucasian. The mean age of patients enrolled to the placebo group was 72.3 ±19.5 years and the mean age of the treatment group was 71.9 ±18.8 years. There was no statistical significant difference in the age parameter between the two groups, nor was there any significant difference in other demographic parameters.

The mean height and weight are listed in Section 15.1 Safety Tables number 2.2

Medical History

A patient listing of medical history is presented in Section 15.4.

The mean duration of the pressure wounds prior to enrolment were 6.7+5 months in the placebo group and 5.8+ 5.1 months in the treatment group. The mean area of the wounds prior to enrolment were 17.4 ± 13.8 cm in the placebo group and 16.1+ 11.6 cm in the treatment group. A summary of wound parameters prior to enrolment are presented in table 3 below (N=62 there was no information regarding duration of wound for patient number 10007). Frequency of wound dressing, drain and characteristics prior to enrolment are presented in section 15.1 table 5.3, 5.4, 5.5 respectively. Wound location is summaries in section 15.1 table 5.6.

Table 3 Summary of wound parameters prior to enrolment

	Placebo					Active				
Parameter	N	Mean	STD	Min	Max	N	Mean	STD	Min	Max
Duration (month)	28	6.7	5	1	22	34	5.8	5.1	1	23
Area	28	17.4	13.8	1	51	35	16.1	11.6	2.5	45.5

9.3 MEASUREMENTS OF TREATMENT COMPLIANCE

The listings of the number of treatments per patient and percent of compliance are summarized in section 15.1 and 15.4

The percent compliance of the placebo and treatment groups are presented in Table 4 below. A mean of 88.9% of the patients were compliant with the protocol procedures from the placebo group and 84.9% of the patients were compliant in the active treatment group.

Table 4 percent of compliance

Active						Placebo						
Max	**Median**	**Min**	**Std**	**Mean**	**N**	**Max**	**Median**	**Min**	**Std**	**Mean**	**N**	
103.2	99.2	12.7	24.1	84.9	35	103.2	100.0	19.8	24.3	88.9	28	**Percent of compliance**

9.4 ANALYSIS OF EFFICACY

The primary efficacy endpoint of this study was Wound Closure (Yes/No) at day 57. There are four methods that were used to analyze efficacy.

CLOSURE RATIO COMPARISON (Model 1):

The straightforward way to evaluate the efficacy is to compare Wound Closure ratios between the treatment group and the control group. This simple analysis ignores all characteristics of the wounds, and compares only closure ratios (total closed from the total wounds of the group).

Based on the findings of the study:

- Higher percentage of wound closing was found in the upper body part than the lower body part in both study groups. This phenomenon has medical causes, and was found statistically significant.
- Higher prevalence of wounds was found in the treatment group in the lower body parts compared to placebo (73% and 48% accordingly). This phenomenon was caused by the randomized sampling method. This sampling bias should not be ignored by the analysis.

Those findings caused an alteration of the simple ratio-comparison, separating the results into two groups: upper body location and lower body location, while still, in each group, comparing the treatment and control sub-groups.

Figure 1 in Section 10, summaries the percent of patients with complete ulcer closure during the study period

ANALYSIS OF FACTORS INFLUENCING CLOSURE RATE (Model 2):

The closure ratio comparison described above can not be used as the only model analyzing the impact of treatment (and location) on wound closure. Both treatment and control groups consisted of variety of wound sizes and shapes. The findings of the study, show that only small wounds (up to 2.7 sqCM, while all population average was 17.4 sqCM) were closed in the control group, while in the treatment group much bigger wounds were closed. Those findings prove that a comprehensive analysis must consider the wound geometry as a factor influencing the closing probability of a wound.

A statistical model was estimated, using a logistic regression with p, the probability of complete closure, defined as follows:

The physical Model underlying the statistical one, assumed that placebo ulcer group and treated ulcer group had each an epithelia progression speed function, normally distributed with different variances around different medians.

We defined the average distance between the perimeter and the center of the ulcer as "average critical path". The "average critical path" describes the distance to be covered by the epithelia in order to close the ulcer. The formula to find the length of the average critical path is twice the area of the ulcer, divided by its circumference. For a round ulcer it will naturally be $(2\angle R^2/2\angle R)$, which is R, the radius of the ulcer. Our physical model hypothesizes that a specific threshold progression speed, within a defined time-frame (57 days, in this study) would close all ulcers whose critical path is smaller than the accumulated epithelia progression. If the specific speed of the epithelia of some patients is lower than the threshold speed, (falling on the lower area of the distribution), then the ulcer will not close. The average critical path of an ulcer relates directly to the ulcer area divided by the ulcer circumference. This is a model that takes into account the area of the ulcer, and its shape, both having impact on the distance within the ulcer that should be covered by epithelia, after being filled with granulation tissue. Ignoring any of those two parameters will bias the analysis results. The average critical path takes into account both area and shape.

The physical model described is of course a simplification of the problem, ignoring other important parameters of the ulcer at baseline impacting its closure, like average depth (or volume), granulation/necrotic/collagen tissues ratios, etc. This is because the geometry of the ulcer opening, including area and circumference, seem to be the only parameters that can be quantified accurately and objectively. Yet, this model chosen is more comprehensive and accurate than other models in use referring only to area in baseline, or referring only to area groups. This physical model led to the statistical Model 1

The initial findings of the study abovementioned, showed that wound location was not equally distributed between treatment and control groups, and showed that wound location does have an impact on wound closure, Those findings showed that wound location can not be ignored as an explanatory variable in the regression.

In the statistical analysis for predicting a complete wound closure, an adjustment for wound location was added to the model.

Therefore, the initial explanatory variables of the model were:

- The Intercept.
- The Group (Treatment vs Placebo)
- The Location (above/below knees)
- Baseline Wound Area divided by Baseline Wound Circumference (half the critical path).
- Group-Location Interaction
- Group-Area/Circumference Interaction
- Location-(Area/circumference) Interaction

Since none of the Interactions was found to be significant, all Interactions were omitted from the Model, which was finally formulated as follows:

Model 2: probit(p)= 〈 + ®1*Group + ®2*(Area/Circumference) + ®3*(Wound Location)

Where Group was either 1 (=Treatment) or 0 (=Placebo), Area/Circumference is computed using the baseline wound area and wound circumference, α was the intercept and β1, β2, & β3 were the regression coefficients. The binary outcome variable was probit which equals 1 (=wound closure) or 0 (=otherwise). The results of this study, including the relevant figures, were analyzed and calculated using Model 1 above. The regression coefficients calculated from the study data, enable the understanding of the impact of treatment, wound location and wound geometry on the probability of closing a wound.

The Logistic Regression model predicts the outcome binary variable Wound Closure (Yes/No). The explanatory variables are: the wound area divided by wound circumference on day 1 (baseline), the treatment group and the location of the wound. In other words: the model calculates the probability for wound closure given the wound area/circumference on day 1 , the treatment group and the wound location.

The significance of the treatment effect was computed using the Likelihood Ratio test.

EPITHELIA PROGRESSION (model 3)

In order to examine the efficacy of the treatment, the Secondary Endpoint was defined as the epithelia progression (progression of new skin into the ulcers area). The total epithelia progression is the accumulation of the incremental changes during each period. Adjusted Change per period: the difference in the measured area between 2 sequential time points adjusted to the mean circumference of the same time points.

Defining epithelia progression as the quantitative parameter describing curing progress seems to be less biased than other models found in the literature, like:

- Ulcer area parametric reduction (measured in SQCM) that “favors” the bigger ulcers, that have more area that can be covered, and longer perimeter for the epithelia to progress from.
- Ulcer area relative reduction (measured in percents) that “favors” the smaller ulcers that can be easily closed, not needing a lot of epithelia progression.

Both models that were not chosen for the analysis totally ignore the shape of the ulcer and its shape, thus “favoring” long & narrow ulcers, whose contours allows for quicker coverage of epithelia, compared to round ulcers. Grouping of the results to several independent groups by ulcer area, and analyzing the groups independently, as recommended by PUSH, can be only a partial solution for the bias of the two models that were not chosen. Area-based grouping does not solve the shape-bias, while it also leads to impossible sample size needed for the study.

The calculation was done for each time point according to the following equation:

Area-cir (progression of epithelia) = {Area(t) – area(t-1)} / {[cir(t) + cir(t-1)] / 2}

The rate of epithelial growth is calculated as the difference between the area of the wound at two time points divided by the mean circumference of the wound at the same two time points.

The AUC defined as the cumulative progression of epithelia per period:

up to day 45

up to day 57

All the parameters are presented by the 2 study groups: Active (treatment) and Placebo.

Statistical comparison was performed between the study groups using' T-test and Wilcoxon Non-Parametric test.

RELATIVE AREA REDUCTION (model 4)

In order to examine the efficacy of the treatment, the Tertiary Endpoint was defined as the ulcer relative area reduction (measured in percents) during the study period.
As discussed in the former section, Ulcer relative area reduction (measured in percents) "favors" the smaller ulcers that can be easily closed or have most of their area reduced, not needing a lot of epithelia progression. It also totally ignores the shape of the ulcer, thus "favoring" long & narrow ulcers, whose shape allows for quicker coverage of epithelia, compared to round ulcers.
Though, we elected this to be the tertiary endpoint, based on the fact that it was originally intended to be an endpoint of the study, and based on its popularity in literature.

The calculation was done for two time points according to the following equation:

Area Relative Reduction = 100*{Baseline Area – Final Area} / {Baseline Area }

Two time frames were used for the test:

up to day 45

up to day 57

All the parameters are presented by the 2 study groups: Active (treatment) and Placebo.

Statistical comparison was performed between the study groups using T-test and Wilcoxon Non-Parametric test.

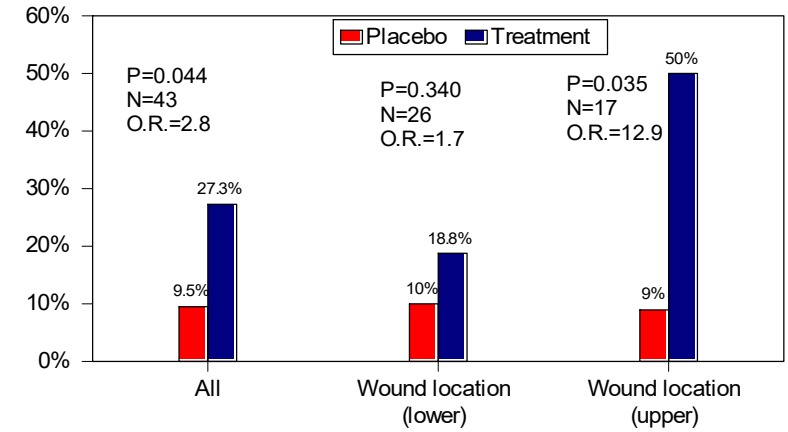
10 EFFICACY RESULTS

RATIO OF FULL WOUND CLOSURE (Model 1).

The rate of complete wound closure at day 57 was 27% in the Active group and 9.5% in the Placebo group (ratio of 2.0), this difference was statistically significant (p=0.044) see figure 1. With baseline adjustment the ratio was 2.8 favoring the treatment group.

A negative correlation was observed between the baseline wound area and the odds for complete closure of the wound, meaning: the larger the wound area is, the odds for complete closure are smaller.
Also, among those who closed the wound, the mean baseline wound area was larger in the Active (treatment) group than in the Placebo group (see figure 5)

Figure 1: Percentage of patients with complete ulcer closure during the study period, by treatment group and Wound location



* Adjusted for Area (Day 0)

Additional analysis was performed by wound location: upper or lower part of the body (lower = below knee; upper = above knee). In both locations a trend of better closing in the Active group than in the Placebo group was observed. The rates of wound closing were better in the upper body than in the lower body: Wound location – Upper body healing of the Active group (50%) was statistically significant better than the placebo group (9%) with p=0.035. In the lower body, although with no statistical significance, it was evident that the active group had caused greater healing than the placebo group (18.8% and 10% respectively) figure 1 presents the percent of complete wound closure by patients' groups and location.

9.3.1.2 ANALYSIS OF FACTORS INFLUENCING CLOSURE RATE (Model 2):

Model 2 : Binary logit : Analysis of Maximum Likelihood Estimates

Wald Confidence Interval for Adjusted Odds Ratios			
P Value	**0.R.**	**Estimate**	**Effect**
0.030		-2.72	**Intercept**
0.040	5.69	0.98	**GROUP** *
0.110	0.62	-0.25	**AREA/CIR (cm)**
0.100	3.35	0.68	**LOCATION****

(*)Group : 0=Placebo , 1=Treatment

(**)Wound Location: 0=Low , 1=Up

The Estimates of the table above are the results of the probit logistic regression performed, expressing the effects of the explanatory variables on the probability of full closure of ulcers within 57 days.

We see:

There is quite significant negative impact of the area/circumference on closure rate, p value is 0.11.

There is quite significant positive impact of an upper body location (above knee level) on closure rate, p value is 0.10.

There is a significant positive impact of the treatment on closure rate, p value is 0.040. The p=0.040 for GROUP impact on full closure in this regression Model 2 is better than the results of the simplistic Model 1, whose p=0.044. This demonstrates that adjusting for wound geometry (AREA/CIR) increases the significance of GROUP contribution to full closure.

9.3.1.3 EPITHELIA PROGRESSION (model 3)

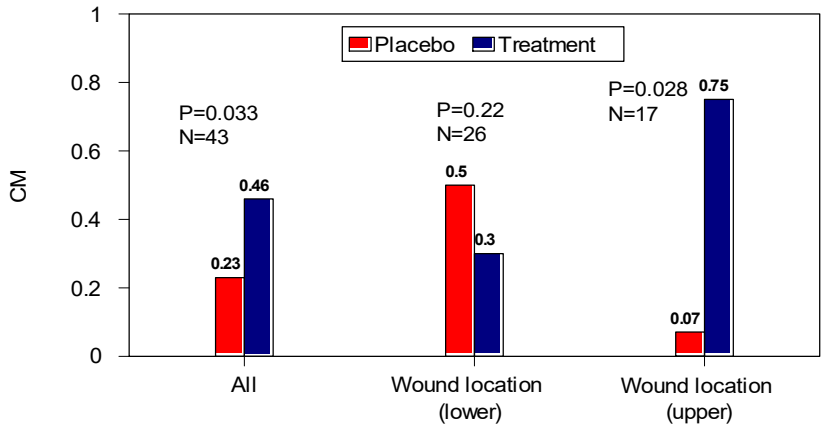
Another parameter of wound healing is the rate of epithelial growth. In the per protocol population: A trend was observed, where the decrease in the AUC per period, which reflects the progression of epithelia, was greater in the Active group than in the Placebo group in all the time points, and was found statistically significant until day 45.

The mean progression of epithelia (new skin) until day 45 was faster in the Active group (-0.46) compared to the Placebo (-0.20). This difference was statistically significant (p=0.032).
(See figure 2).

An analysis of progression of epithelia until day 45 by the wound location (lower body = below knee; upper body = above knee) showed better results in the upper part of the body: -0.75 in the Active group v.s.-0.06 in the Placebo group (p=0.027) (see figure 2).

The effect shown here was not found significant for the period between day 45 and day 57.

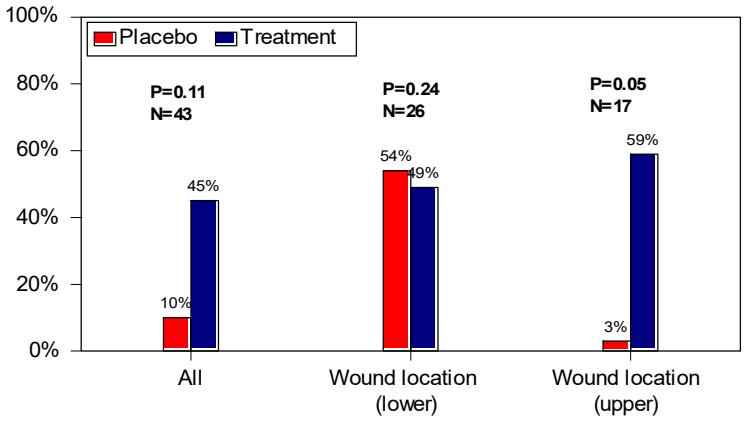
Figure 2: Mean progression of epithelia (New skin) from day 1 to day 45, by treatment group & Wound location



9.3.1.4 RELATIVE AREA REDUCTION (model 4) Wound Area

Based on the computerized analysis of wound area, a comparison between the placebo and the treatment group in the relative percent change from baseline showed higher decrees rate in the treatment group.

Figure 3: Mean percent of decreased ulcer area from day 1 to day 45, by treatment group & Wound location



The percentage of wound closing was 45% in the Active group and 10% in the Placebo group (p=0.11). Section 12. summaries the results described in Figure 3. It should be noted that wounds in the upper parts of the body heal much better in the treated group when compared to the placebo group. This difference (59% and 5% respectively) is statistically significant with p=0.05.

The effect shown here was not found significant for the period between day 45 and day 57.

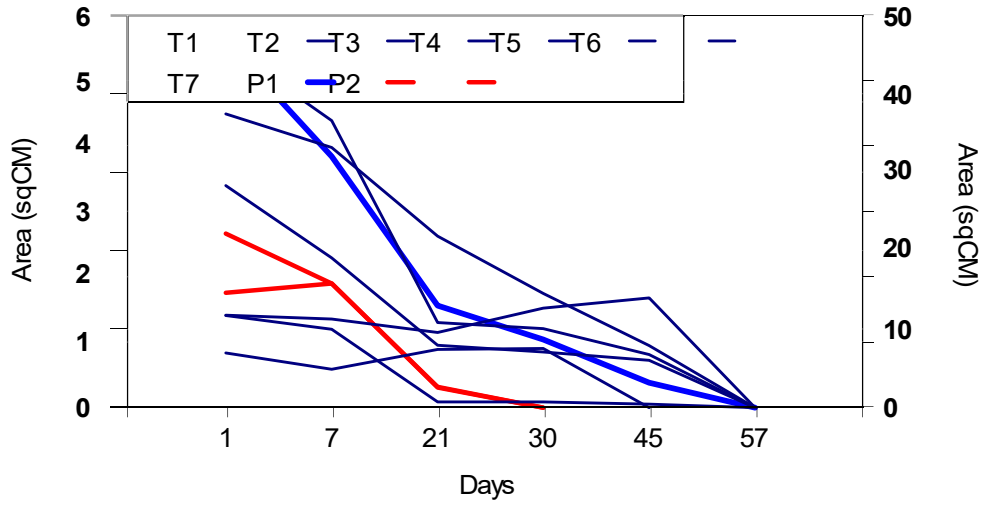
Complete closure of wound

Wound was defined as closed if either area was determined as 0 by both assessors or the investigator defined the ulcer as closed (as recorded in the CRF).

Although data was collected for 147 days from the beginning of the study, this analysis was concerned only with measurements collected until day 57, which is the last day in which treatment was applied.

The results are presented: for PP^2 population in section 15.2 tables.
Figure 4 describes the complete closure of the wound during study period by treatment groups. (blue lines are treated group and red line – placebo)

Figure 4: Patients with complete closer of ulcer during the study period, by treatment group



Tabulation of individual response data

Individual efficacy response data are provided in Section 15.4

(see table 29 which contains data collected from the CRFs and table 26 which contains data collected from the photographs that were reassessed by two assessors. The efficacy evaluation was based on this data which was deemed more accurate.

11 STATISTICAL/ANALYTICAL ISSUES

Handling of Dropouts or Missing Data

Imputation of missing data was done using Linear Interpolation method:

Linear Interpolation – Missing values were imputed using a linear interpolation of the nearest two non-missing values, before and after the missing value. Missing values with no subsequent non-missing value were given the nearest previous non-missing value.

12 EFFICACY CONCLUSIONS

Rate of wound closure, area of wound and rate of epithelia progression all had better results in the treatment group when compared to placebo. The percent of patients with complete ulcer closure during the 57 days study period was 27% in the active group and 9.5% in the placebo group (p value 0.044). The Mean percent of decreased ulcer area from day 1 to day 45 was 45% in the treatment group and 10% in the placebo group (p value 0.11). The Mean Progression of Epithelia (new skin) from day 1 to day 45 was 46% in the active group and 23% in the placebo group (p value 0.033).

13. SAFETY EVALUATION

13.1 EXTENT OF EXPOSURE

The maximal number of treatments per patient was 126 (3 treatments daily for the first 14 days, followed by twice daily for 6 weeks). Each treatment lasted 20 minutes of electrical stimulation. The listings of number of treatment per patient are summarized in Section 15.4 -

13.2 ADVERSE EVENTS (AEs)

Eighty six adverse events were reported in the placebo group and one hundred fifty seven were reported in the treatment group. The frequency of adverse events by type is presented in Section 15.1 Table 9.2. Although there were significantly more adverse events in the active treatment group, only 9 out of the 243 adverse events were considered by the investigators as related to the study device (3 in the placebo group and 6 in the treatment group). The rest of the adverse events were considered as related to concurrent medical situation.

The following adverse events were considered as related to the device (in the treatment group): pain in the treated area during treatment, infection of the wound, bleeding from the ulcer, gangrene and deterioration of wound condition.

Listings of adverse events by subject are summaries in Section 15.4.

13.3 DEATHS AND OTHER SERIOUS ADVERSE EVENTS

Thirteen serious adverse events (SAEs) were reported. Twelve patients have died during the study and the follow-up period. None of these events were considered by the investigators as probably related to the study device. It needs to be noted that the patient population was of a high age and in poor physical health. In general life expectancy in cases where pressure wounds are developed

and reach stage II to III, and patients are bed-ridden, is lower than in the healthy population of the same age. All death reports were reviewed and were considered as a result of concurrent diseases.
The narratives of all serious adverse events are given in Section 15.5.

13.4 CLINICAL LABORATORY EVALUATION

Blood tests were performed during baseline visit and on days 30, 57 and 90. It was observed that in general the hematological and biochemical picture of patients that participated in the study has improved. This may be attributed to the special day to day care that these patients received during the study as opposed to other patients. This “placebo” effect may have improved the safety profile of the treatment however; it is evident that the device does not put the patients in any risk of worsening medical condition.

The summaries of normal values, above and below ranges of total blood count and blood chemistry are presented in section 15.1 tables , 4.0 through 4.5.
Urinalysis was performed during baseline visit and on days 30, 57 and 90. Summary statistics are presented in Section15 table 53.

13.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Temperature, blood pressure, pulse and respiratory rates were measured at baseline visit at on the 7th, 14th, 21st, 30th, 45th, 57th and 90th days of treatment.
Weight of the participating patients has increased during the study probably attributed to the special attention and controlled care imposed by the participation of the trial. In general, blood pressure and pulse have remained stable until the end of the study.
Summary statistics are presented in section 15.1 table 3.1.
Summary statistics of physical exam are presented in Section 15.1 table 2.5.

13.6 SAFETY CONCLUSIONS

A comparison between the two groups (placebo and treatment) in all safety parameters including adverse events, blood and urinary tests, vital signs and physical exam did not demonstrate any major differences between the groups. It was noted however, that the general health condition, based on laboratory results and vital signs, has either remained stable or even improved. This is probably due to the special day to day care that was more applied to the patients that participated in the study. There were medical students that were present near the patients during the treatment and noted also detailed of patient condition. This close observation of the patients by an external body may have alerted the medical staff to pay more attention to the participating patients thus improving their health condition.

Most of the adverse events reported were related to the medical condition and age of patients and not related to the treatment.

The treatment with the DDCT device for the duration of 8 weeks has shown to be safe for use.

14 DISCUSSION AND OVERALL CONCLUSIONS

The DDCT device is a non invasive device used on the elderly and health challenged population with stage III pressure wounds. The device is safe for use both from the electrical point of view and the usage aspect. Significant treatment efficacy was observed. This significance was observed in several parameters that define wound healing – closure, change in area, epithelial growth.
The efficacy and significance of efficacy for epithelial growth and area reduction, were both higher in day 45 compared to the planned check-point in day 57.

The original protocol used a different method of calculation of the wound area, not taking into consideration the variability in wound size and shape. In order to make the a more accurate calculation the photographs taken during the study, were re-traced and processed with the TRACER ver 2.3 software (http://www.comp.glam.ac.uk/pages/staff/pplassma/MedImaging/) . This software was upgraded according to LifeWave's requirements and used for this analysis.

This study was performed as the first in a series of studies that are required in order to optimize the duration of treatment for various types and locations of pressure wounds.

15. TABLES AND LISTINGS

15.1 SAFETY TABLES

15.2 PP2 CALCLULATIONS

15.3 TABLES FOR WOUND CALCULATIONS

15.4 LISTINGS

16. APPENDICES

16.1 – LIST OF ALL ETHICS COMMITTEES

- Sheba Medical center - The Helsinki Committee of the Sheba Medical center, Tel-Hasomer, Ramat Gan, Israel. (for both centers at Sheba)
- Reuth Hospital – The Helsinki Committee of the Reuth Hospital, Tel-Aviv, Israel
- Herzog Hospital – The Helsinki Committee of the Herzog Hospital, Jerusalem, Israel
- Assaf Harofeh Medical Center – The Helsinki Committee of Assaf Harofe Medical Center
- Harzfeld Hospital – The Helsinki Committee of Kaplan Medical Center, Rehovot, Israel.
- Migdaley Hazahv Hospital – The Helsinki Committee of Assuta Medical Centers, Tel-Aviv, Israel.
- Rambam Medical Center – The Helsinki Committee of Rambam Medical Center, Haifa, Israel.
- Geriatric Center Shoham – The Helsinki Committee of the Geriatric Medical Center, Pardes Hanna, Israel.
- Beit Loewenstein Rehabilitation Center – The Helsinki Committee of the Beit Loewenstein Rehabilitation Center, Raanana, Israel.
- Shaare Zedek Medical Center – The Helsinki Committee of the Shaare Zedek Medical Center, Jerusalem, Israel.
- Hopital Francias Saint Louis - The Helsinki Committee of the Hadassah Medical Center, Ein Karem, Jerusalem, Israel.
- Shmuel Harofe – The Helsinki Committee of Shmuel Harofe, Beer Yaacov, Israel

16.2 – LIST OF ALL INVESTIGATORS AND CENTERS.

101 Tel Hashomer Hospital Geriatric departments, Ramat Gan, **ISRAEL**
Chief Investigator: Dr. Abrahan Adonsky

103 Tel Hashomer Department of Neurological Rehabilitation, Ramat Gan, **ISRAEL**
Chief Investigator Dr. Gabi Zeilig

102 Reuth Medical Center, Tel Aviv, **ISRAEL**
Chief Investigator: Dr. Polivkin

113 Assaf-Harofeh Medical center and Shmuel Harofeh Geriatric Hospital, Zrifin
Chief Investigator, Dr. Arthur Laibowitch

109 Herzog Hospital, Jerusalem, **ISRAEL**
Chief Investigator: Dr. Yaul

107 Harzfeld Hospital, Gedera, **ISRAEL**
Chief Investigator, Dr. Shmuel Levy

106 Migdaley Hazav, Hospital, Bat-Yam, **ISRAEL**
Chief Investigator, Dr. Orna Ofir

111 Rambam Hospital, Haifa, **ISRAEL**
Chief Investigator, Dr. Ramon Itzhak

112 Geriatric Center Shoham, Pardes Hana, **ISRAEL**
Chief Investigator, Dr. Joshua Ben-israel.

104 Beit Loewenstein Rehabilitation Center, Raanana, **ISRAEL**
Chief Investigator, Prof. Eli Isakov.

108 Shaare Zedek Hospital, Jerusalem, **ISRAEL**

Chief Investigator, Dr. Zvi Devoltzky.

110 Hopital Francias Saint Louis, Jersusalem, **ISRAEL**
Chief Investigator , Dr. Lev Symmer also of Hadassah Medical Center.

105 Shmuel Harofe, Beer Yaacov, **ISRAEL**
Chief Investigator, Dr. Lifshitz