



## **Pilot Wound Healing Study in the treatment of Diabetic Ulcers**

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## Abstract

This clinical study was initiated as a result of physician feedback showing wound healing potential from use of an Alginate Hydrogel product FDA 510k approved in 1998. It was designed to test the hypothesis that the Alginate Hydrogel dressing facilitated the healing of diabetic ulcers at a greater rate than the Hydrogel vehicle alone, and that the fragrant botanical base used to impart a pleasant fragrance, might be the source of the perceived positive clinical effect. A 21-patient, 8-week comparative study evaluated the accelerated wound healing potential of the Alginate Hydrogel dressing, the Hydrogel vehicle (placebo control) and becaplermin gel 0.01% (active control) in the treatment of diabetic ulcers.

ANOVA was used to analyze wound length, width, depth and global scores for epithelialization and granulation. A primary wound efficacy measure is % epithelialization of the wound. When change from baseline to week 8 for the parameter of global evaluation score for epithelialization was analyzed, the Alginate Hydrogel dressing demonstrated a statistically significant mean difference of  $-2.571$  when compared to the Hydrogel vehicle and a statistically significant mean difference of  $-2.571$  when compared to the becaplermin gel.

The average daily per patient cost of treatment medication and supplies for the becaplermin gel (\$15.05/day) was 2.3 times more than the Alginate Hydrogel (\$6.56/day). The Alginate Hydrogel dressing demonstrated both accelerated wound healing and more cost effectiveness when compared to becaplermin gel in patients with late stage diabetic ulcers.

## Introduction

The demographics of the American population are shifting, and one aspect of that shift is an increase in the number of people age 65 and over. There are almost 34 million Americans over age 65, representing 13 percent of all Americans. This number will grow to over 69 million (20% of all Americans) by the year 2030 and to almost 80 million by 2050 according to United States Census Bureau projections<sup>1</sup>. The incidence of obesity, defined as Body Mass Index (BMI) of 30 kg/m<sup>2</sup> or greater according to the National Institutes of Health (NIH), is 22.3% among adults or approximately 39.8 million people<sup>2,3</sup>. It is estimated that 16 million people are currently diagnosed with diabetes in the United States and this number will continue to rise due to dramatic shifts in the aging population, the incidence of obesity, and sedentary lifestyles.<sup>4</sup>

Approximately 15% of patients with diabetes will develop foot ulcers and 15 – 20 percent of those will progress to lower-extremity amputations. It has been reported that foot ulcers precede 85 percent of all nontraumatic, lower extremity amputations. The cost of treating diabetic foot ulcers is reported to range between \$4,000 and \$8,000 per ulcer episode and rise to \$28,000 within the first 2 years of diagnosis. The attributable cost of amputation is estimated at \$20,000 to \$60,000.<sup>5</sup>

The disease trends of diabetes and obesity coupled with an aging population and rising health care costs underscores the urgent need to identify and evaluate cost effective and efficacious wound healing treatments. Medical professionals are constantly searching for novel and efficacious therapies to treat the ever-increasing number of venous, diabetic and pressure ulcer wounds. Despite major recent advances in wound treatment technology, a high prevalence of chronic wounds exists, underscoring the need for topical agents that can actively promote wound healing. Treatments have been developed to better address the needs of the wound - e.g., vacuum-assisted closure (VAC) and added growth factors and cells to enhance healing. These therapies have met with mixed success in the clinic; none, as yet, have been definitively proven to be cost-effective.<sup>4</sup> At present the number of approved choices for diabetic ulcer patients is very limited and the high treatment cost of these therapies severely limits the availability of these options to the large number of patients who could benefit most. Medical professionals can best serve their patients by having at their disposal a variety of approved and cost effective therapies with which to treat the ever-increasing number and type of wounds and ulcers prevalent in today's changing population.

Since its FDA 510k approval in 1998, physician feedback from use of an Alginate Hydrogel dressing raised questions about whether the product may be facilitating the healing of diabetic ulcers more rapidly than would be expected from a standard Hydrogel dressing. Since the most unique component in the Alginate Hydrogel formula was the fragrant botanical base, which imparted a pleasant fragrance, it was theorized that the fragrance might contain some components or micronutrients that in specific combination, synergistically enhanced the product's wound healing potential. This study was designed to determine if a significant clinical effect could be observed under controlled conditions.

## Materials

The Phytacare<sup>®</sup> Alginate Hydrogel dressing (CuraPharm, Inc., Santee, CA) is a hydrogel with a fragrant botanical base impregnated on 4in. X 4in. sterile gauze pads and packaged in 6in. X 6in. single use foil laminate pouches. The Phytacare<sup>®</sup> Alginate Hydrogel dressing was approved by the FDA as a 510k medical device in June 1998. It is indicated for diabetic ulcers Stages I-IV, venous stasis ulcers, pressure ulcers, 1<sup>st</sup> and 2<sup>nd</sup> degree burns, wounds, cuts and abrasions. It is contraindicated for 3<sup>rd</sup> degree burns.

There is evidence that the Phytacare<sup>®</sup> gel contains compounds and micronutrients within some of the ingredients which may provide essential micronutrients needed in the healing process, act as a bacteriostatic agent, or stimulate the skin at the cellular level to repair itself.<sup>6</sup>

The Hydrogel vehicle (placebo control) is the alginate hydrogel of the Phytacare<sup>®</sup> formulation excluding the fragrant botanical base. The Hydrogel vehicle was impregnated on 4in. X 4in. sterile gauze pads and packaged in single use foil laminate pouches.

CuraPharm sponsor of the study provided the Hydrogel vehicle and Phytacare Alginate Hydrogel dressings.

Becaplermin gel, 0.01% (Regranex<sup>®</sup>, Ortho-McNeil Pharmaceutical; Raritan, New Jersey) is a recombinant human platelet-derived growth factor (rPDGF) formulated in a sodium carboxymethylcellulose (NaCMC) water based gel. It received FDA drug approval in December 1997 for lower extremity diabetic ulcers that had extended into the subcutaneous tissue or beyond and have an adequate blood supply. Becaplermin gel was used in this study as an FDA approved dressing for purposes of comparison and is termed the “positive control” in this article.

Becaplermin gel has biological activity similar to that of naturally occurring derived-growth factor, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair. Becaplermin gel was supplied in 15-gram tubes and stored by manufacturer’s specifications (8 to 15 degrees Celsius or refrigerated). The secondary dressings were used as extraneous bandages and were included in a cost analysis (Table 3) but not used as a comparator in the evaluation of the healing process and were purchased from Davidson Drugs, Sarasota, Florida.

The sterile Puritan DM Stick Foam tipped Wound Measuring Device was used to take the wound measurements during the evaluation visits and was provided by Hardwood Products Co., Gullford, Maine.

A Sony Electronics (Park Ridge, New Jersey) DSC-F707, 5 mega-pixel, high-resolution digital camera with a Smith-Victor (Griffith, Indiana) KT500 lighting kit with DP-12 diffusion screens were used to take the patient evaluation photographs.

## Study Design

The three-arm, multi-center comparative study enrolled eligible candidates between 21 and 90 years of age with a Stage III diabetic ulcer of the lower extremity. Patients were assigned one of three treatment regimens, the Alginate Hydrogel dressing, Test Product “A”, Hydrogel vehicle dressing, Test Product “B” (placebo control) or the becaplermin gel, Test Product “C” (active control) in a random sequential order after an IRB informed consent was obtained. Patients and investigators were blinded to the Test Product “A” and Test Product “B” treatment options, however, because of the obvious differences in the physical appearance of the becaplermin gel (15 gram tube) the study was carried out in a single-blind fashion.

Protocol parameters including choosing an approved drug as the active control and an appropriate vehicle as the placebo, patient self-treatment, wound data measurements (length, width, depth and area), study endpoint defined as 100% epithelialization of the wound flush with the level of the surrounding skin, inclusion and exclusion criteria and

consistent pressure off-loading were modeled after previous drug clinical trials and the FDA guidance document for wound healing clinical studies and botanical drugs<sup>7</sup>.

A pre-treatment medical history was recorded at screening and laboratory tests (serum albumen, cholesterol, hemoglobin, urea nitrogen, creatine and glucose) were performed at screening and week 4. The ulcer was cleansed with normal saline and sharp debridement and a scalpel was used to remove eschar, necrotic tissue and fibrin as needed before wound characteristics were recorded. The foam tipped measuring device was used to measure wound dimensions. The patient's target ulcer was evaluated every two weeks over an eight-week period. Wound measurements, length, width and depth, % epithelialization, % granulation, morphologic characteristics of erythema, wound exudate characteristics and a digital photograph were recorded at screening, week 2, week 4, week 6 and week 8 evaluation visits.

After the data was recorded wounds were packed with Test Product "A", Test Product "B" or the Test Product "C", ensuring that the becaplermin gel was applied according to the manufacturer's specifications for dose and administration. Patients were instructed in the proper application of the becaplermin gel. A secondary sterile gauze dressing, saran covered gauze or occlusive dressing was used to cover, protect and keep the ulcer moist. A standard paper tape or roll gauze was used to hold the dressings in place. No other topical agents or other primary dressings were used through the duration of the study. Dressing changes and becaplermin gel application were performed once daily according to manufacturer's specifications.

Patients were all outpatients and regularly instructed to keep the affected extremity elevated to maximize blood flow to the ulcer when sitting with ambulation kept to a minimum. Patients were instructed to try to control their diabetes and to incorporate caloric and nutrient content in their diet. Patients were not instructed to follow any special diet or keep a dietary diary. Appropriate off loading footwear was used to alleviate pressure points, minimize further injury and maximize the healing potential. Patients were instructed in proper wound care and given written wound care instructions for reinforcement. Patients were also instructed to keep the ulcer dry and cover the entire limb with a plastic bag when showering or bathing. The ulcerated limb was washed separately with a washcloth. If the underlying gauze or secondary dressing got wet, patients were instructed to change it. Patients were monitored on a weekly basis for compliance to study parameters and were routinely instructed and reinforced about the importance of following the good wound care directions. Prestudy medications were continued at the same dosage and schedule, but any changes or additions were noted. Patients were not excluded from the study because of any pre-existing medical condition or medication use except for the presence of an infection. A protocol compliance assessment by the study coordinator was used to screen patients for enrollment. Dressings were dispensed and dressing changes were monitored weekly.

## Patient Population and Disposition

All patients were diabetic and had a chronic ulcer not progressing toward healing that had remained unhealed for at least 4 weeks. The classification was a Stage III ulcer with full-thickness skin loss involving subcutaneous tissue damage or necrosis and extending to but not through fascia as described by the National Pressure Ulcer Advisory Panel staging system<sup>8</sup> of the lower limb below the knee. The minimum lesion size was .5cm X .5cm and a maximum size of 8cm X 8cm. Patients were excluded if they did not have a palpable dorsalis pedis or posterior tibial pulse, had previously failed becaplermin gel treatment or had limb edema that could not be controlled. For two weeks prior to the start date patients had no topical steroid, antibiotic or topical emollient use in the ulcer area. The baseline patient populations and target ulcer characteristics are listed in Table 1.

In total, 24 patients were randomized for the study and of these, 21 patients completed the study. One patient expired during the course of the study from medical complications unrelated to the study medication. One patient developed an infection unrelated to the study material and was withdrawn due to non-compliance. One patient developed osteomyelitis in the same foot unrelated to the treatment course and was rendered untreatable because of other medical complications.

The study population reflected a high degree of co morbid conditions prevalent in patients with late stage diabetic ulcers. Four patients were kidney dialysis patients of which two patients had been randomized to the Alginate Hydrogel and two to the Hydrogel (placebo) treatment arms. One patient in the Alginate Hydrogel treatment group was waiting for an organ transplant. Two patients in the Alginate Hydrogel group developed infections after the first week unrelated to the treatment course, and were taken off the study medications, but subsequently restarted on the same course once the infection was under control.

**TABLE 1: Baseline Patient and Wound Characteristics**

	<b>Alginate Hydrogel</b>	<b>Hydrogel Vehicle</b>	<b>Becaplermin Gel</b>
	(Test Product A)	(Test Product C)	(Test Product B)
	N=7	N=7	N=7
<b>Age (years)</b>			
Median	61	55	62
Range	72 -49	79 -37	84 - 49
<b>Ulcer Duration (months)</b>			
Mean	9.0	9.4	11.0
Median	5	9	9
Range	25 - 2	24 - 2	26 - 1
<b>Ulcer Size (cm<sup>2</sup>)</b>			
Mean	3.57	2.15	2.63
Median	1.2	1.2	1.4
Range	10.88 - 0.56	6.72 - 0.72	9.99 - 0.54
<b>Ulcer Depth (cm)</b>			
Mean	0.61	0.71	0.37
Median	0.3	0.6	0.3
Range	1.8 - 0.2	1.7 - 0.2	0.7 - 0.2

## Study Evaluations

A baseline screening evaluation was performed and data recorded prior to the initial treatment course application, but after the ulcer was debrided. The test site lesion was measured using the perpendicular method described as measuring the longest measurement of the wound as the length, regardless of the orientation, and the longest measurement perpendicular to the length as the width.<sup>9</sup> The depth was always measured at the deepest part of the wound. A screening digital photograph with an identifying label and metric scale placed in the photographic field was taken at a distance of 2-3 feet. At screening, week 2, week 4, week 6 and week 8 evaluations and photographs were taken to assess changes to the target ulcer. Wound measurements (cm) of length, width and depth were recorded with the sterile, scaled measuring stick. Wound measurements of length and width measured the non-epithelialized wound area. Global scores for % epithelialization and % granulation (Global Evaluation Scale: 0=complete healing of the lesion, 1=75% to 100% improvement, 2=50% to 75% improvement, 3=<50% improvement, 4=No Change, 5=exacerbation of the lesion) documenting the overall change in the lesions status relative to its status at the screening visit were also taken at each evaluation visit. An estimate of the degree of erythema (0=none, 1=slight or mild, 2=moderate or average, 3=severe) and exudate nature characterization (1=clear, 2=slightly cloudy, 3=cloudy, 4=frank purulence) surrounding and within the target lesion were also made.

## Average Daily Cost of Treatment Supplies Analysis

Over the eight-week period primary and secondary treatment supply data was recorded for the Alginate Hydrogel and becaplermin gel study arms. The Hydrogel vehicle treatment course cost data was not used in this analysis. Data consisted of the number of primary treatment course Alginate Hydrogel dressings, the number of 15 gram tubes of becaplermin gel, the number and type of secondary dressings, tape and roll gauze to secure the dressings and number of standard 5 ml. Normal saline vials to cleanse the wound. The supply use data for the eight-week period was recorded for the purpose of determining an average daily cost of treatment supplies.

A simple average daily cost (total cost of study medications, the Alginate Hydrogel dressings or becaplermin gel only, secondary dressings and supplies to cover and secure the primary dressing and saline to cleanse the wound divided by the number of treatment days in the patients study period) was determined. Since all secondary medical supplies and the becaplermin gel were purchased from a community retail pharmacy (Davidson Drugs, Sarasota, Florida), the cost of these supplies were based on the retail prices of these supplies from the pharmacy. The National Medicare Reimbursement rate for a Hydrogel impregnated gauze less than 16 square inches, HCPCS Code A-6231 is \$4.67 per dressing. Since the current retail price of the Alginate Hydrogel dressing is less than the National Medicare Reimbursement rate, a cost of \$4.67 per dressing was used to determine the average daily cost of treatment.

Patients were instructed to use an unopened Alginate Hydrogel or Hydrogel vehicle dressing daily and discard any opened dressings. The cost of treatment analysis does not take into account any increase in the rate of healing, the cost of medical services associated with treating the target ulcer or any pre-study medications.

Table 2 summarizes the average daily cost per patient of treatment medication and supplies for both the Alginate Hydrogel and becaplermin gel treatment groups and the overall average daily cost for all patients within each group.

**TABLE 2: Average Daily Cost of Supplies per Patient**

<b>Alginate Hydrogel</b>		<b>BecaplerminGel, 0.01%</b>	
<b>Patient #</b>	<b>Average Daily Cost of Supplies (\$ / day)</b>	<b>Patient #</b>	<b>Average Daily Cost of Supplies (\$ / day)</b>
Pt # 1**	3.90	Pt # 3	11.12
Pt # 4	6.94	Pt # 6	14.57
Pt # 7	8.83	Pt # 9	15.79
Pt # 13*	3.31	Pt # 12	12.30
Pt # 20	8.66	Pt # 18	13.76
Pt # 23	7.16	Pt # 21	12.99
Pt # 24	7.15	Pt # 22*	24.50
<b>AVERAGE DAILY COST OF MEDICATION AND SUPPLIES ALL PATIENTS</b>			
All Pts.	6.56	All Pts.	15.05

\*\* Dressing changes occurred once every other day

\* Patients #13 and #22 healed at week 3

## Statistical Analysis

DermTech International, San Diego, California, carried out the statistical analysis. The products tested were listed as Test Article A (Alginate Hydrogel), Test Article B (Hydrogel vehicle) and Test Article C (becaplermin gel). ANOVA was used to analyze the data.

A primary wound efficacy measure is % epithelialization of the wound (see Table 3). When change from baseline to week 8 for the parameter of global evaluation score for epithelialization was analyzed, Test Article A demonstrated a statistically significant mean difference of -2.571 when compared to Test Article B and a statistically significant mean difference of -2.571 when compared to Test Article C (See Tables 3A and 3B).

For the parameter of wound width, Test Article A change from baseline to week 6 demonstrated a statistically mean difference of  $-1.200$  when compared to Test Article B. Additionally, Test Article A change from baseline to week 8 demonstrated a statistically mean difference of  $-1.014$  compared to Test Article C and Test Article C demonstrated a statistically significant mean difference of  $-1.229$  when compared to Test Article B (see Tables 4A and 4B).

The three treatment groups were compared with respect to change from baseline at week 8 in wound area, using one-way ANOVA. Although the average wound area reduction ( $A = -3.37$ ;  $B = -0.4$ ;  $C = -0.61$ ) for Treatment A was considerably larger than for both treatments B and C, it was not statistically significant. The P value for the comparison of A vs. B was 0.08, indicative of better efficacy of A as compared to B, but it is not significant in this trial with this sample size (see Tables 5A and 5B).

Although no statistical difference was demonstrated among the three test articles A, B and C for the following parameters: wound width (Table 6A) and depth (Table 7A), global evaluation score for granulation (Table 8A), level of exudate (Table 9A), and degree of erythema (Table 10A), test article A demonstrated positive trends towards statistical significance (but not significant) for reduction in ulcer width (Table 6B), depth (Table 7B), % granulation (Table 8B), level of exudate (Table 9B), and erythemia (Table 10B).

Because the sample size of  $N=7$  per treatment group was small and on the ordinal scale, the nonparametric test of Kruskal-Wallis was used for the overall comparison of the 3 treatment groups and the Wilcoxon Rank-Sum test was used for the pair wise comparisons of the treatment groups. These results also confirm the significance of the comparisons in the previous analyses.

**TABLE 3 Epithelialization Score for all Patients**

<b>Primary Efficacy Measure, Epithelialization Score</b>			
<b>(Difference between screening and week 8)</b>			
<b>Patient #</b>	<b>Test Article A</b>	<b>Test Article B</b>	<b>Test Article C</b>
<b>For each group</b>			
#1	1	3	5
#2	1	3	2
#3	0	5	4
#4	2	4	4
#5	0	4	5
#6	1*	5	4
#7	0	0	0

**% Epithelialization Scoring**

A score of: 0 = 100%, Complete healing of the ulcer, 1 = 75 – 100%, 2 = 50 – 75%, 3 = < 50%, 4 = No Change, 5 = Worse, exacerbation of the ulcer condition

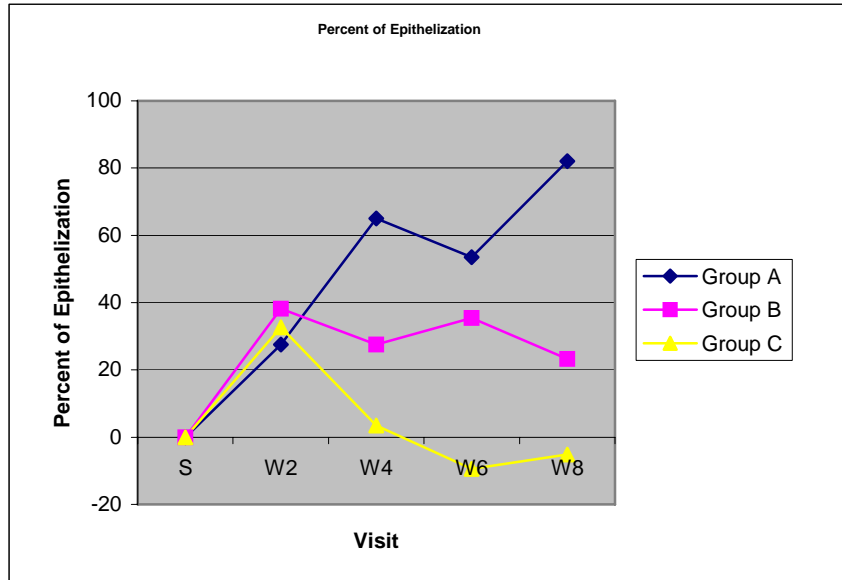
Patient developed wound infection during week 8. Wound measurements only taken at week 7 were carried forward to week 8. All other data taken at week 6 was carried forward to week 8 for the final analyses.

**Percent Epithelialization – All Patients – Computed Mean Values**

Group A – Phytacare Alginate Hydrogel;

Group B - Regranex becaplermin gel;

Group C - Placebo Vehicle



**Result Summary:** Even though the number of patients was very small, when change from baseline for the global evaluation score for epithelialization was compared for the three treatments, the Phytacare® Alginate Hydrogel dressing demonstrated a statistically significant improvement compared with both the Hydrogel vehicle and becaplermin gel at week eight. The change from baseline for wound width was also significantly greater at week eight for the Phytacare® Alginate Hydrogel Dressing compared to the becaplermin gel. Although not statistically significant in this small study, positive trends toward greater improvement by the Phytacare® Alginate Hydrogel Dressing were also observed for wound length, wound area, global evaluation score for granulation, level of exudate, and degree of erythema.

**TABLE 3A**

EPITHELIALIZATION - PERCENT (%)*						
Treatment	N =	Test Group	Week 2	Week 4	Week 6	Week 8
Alginate Hydrogel	7	A	2.50	1.57	1.29	0.86
Becaplermin Gel	7	B	2.86	2.86	2.43	3.43
Hydrogel Vehicle	7	C	2.86	3.00	3.00	3.43

\*Global Scores = 100%, 1 = > 75% > 100%, 2 = > 50%, 3 = < 50%, 4 = No Change, 5 = Worse

**Table 3B**

EPITHELIALIZATION - STATISTICAL ANALYSIS							
Week	Compare	Sig.	P value	q	Mean •	95% CL	
						LCL	UCO
2	P = 0.8473 – Not Significant						
4	P = 0.1887 – Not Significant						
6	P = 0.0506 – Nearly Significant						
8	A vs. B	Yes	<b>P &lt; 0.05</b>	4.4390	-2.5710	-4.662	-0.0221
8	A vs. C	Yes	<b>P &lt; 0.05</b>	4.4390 to	-2.5710	-4.662	-0.2364
8	B vs. C	No	P > 0.05	0.0000	-0.2143	-2.091	0.7779

**TABLE 4A**

MEAN ULCER WIDTH - INITIAL /CHANGE (cm)							
Treatment	N =	Test Group	Initial Width	Change Week 2	Change Week 4	Change Week 6	Change Week 8
Alginate Hydrogel	7	A	1.60	-0.80	-1.14	-1.21	-1.33
Becaplermin Gel	7	B	1.27	-0.26	-0.29	-0.43	-0.31
Hydrogel Vehicle	7	C	1.26	-0.07	-0.33	-0.01	-0.10

**TABLE 4B**

ULCER WIDTH CHANGE - STATISTICAL ANALYSIS							
Week	Compare	Sig.	P value	q	Mean A	95% CL	
						LCL	UCO
2	P = 0.0553 - Not Quite Significant						
4	P = 0.1334 - Not Significant						
6	A vs. B		P > 0.05	2.9220	-0.7857	-1.756	0.1848
6	A vs. C	<b>Yes</b>	<b>P &lt; 0.05</b>	4.4620	-1.2000	-.217	-0.2295
6	B vs. C	No	P > 0.05	1.5410	-0.4143	-1.385	0.5562
8	A vs. B	<b>Yes</b>	<b>P &lt; 0.05</b>	3.6890	-1.0140	-2.006	-0.0221
8	A vs. C	<b>Yes</b>	<b>P &lt; 0.05</b>	4.4690	-1.2290	-2.221	-0.2364
8	B vs. C	No	P > 0.05	0.7795	-0.2143	-1.206	0.7779

**TABLE 5A**

MEAN ULCER AREA - INITIAL /CHANGE (cm <sup>2</sup> - Length x Width)							
Treatment	N =	Test Group	Initial Area	Change Week 2	Change Week 4	Change Week 6	Change Week 8
Alginate Hydrogel	7	A	3.57	-1.95	-2.70	-3.11	-3.38
Becaplermin Gel	7	B	2.63	-0.40	-0.49	-0.97	-2.60
Hydrogel Vehicle	6	C	2.15	-0.25	-0.26	-0.37	-0.44

**TABLE 5B**

ULCER AREA CHANGE - STATISTICAL ANALYSIS				
Tests	Week 2	Week 4	Week 6	Week 8
ANOVA	N/S	N/S	N/S	N/S
P =	0.1448	0.2316	0.1530	0.1918

**TABLE 6A**

MEAN ULCER LENGTH - INITIAL/CHANGE (cm)							
Treatment	N =	Test Group	Initial Length	Change Week 2	Change Week 4	Change Week 6	Change Week 8
Alginate Hydrogel	7	A	1.76	-0.37	-0.64	-0.87	-1.30
Becaplermin Gel	7	B	1.67	-0.37	-0.56	-0.61	-0.54
Hydrogel Vehicle	7	C	1.51	-0.08	-0.13	-0.44	-0.37

**TABLE 6B**

ULCER LENGTH CHANGE - STATISTICAL ANALYSIS				
Tests	Week 2	Week 4	Week 6	Week 8
ANOVA	N/S	N/S	N/S	N/S
P =	0.7416	0.5478	0.6503	0.2239

**TABLE 7A**

MEAN ULCER DEPTH - INITIAL/CHANGE (cm)							
Treatment	N =	Test Group	Initial Depth	Change Week 2	Change Week 4	Change Week 6	Change Week 8
Alginate Hydrogel	7	A	0.61	-0.03	-0.39	-0.39	-0.50
Becaplermin Gel	7	B	0.37	-0.11	-0.17	-0.16	-0.17
Hydrogel Vehicle	7	C	0.71	-0.35	-0.29	-0.17	-0.26

**TABLE 7B**

ULCER DEPTH CHANGE - STATISTICAL ANALYSIS				
Tests	Week 2	Week 4	Week 6	Week 8
ANOVA	N/S	N/S	N/S	N/S
P =	0.1914	0.5400	0.4395	0.2380

**TABLE 8A**

MEAN GRANULATION - PERCENT (%)*						
Treatment	N =	Test Group	Week 2	Week 4	Week 6	Week 8
Alginate Hydrogel	7	A	2.50	1.00	0.86	1.00
Becaplermin Gel	7	B	1.29	0.17	1.00	1.86
Hydrogel Vehicle	7	C	2.00	1.57	1.43	2.71

\*Global Scores = 100%, 1 = > 75% > 100%, 2 = > 50%, 3 = < 50%, 4 = No Change, 5 = Worse

**TABLE 8B**

GRANULATION - STATISTICAL ANALYSIS				
Tests	Week 2	Week 4	Week 6	Week 8
ANOVA	N/S	N/S	N/S	N/S
P =	0.2884	0.4983	0.6637	0.2630

**TABLE 9A**

MEAN LEVEL OF EXUDATE - INITIAL /CHANGE (SCORE)*							
Treatment	N =	Test Group	Initial Level	Change Week 2	Change Week 4	Change Week 6	Change Week 8
Alginate Hydrogel	6	A	1.50	-0.83	-0.67	-0.83	-1.00
Becaplermin Gel	7	B	1.14	-0.14	-0.00	-0.14	-0.14
Hydrogel Vehicle	7	C	1.14	-0.00	-0.14	-0.43	-0.14

\*Score: 1 = Clear, 2 = Slightly Cloudy, 3 = Cloudy, 4 = Frank Purulence

**TABLE 9B**

LEVEL OF EXUDATE - STATISTICAL ANALYSIS				
Tests	Week 2	Week 4	Week 6	Week 8
ANOVA	N/S	N/S	N/S	N/S
P =	0.7416	0.5478	0.6503	0.2239

**TABLE 10A**

ERYTHEMA – MEAN INITIAL /CHANGE (LESION RATING SCALE)*							
Treatment	N =	Test Group	Initial	Change Week 2	Change Week 4	Change Week 6	Change Week 8
Alginate Hydrogel	7	A	0.86	-0.43	-0.57	-0.57	-0.71
Becaplermin Gel	7	B	0.71	-0.43	-0.43	-0.57	-0.14
Hydrogel Vehicle	7	C	0.86	-0.29	-0.57	-0.14	-0.29

\*Scale: 0 = None or Absent, 1 = Slight or mild, minimal, 2 = Moderate or Average, Easily Discernable  
3 = Severe or Marked, Evident

**TABLE 10B**

ERYTHEMA - STATISTICAL ANALYSIS				
Tests	Week 2	Week 4	Week 6	Week 8
ANOVA	N/S	N/S	N/S	N/S
P =	0.8397	0.9110	0.4123	0.3397

## Results

At each of the evaluation visits all patients were asked about any side effects or discomfort associated with their treatment course. The application of the Alginate Hydrogel, Hydrogel vehicle or the becaplermin gel was not associated with any pain or discomfort; however, one patient did experience a slight burning sensation at one evaluation visit when the Alginate Hydrogel dressing was first applied. Some patients exhibited signs of maceration in the skin surrounding the target ulcer in all three-treatment courses. This problem was corrected either by packing the impregnated dressing into the wound area preventing contact with the surrounding skin or by changing the secondary dressing to one that was more permeable allowing for better moisture equilibrium. No other adverse effects were observed on any treatment course in any of the patients.

Sex and age, wound characteristics, and ulcer area and depth were not significantly different between treatment with the Alginate Hydrogel, Hydrogel vehicle (placebo) or becaplermin gel (Table 1).

Table 2 summarizes the average daily cost of treatment medication and supplies for each patient using the Alginate Hydrogel dressing and becaplermin gel. The average cost for 7 patients on the becaplermin gel was \$15.05/day compared to \$6.56/day for the Alginate Hydrogel dressing. This amounted to an average daily cost 2.3 times greater for the becaplermin gel group than for the group that used the Alginate Hydrogel dressing.

At the end of the 8-week treatment course patients were given the option in consultation with their physician to continue with their study treatment course or switch to an alternative course of treatment of their choosing. Follow-up contact was done at one, two and three months after the final study evaluation to assess the status of the target ulcer. Five of the seven study patients using the Alginate Hydrogel had a 100% healing rate either during the eight-week study period or during the three-month follow-up period. At the end of the 3-month follow-up period the target ulcers for these five patients remained closed. Two of the seven patients using the Alginate Hydrogel regimen were partially healed following the 8-week treatment course and the 3-month follow-up period due to poor compliance. One patient using becaplermin gel healed during the study period, one patient expired during the follow-up period unrelated to the study medication,

two patients continued to use the becaplermin gel and three patients chose alternative treatments. One patient on the Hydrogel vehicle healed during the eight-week study period and six patients chose to use alternative treatments during the three-month follow-up period.

## Discussion

Becaplermin gel was used in the current study as a “positive control” over a “good wound care” standard of care as a result of data submitted to obtain US FDA drug approval showing that the becaplermin gel outperformed “good ulcer care” in clinical trials. In a multicenter, evaluator-blind controlled study of 250 patients, the incidence of complete ulcer closure after 20 weeks was 36% in the becaplermin gel, 0.01% arm (n=128) while good ulcer care alone was 32% (n=122).<sup>10,11,12,13</sup> Further investigation of the becaplermin gel, 0.01% clinical trials shows that in a multi-center, double-blind, placebo controlled trial of 382 patients the incidence of complete ulcer closure for becaplermin gel, 0.01% (n=123) at week 8 was 16%.<sup>13</sup> In this study complete ulcer closure (100% epithelialization of the wound) for the becaplermin gel treatment course was 14%. This compares to the complete ulcer closure of 42% at week 8 for the Alginate Hydrogel treatment course in this study.

To further evaluate the accelerated wound healing potential of the Alginate Hydrogel product, the authors explored the “normal” rate of healing for diabetic ulcers in patients with adequate arterial blood flow who follow a good ulcer care regimen of treatment. Data of 586 individuals from the standard care/placebo arm of 5 randomized clinical trials provided important information to better understand the normal rate of diabetic ulcer healing. The mean wound size of this group was 1.61 cm<sup>2</sup> and ranged from 0.11 cm<sup>2</sup> to 111.22 cm<sup>2</sup>. The mean duration was 30 weeks.<sup>14</sup> Table 11 summarizes the percentage of diabetic ulcers (N=586) that healed at 4 to 20 weeks of good ulcer care.<sup>14</sup> Table 11 also depicts the slow and limited healing of diabetic neuropathic ulcers using only good ulcer care and further provides an important measure for evaluating the accelerated wound healing potential of the Alginate Hydrogel dressing.

The risk of infection among late stage diabetic ulcer patients is a primary concern especially since many of these patients have underlying co morbid conditions and neuropathies, making it more difficult to recognize when initial signs of infection are present. Moreover, these patient’s immune systems are often severely compromised. Diabetic ulcer patients are also at increased risk for depression because many recognize the impending fate of an unhealed wound is limb amputation. The longer any ulcer remains open, the greater the chance of infection and amputation. The timely closure of any ulcer will not only reduce the probability of secondary complications but also affords the patient peace of mind knowing that their wound and their health is in control. Advanced ulcer treatments, like the Alginate Hydrogel dressing that work expeditiously to close wounds may significantly reduce the high morbidity, mortality and cost of care associated with diabetic foot ulcers.

Healthcare providers may be hesitant to deviate from their medical training or from community norms. New treatment modalities are neglected when the clinician has become comfortable with past treatment regimens. Clinicians need to be encouraged to carefully read literature associated with new products, and when supported by well-designed clinical trials and scientific literature, apply the modalities as a means to expedite wound closure. Product cost, ability to significantly reduce the time to closure, advantages over other treatment modalities, and patient compliance are all considerations for the final treatment selection.<sup>15</sup> Healthcare professionals faced with the time constraints of busy schedules are constantly bombarded with case study product profiles documenting efficacy which leaves them the difficult task of evaluating the performance on their patients of a multitude of new products that are released every year. Small well-designed pilot clinical studies under controlled conditions, like this one, offer healthcare professionals the opportunity to review valid clinical data to evaluate the potential of new and existing products. This type of clinical data may also provide insight for qualified practitioners to explore the potential off label use of approved products. By providing important and useful clinical data on new products, healthcare professionals are better able to ascertain product effectiveness in treating conditions and apply these modalities quickly to benefit their patients allowing them the opportunity to better serve their patients.

**TABLE 11 Percentages of Diabetic Ulcers 100 % Healed At 4 to 20 Weeks**

Weeks	Good Ulcer Care * (N = 586) % Healed
4	-
8	16
12	24
16	28
20	33

***\* Good ulcer care included a daily, saline-moistened dressing change and limited weight bearing on the affected limb.***



## Conclusion

Although the number of study patients was relatively small (N=21), the Alginate Hydrogel dressing demonstrated significant potential for accelerating wound healing compared to either the Hydrogel vehicle or becaplermin gel for Stage III diabetic ulcer patients. The outcome of this study with the new Alginate Hydrogel dressing offers diabetic ulcer patients both accelerated wound healing and cost of treatment advantages over becaplermin gel. The authors believe that the Alginate Hydrogel product warrants further investigation to determine its full potential for accelerated wound healing and closure of early and late stage diabetic ulcers and other types of wounds as well as the specific healing mechanism responsible for the findings herein.

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