

# Pulsed Acoustic Cellular Expression Technology in the Treatment of Diabetic Foot Ulcers:

A Sham-controlled, Double-blinded, Randomized  
Clinical Trial

24-Week Top-Line Safety and Efficacy Data

July 12, 2011

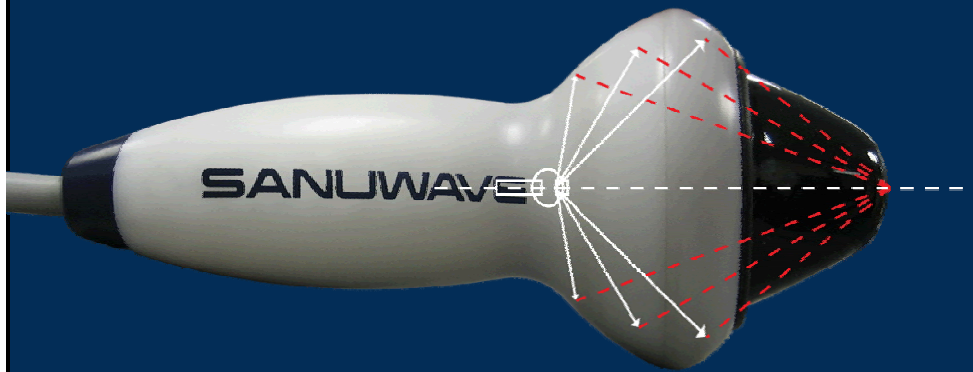
## Pulsed Acoustic Cellular Expression (PACE®)

PACE is a proprietary form of ESWT that utilizes high-energy acoustic pressure waves in the shock wave spectrum created through an electrohydraulic method.

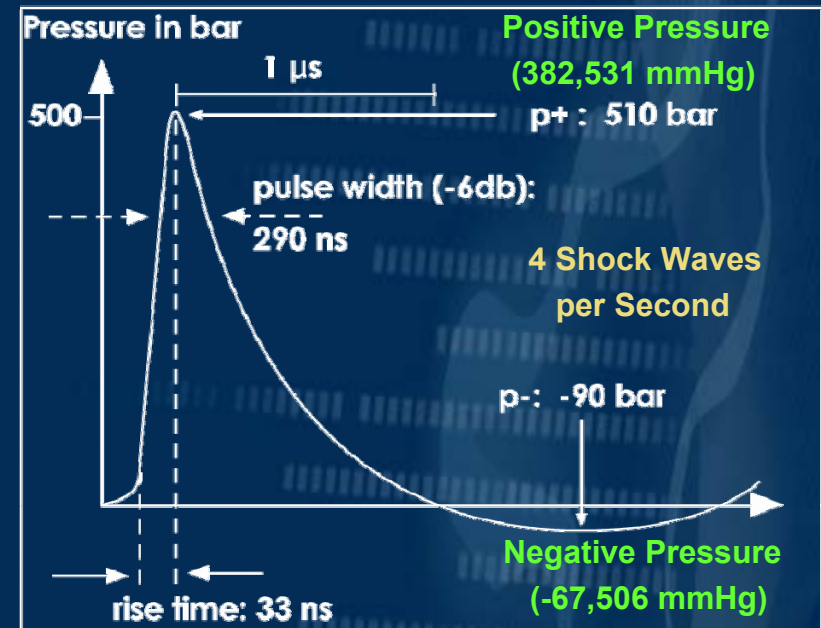
PACE consists of a procedure console and applicator.



## PACE® Procedures Deliver Positive and Negative Pressure



Shock Wave Pressure-Time Diagram

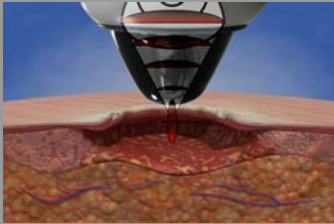


## PACE Energy Causes Mechanical Stresses on Cells

High pressure amplitude (510 bar), rapid rise time (<33ns) and short life cycle (2-8 $\mu$ s)

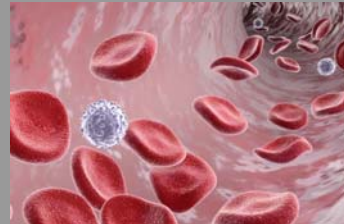
Frequency spectrum ranging from the audible to the ultrasonic region (16Hz-20MHz)

## PACE® Elicits a Biologic Response



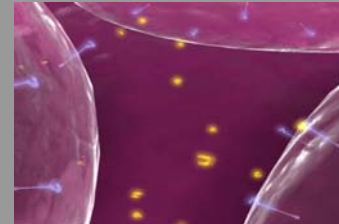
High-energy PACE acoustic pressure waves are applied to wound surface.

Immediate microcirculatory improvement, acute inflammatory and perfusion response



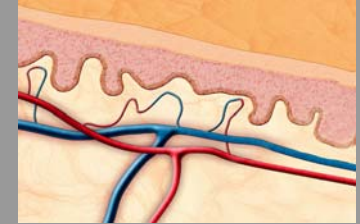
Increase in capillary perfusion and vessel permeability.

Cellular signaling initiates angiogenic growth factor and protein upregulation



Inflammatory response that activates vessel endothelial cells and initiates proangiogenic growth factor production.

Lasting new microcirculation and new vascularization



Chronic condition is returned to an acute condition helping the body's own healing response to reinitiate, culminating in reepithelialization.

Tissue granulation and complete wound healing

## dermaPACE® Pivotal Phase III DFU Study

- 206-patient, randomized, double-blinded, parallel-group, sham-controlled, multicenter, 24-week pivotal clinical trial.
- Purpose: Compare safety and effectiveness of the dermaPACE device to sham application, when both are administered in conjunction with standard of care.
- Only patients successfully meeting the pre-specified screening criteria and completing a two-week run-in period were considered for randomization.
- Patients received up to four, 20-minute, noninvasive procedures with dermaPACE (500 impulses) or with a Sham-control device, delivered over a two-week period.
- Standard of care continued for 12 weeks or until the target ulcer healed.
- Follow-up period continued after the initial 12 weeks for an additional 12 weeks for safety and efficacy assessment.



## Robert Galiano, M.D.

Assistant Professor, Division of Plastic Surgery,  
Department of Surgery at the Northwestern University  
Feinberg School of Medicine

## Baseline Subject and Target Ulcer Characteristics

- The average age for all subjects treated with dermaPACE® was significantly higher than subjects treated with Sham-control,  $60.4 \pm 10.4$  years versus  $56.2 \pm 9.4$  years ( $p=0.005$ ) with a median age of 62 and 57, respectively.
- Subjects treated with dermaPACE had a history of diabetes prior to treatment that was highly suggestive of a significant difference averaging  $18.0 \pm 10.0$  years, compared to Sham-control subjects of  $15.7 \pm 11.1$  years ( $p=0.055$ ).
- In general, target ulcers treated with dermaPACE were larger in average area than those in Sham-control subjects,  $3.5 \pm 3.2$  cm<sup>2</sup> versus  $2.8 \pm 1.8$  cm<sup>2</sup>, respectively.
- In general, baseline patient disease characteristics for dermaPACE subjects as compared to Sham-control subjects did not differ significantly; Body Mass Index (BMI), HbA1c, ankle-brachial index (ABI), toe pressures and TCPO2 were all very similar between the two groups.
- Target ulcers were predominantly plantar; 42 (39%) and 43 (43%) in dermaPACE and Sham-control, respectively.

## Subject Enrollment and Disposition

Subject Enrollment and Disposition	Total Subjects (n)
Subjects Screened	293
Subjects Fail Screening	87
Subjects Randomized (ITT Population) <sup>1</sup>	206
Efficacy Evaluable Population (EE) <sup>2</sup>	194
Remaining Subjects at 12-Week Visit (Visit 11)	164
Remaining Subjects at 24-Week Visit (Visit 17)	149

<sup>1</sup> The Intent-to-Treat (ITT) population included any subject that was randomized and received at least one active dermaPACE<sup>®</sup> or sham-control treatment.

<sup>2</sup> The Efficacy Evaluable (EE) population consisted of subjects who had a diabetic foot ulcer at baseline equal to or between 1cm<sup>2</sup> and 16cm<sup>2</sup> and that did not decrease in volume by more than 50% during the two-week run-in period, and who followed the protocol without significant protocol deviations.

## dermaPACE® Pivotal Phase III DFU Study (Rigorous Design)

- Double-blinded (patient and physician), sham-controlled clinical trial that eliminated study bias regarding patient selection, evaluation and treatment assignment.
- No allowance for surgical closure by secondary intervention.
- Closure defined as 100% epithelialization, no dressing or draining requirements, verified at two consecutive visits (2 weeks apart).

## dermaPACE® Pivotal Phase III DFU Study (Rigorous Design)

- dermaPACE was tested in a double-blinded (patient and physician), sham-controlled study that **eliminated study bias** regarding patient selection, evaluation and treatment assignment.
- **83% of all patients and 73% of the Sham-control group believed** they had received the active dermaPACE treatment.

### Study Bias (Influenced by Blinding)

dermaPACE	Apligraf	Dermagraft	V.A.C.
			
Investigator/Patient Blinded	Not Blinded	Not Blinded	Not Blinded

## dermaPACE® Pivotal Phase III DFU Study (Effectiveness Analysis and Results)

In the 12-week analysis, the dermaPACE patients showed a strong positive trend in the primary endpoint of 100% wound closure, but this was not statistically significant. By 12 weeks, 22/107 patients (21%) closed in the dermaPACE group, whereas 15/99 patients (15%) closed in the Sham-control group ( $p=0.363$ ).

In the 24-week analysis in the ITT population, statistical significance was achieved in the endpoint of 100% wound closure as 39/107 (36%) dermaPACE subjects achieved complete wound closure compared with 23/99 (23%) Sham-control subjects ( $p=0.047$ ) at 20 weeks and continued through 24 weeks with 42/107 (40%) dermaPACE subjects closed compared with 26/99 (26%) Sham-control subjects ( $p=0.054$ ).

In the 24-week analysis in the EE population, 38/101 (38%) dermaPACE subjects compared to 20/93 (21%) Sham-control subjects achieved complete wound closure which was significant at 20 weeks ( $p=0.018$ ) and continued with statistical significance through 24 weeks ( $p=0.022$ ).

## dermaPACE® Pivotal Phase III DFU Study (Effectiveness Analysis and Results)

- Based on the pure, controlled design of the study restricting investigators from closing the wound surgically, a  $\geq 90\%$  wound closure endpoint was determined to be clinically meaningful and demonstrated statistical significance ( $p=0.016$ ) at 12 weeks in favor of dermaPACE (51/107, 48%) compared to Sham-control patients (31/99, 31%).
  - Of the patients who achieved the  $\geq 90\%$  closure threshold within 12 weeks of the initial dermaPACE treatment, the median percent reduction exceeded 99%.
  - The dermaPACE patients in this composite analysis of  $\geq 90\%$  closure had, at baseline, a 58% larger wound area than in Sham-control patients.

## Efficacy Primary and Secondary Endpoints per Randomized Group and Population

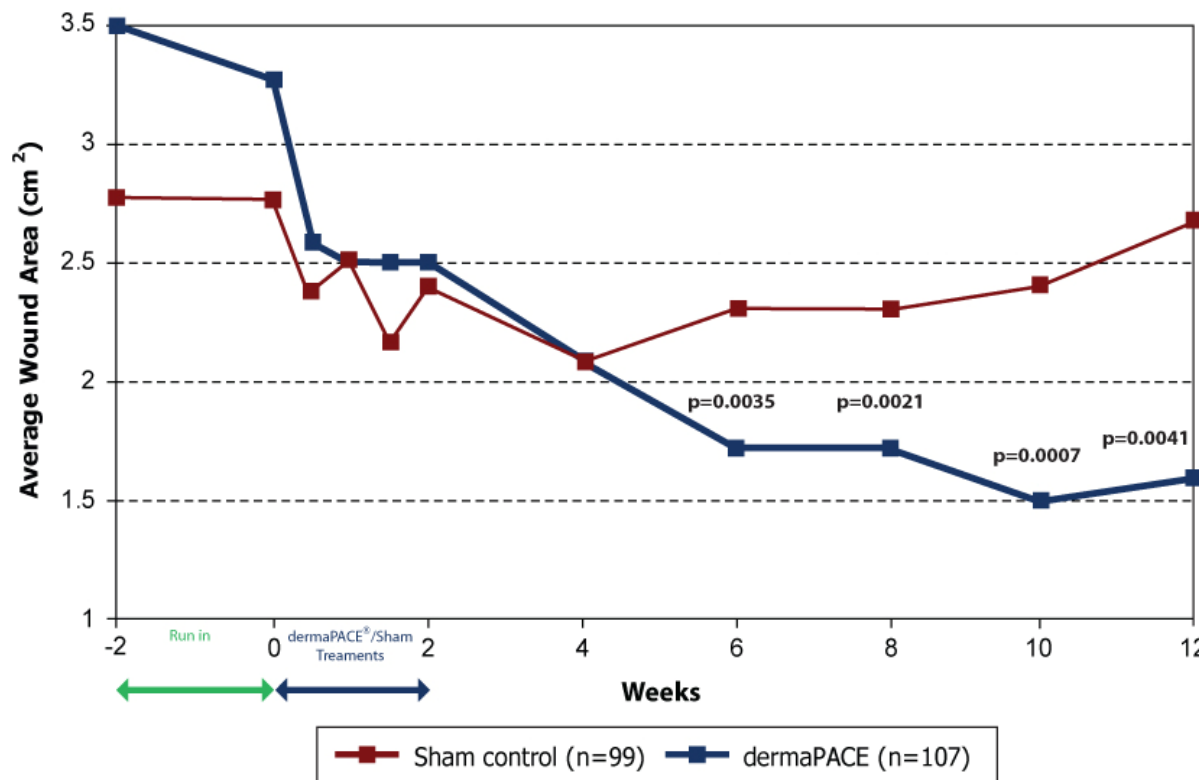
Efficacy Endpoints			
Primary Endpoints	dermaPACE® (n=107)	Sham-control (n=99)	
Efficacy – ITT	n (%)	n (%)	p-value
Complete Wound Closure at 12 Weeks	22 (20.6%)	15 (15.2%)	0.363
Complete Wound Closure at 20 Weeks	39 (36.4%)	23 (23.2%)	0.047
Complete Wound Closure at 24 Weeks	42 (39.3%)	26 (26.3%)	0.054
	dermaPACE (n=101)	Sham-control (n=93)	
Efficacy – EE	n (%)	n (%)	p-value
Complete Wound Closure at 12 Weeks	21 (20.8%)	13 (14.0%)	0.256
Complete Wound Closure at 20 Weeks	38 (37.6%)	20 (21.5%)	0.018
Complete Wound Closure at 24 Weeks	41 (40.6%)	23 (24.7%)	0.022
Secondary Endpoint	dermaPACE (n=107)	Sham-control (n=99)	
Efficacy – ITT	n (%)	n (%)	p-value
Complete Wound Closure or $\geq 90\%$ at 12 Weeks	51 (47.7%)	31 (31.3%)	0.016

## dermaPACE® Pivotal Phase III DFU Study (Effectiveness Analysis and Results)

- dermaPACE patients were **twice as likely to achieve 90% to 100% wound closure** compared to Sham-control patients within 12 weeks of the initial treatment.
- Of the patients who achieved complete wound closure at 12 weeks, the **recurrence rate was only 4.5%** in the dermaPACE group as compared to 20% in the Sham-control group at 24 weeks.

## Change in Wound Area – Secondary Efficacy Endpoint

By 12 weeks, the average percent reduction in the size of the target ulcer in patients treated with dermaPACE<sup>®</sup> was **54%**, compared to only 7% in the Sham-control group patients.

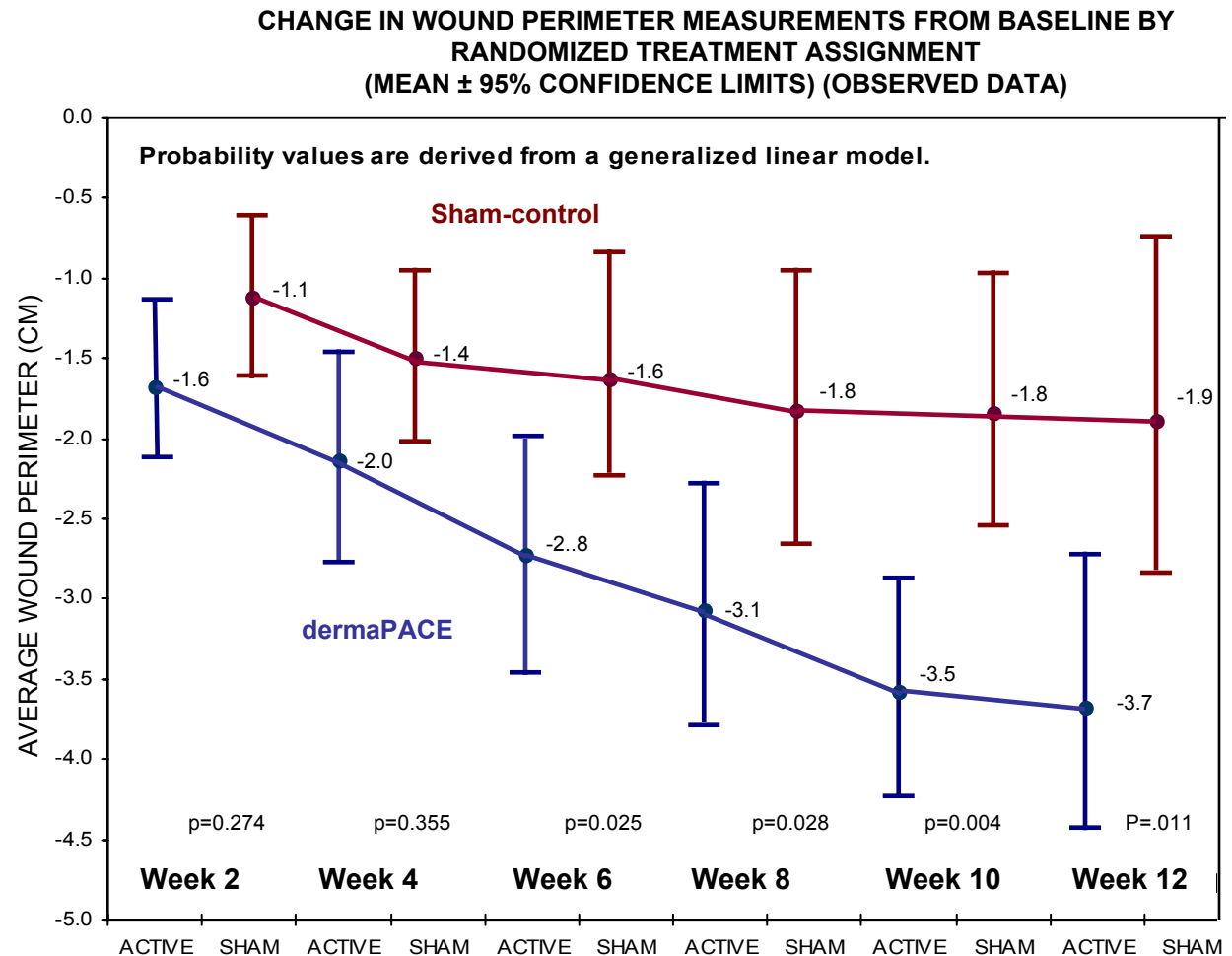


- Within 4 weeks following the final treatment with dermaPACE (6-week point), and consistently throughout the 12-week evaluation period, there was a highly significant reduction in the size of the target ulcer for dermaPACE treated patients compared with Sham-control subjects ( $p < 0.01$ ).
- Change in wound area reduction remained significant in favor of dermaPACE through the 24 weeks ( $p < 0.05$ ).

Change in wound area measurements from baseline by randomized treatment assignment (mean  $\pm$  95% confidence level) (observed data)

# Change In Wound Perimeter – Secondary Efficacy Endpoint

- At 12 weeks, p=0.011
- dermaPACE® n=85  
Avg. wound perimeter reduction was 3.7 cm.  
(Baseline: 7.1 cm, 12 Weeks: 3.4 cm)
- Sham-control n=71  
Avg. wound perimeter reduction was 1.9 cm.  
(Baseline: 6.6 cm, 12 Weeks: 4.7 cm)



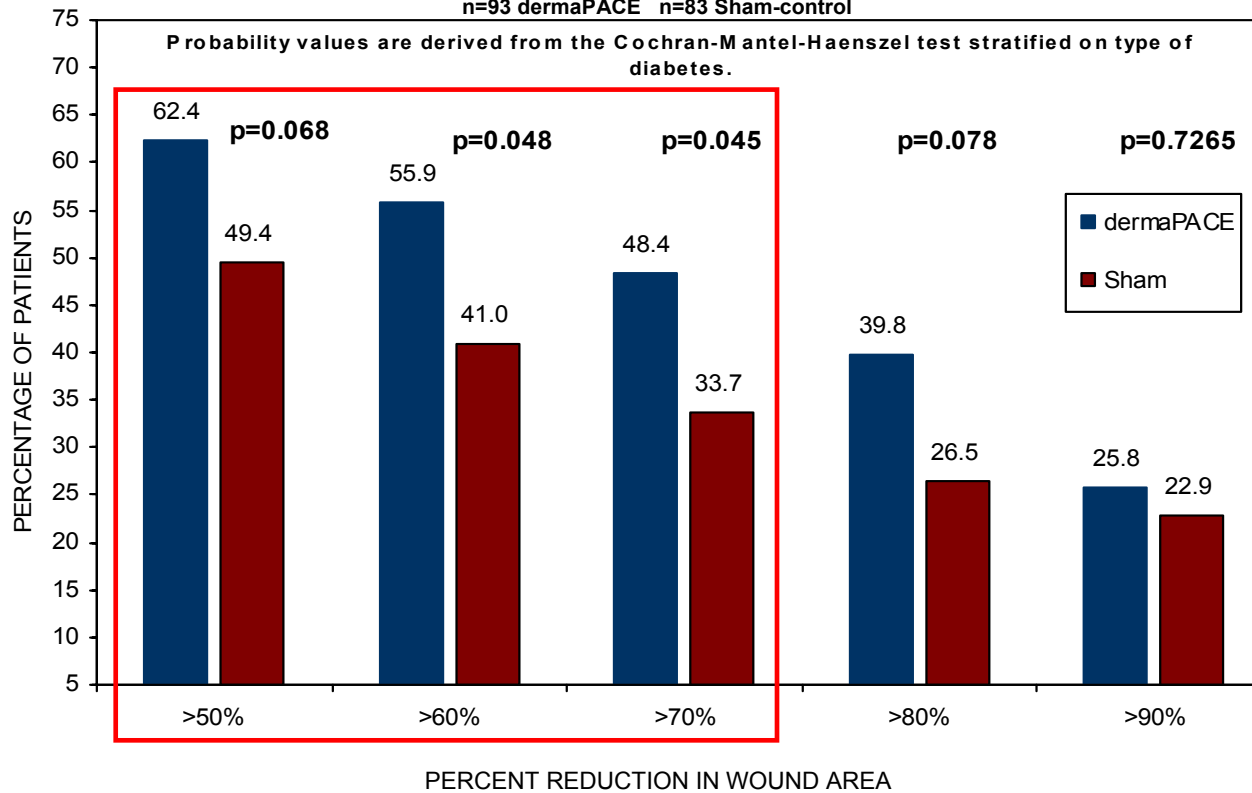
## Percent Reduction in Wound Area – Secondary Efficacy Endpoint

The change from baseline results in wound area first achieved statistical significance at 6 weeks (4 weeks from last treatment) with 60% or greater reduction in wound area in 56% of all dermaPACE® subjects (p=0.048).

**6 Weeks**

### PROPORTION OF PATIENTS WHO ACHIEVE A ≥ 50% THROUGH ≥ 90% REDUCTION IN WOUND AREA FROM BASELINE AT WEEK 6 BY RANDOMIZED TREATMENT ASSIGNMENT (OBSERVED DATA)

n=93 dermaPACE n=83 Sham-control

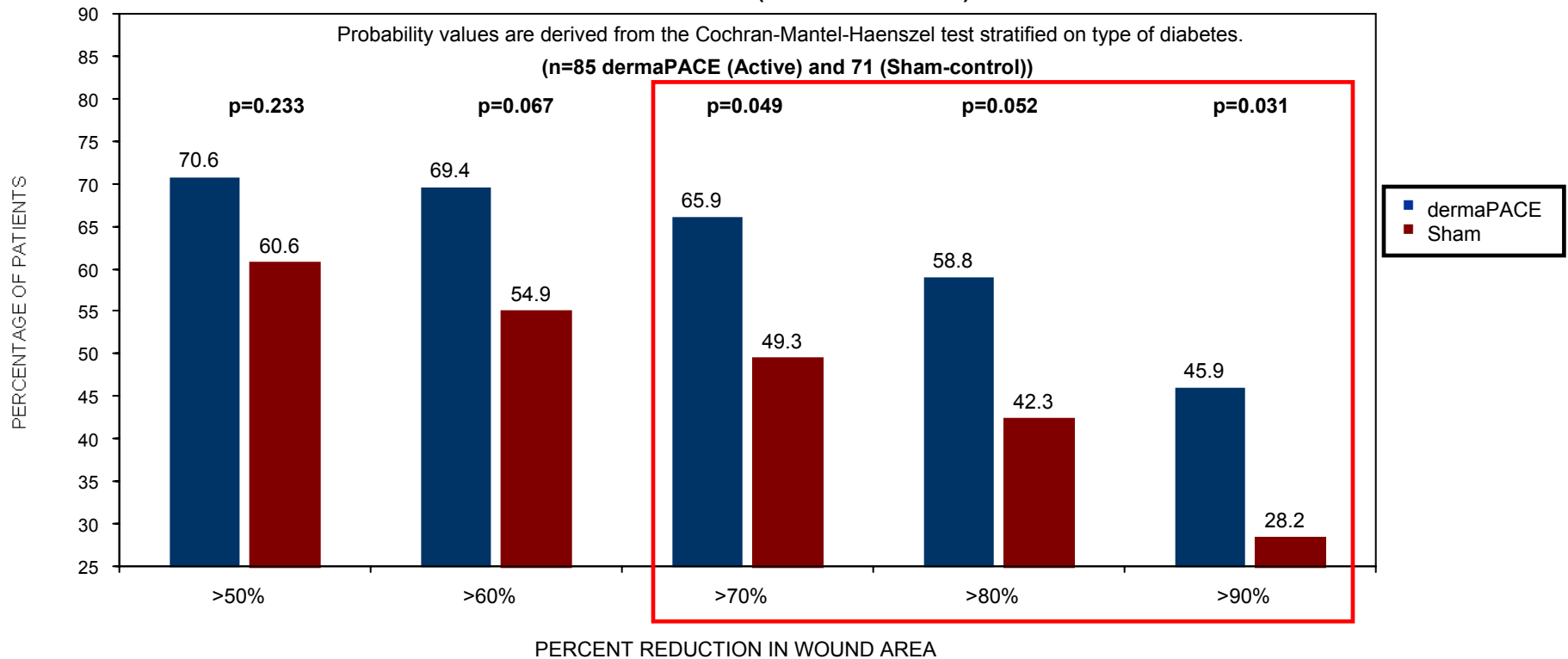


# Percent Reduction in Wound Area – Secondary Efficacy Endpoint

- The separation in the wound area healing rates steadily increases from  $\geq 50\%$  (week 6) to  $\geq 90\%$  reduction by 12 weeks.
- By 12 weeks, 46% of all dermaPACE<sup>®</sup> subjects experienced a  $\geq 90\%$  closure as compared to 28% of Sham-control subjects ( $p=0.031$ ).

**12 Weeks**

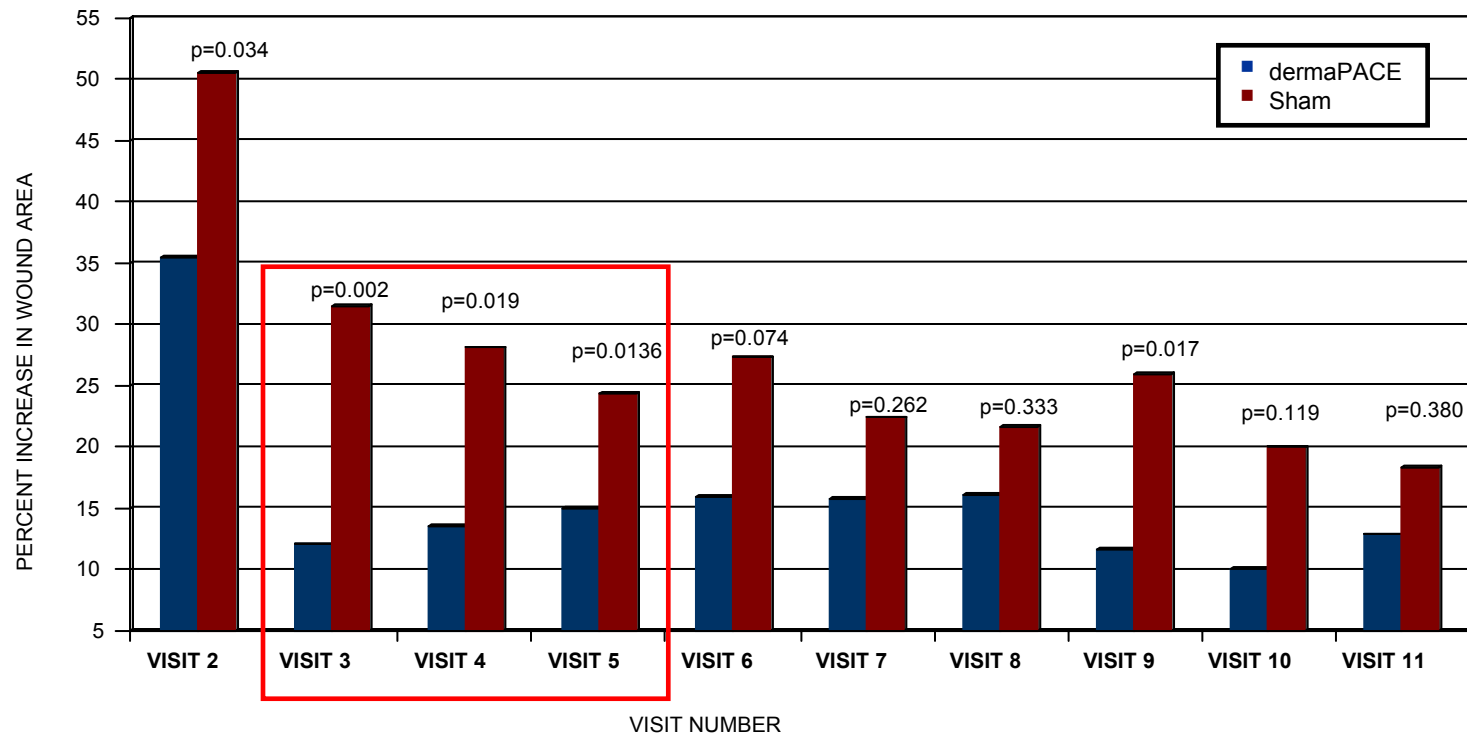
**REDUCTION IN WOUND AREA FROM BASELINE AT WEEK 12 BY PROPORTION OF PATIENTS WHO ACHIEVE A  $\geq 50\%$  THROUGH  $\geq 90\%$  BY RANDOMIZED TREATMENT ASSIGNMENT POPULATION (OBSERVED DATA)**



# Percent Increase in Wound Area – Secondary Efficacy Endpoint

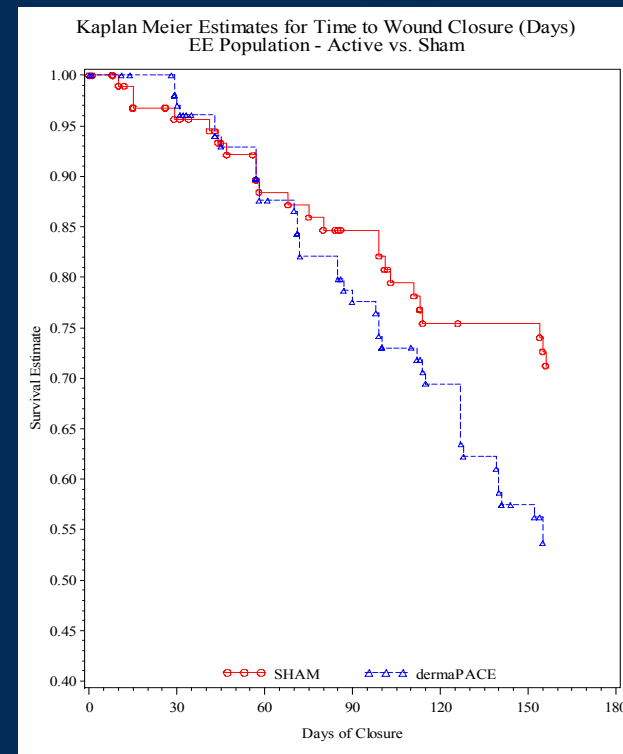
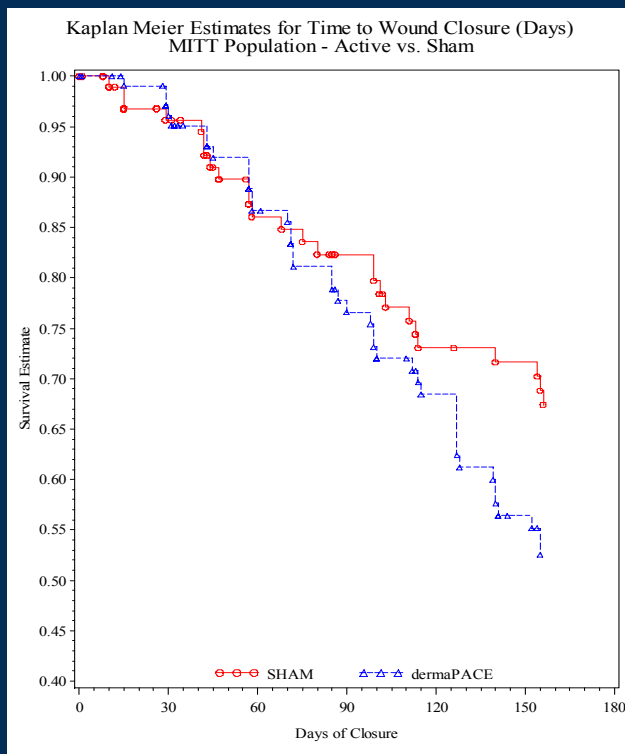
When comparing patients with an increase in wound area as compared to baseline from the outset, after the first application, the Sham-control group shows a significant number of patients whose wounds got worse as compared to the dermaPACE® group.

**PERCENTAGE OF PATIENTS WHO EXPERIENCED AN INCREASE IN WOUND AREA BY RANDOMIZED TREATMENT ASSIGNMENT BY 12 WEEKS (OBSERVED DATA)**



## Time to Complete Wound Closure

- The point estimates for the median time to complete wound closure were not estimable for both the dermaPACE® and Sham-control treatment groups, since less than 50% of the subjects achieved the endpoint.
- Kaplan-Meier estimates were not statistically significant for the ITT Population at the 0.05 level ( $p=0.102$ ), although in the Efficacy Evaluable (EE) Population, the time to complete wound closure was statistically significant ( $p=0.043$ ).



The effect responder is first seen at 70 days (10 weeks) in the ITT and EE populations, and then it continues throughout the 24 weeks.

Examples of dermaPACE®  
Study Patients Who Achieved  
100% Wound Closure

# dermaPACE® Subject A Visit 11- Fully Closed at Week 8

Distant

Close-Up

Visit 1



Visit 11



This picture represents a patient treated with dermaPACE that by the study design endpoint was fully closed at week 12 as confirmed at two consecutive visits.

# dermaPACE® Subject B Visit 11- Fully Closed at Week 6

Distant

Close-Up

Visit 1



Visit 11



This picture represents a patient treated with dermaPACE that by the study design endpoint was fully closed at week 12 as confirmed at two consecutive visits.

# dermaPACE<sup>®</sup> Subject C Visit 11- Fully Closed at Week 8

Distant

Close-Up

Visit 1



Visit 11



This picture represents a patient treated with dermaPACE that by the study design endpoint was fully closed at week 12 as confirmed at two consecutive visits.

Examples of dermaPACE®  
Study Patients Who Achieved  
90% - 99% Wound Closure

# dermaPACE® Subject D Visit 11- 97% Improved

Distant

Close-Up

Visit 1



Visit 11



This picture represents a patient treated with dermaPACE that by the study design endpoint was not considered fully closed at week 12.

# dermaPACE<sup>®</sup> Subject E Visit 11- 96% Improved

Distant

Close-Up

Visit 1



Visit 11



This picture represents a patient treated with dermaPACE that by the study design endpoint was not considered fully closed at week 12.

# dermaPACE<sup>®</sup> Subject F Visit 11- 99% Improved

Distant

Close-Up

Visit 1



Visit 11



This picture represents a patient treated with dermaPACE that by the study design endpoint was not considered fully closed at week 12.

# Lawrence Bass, M.D.

Safety Monitor

Clinical Assistant Professor of Plastic Surgery  
Department of Plastic Surgery  
NYU School of Medicine

## dermaPACE® Pivotal Phase III DFU Study (Safety Results)

- No statistical differences in the overall adverse event rates were seen between the two groups.
- Lower overall incidence of infection in the dermaPACE group.
- There were **no issues regarding the tolerability** of the dermaPACE procedure, suggesting additional procedures could be administered if clinically indicated and removing a major hurdle to patient selection.

## Conclusions Drawn From The Study

### Efficacy of dermaPACE<sup>®</sup>

- The overall results of this study revealed that a significant proportion of dermaPACE subjects achieved complete wound closure beginning at 20 weeks following the initial application in the ITT population (p=0.047) and EE population (p=0.018), which remained statistically significant throughout the study at 24 weeks in the ITT population (p=0.054) and EE population (p=0.022).
- Within 6 weeks following the initial application with dermaPACE, and consistently throughout the 12-week evaluation period, dermaPACE reduced the size of the target ulcer from baseline with high statistical significance compared with subjects randomized to receive Sham-control (p<0.01) and remained significant through 24 weeks (p<0.05).
- dermaPACE patients achieved a significant increase in the rate of complete wound closure or ≥ 90% wound area reduction by or at 12 weeks at the 0.05 level (p=0.016).
- Of the patients who achieved complete wound closure at 12 weeks, the recurrence rate at 24 weeks was only 4.5% in the dermaPACE group as compared to 20% in the Sham-control group.

### Safety of dermaPACE

The overall rate of adverse events between the two groups showed no significant difference. The total number of serious adverse events related to application site infections was reduced in dermaPACE, and no issues regarding the tolerability of dermaPACE treatment was shown.

## Overall Observation:

The highly positive clinical results from this rigorous Phase III study validate the ability of dermaPACE to safely heal diabetic foot ulcers.

The study showed a high degree of significance in the size reduction of ulcers treated with dermaPACE at 12 weeks, which achieved statistical significance of complete wound closure at 20 weeks and remained significant through the 24 week visit.

Importantly, the study showed that dermaPACE achieved robust closure with very low recurrence rates (4.5%) versus the recurrence rates in Sham-control group (20%).