

# Randomized Clinical Trial Comparing OASIS Wound Matrix to Regranex Gel for Diabetic Ulcers

Jeffrey A. Niezgoda, MD, FACHM, FAPWCA, FACEP; Carl C. Van Gils, DPM, MS, CWS; Robert G. Frykberg, DPM, MPH, FAPWCA; Jason P. Hodde, MS; and the OASIS Diabetic Ulcer Study Group

## ABSTRACT

**OBJECTIVE:** To compare healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel.

**DESIGN:** Randomized, prospective, controlled multicenter trial at 9 outpatient wound care clinics.

**SUBJECTS:** A total of 73 patients with at least 1 diabetic foot ulcer were entered into the trial and completed the protocol.

**INTERVENTION:** Patients were randomized to receive either OASIS Wound Matrix (n = 37) or Regranex Gel (n = 36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly clinic visit. Dressings were changed as needed. The maximum treatment period for each patient was 12 weeks.

**PRIMARY OUTCOME MEASURE:** Incidence of healing in each group at 12 weeks.

**RESULTS:** After 12 weeks of treatment, 18 (49%) OASIS-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients.

**CONCLUSION:** Although the sample size was not large enough to demonstrate that the incidence of healing in the OASIS group was statistically superior ( $P = .055$ ), the study results showed that treatment with OASIS is as effective as Regranex in healing full-thickness diabetic foot ulcers by 12 weeks.

ADV SKIN WOUND CARE 2005;18:258-66.

tion and eventual amputation as a result of increasing ulcer severity.

The attendant burden to society cannot be easily quantified. However, 1 report suggests monthly health care costs of approximately \$1200 for each ulcer, with total estimated annual treatment costs in the United States alone exceeding \$1 billion.<sup>1</sup> Another study estimated the total cost of treating a lower-extremity ulcer at \$4595 per episode.<sup>2</sup> Other reviews have reported total costs for treating a diabetic foot ulcer to range from \$10,000 to \$60,000,<sup>3-5</sup> depending on the severity of the ulcer and the clinical outcome. As a typical example, a recent study reported that the attributable cost for a middle-aged man with diabetes and a new foot ulcer is \$27,987 for the first year after diagnosis.<sup>1</sup> Because medical costs are directly related to ulcer severity, preventing ulcer progression and eventual hospitalization through early aggressive and effective treatment results in a substantial decrease in the total amount of health care dollars required to treat a chronic wound.<sup>6</sup>

The current standard of care for diabetic ulcers lacks efficacy. Standard care alone—consisting of removal of mechanical stress, sharp debridement, and maintenance of a moist wound environment—has been reported to heal approximately 24% of ulcers after 12 weeks.<sup>7</sup>

In recent years, wound care materials derived from biologic sources have been shown to promote granulation and epithelialization of dermal wounds versus standard care. They have had varying degrees of efficacy,<sup>8-13</sup> and numerous factors, such as variable entry criteria and different off-loading and glucose control procedures, make it difficult to directly compare these trials.

Highly purified collagen products produce 12-week healing rates slightly higher than standard care therapies.<sup>8,9</sup> Growth factor therapy with a recombinant human platelet-derived growth factor (becaplermin [Regranex Gel]; Johnson & Johnson Wound Management, Somerville, NJ), is widely used. This

Diabetic foot ulcers and their related morbidity and mortality represent major health challenges. In any given year, between 3% and 8% of the more than 18 million Americans who have diabetes will experience a foot ulcer associated with their disease.<sup>1</sup> Many will require prolonged hospitaliza-

Jeffrey A. Niezgoda, MD, FACHM, FAPWCA, FACEP, is Medical Director, Center for Comprehensive Wound Care and Hyperbaric Oxygen Therapy, St. Luke's Medical Center, Milwaukee, WI; Carl C. Van Gils, DPM, MS, CWS, is Medical Director, Dixie Regional Medical Center Wound Clinic, St. George, UT, and a member of the Foot & Ankle Institute, St. George, UT; Robert G. Frykberg, DPM, MPH, FAPWCA, is Associate Chair, Department of Surgery, and Chief, Podiatry Section, Carl T. Hayden VA Medical Center, Phoenix AZ; and Jason P. Hodde, MS, is a Research Scientist, Cook Biotech Incorporated, West Lafayette, IN. Members of the OASIS Diabetic Study Group include Mark Block, DPM, Boca Raton, FL; Jeffrey Jensen, DPM, Denver, CO; Michael Miller, DO, Terre Haute, IN; Matthew Parmenter, DPM, Bloomington, IN; Gary Sibbald, MD, Mississauga, Ontario, Canada; John Steinberg, DPM, San Antonio, TX; MED Institute, West Lafayette, IN; and StatKing Consulting Incorporated, Fairfield OH. The authors have disclosed that the study sponsor, Cook Biotech Incorporated, provided the study supplies, including the treatment products, dressing supplies, and pressure-relief shoes. Submitted November 22, 2004; accepted in revised form April 14, 2005.

product has been reported to improve 12-week healing rates to 34%.<sup>10,11</sup> A newer wound dressing consisting of collagen and oxidized regenerated cellulose (Promogran; Johnson & Johnson Wound Management) has a reported 12-week healing rate of 37%.<sup>12</sup> Tissue-engineered options, such as Dermagraft (Smith & Nephew, Largo, FL), have efficacy similar to these other options when used to stimulate healing of neuropathic diabetic foot ulcers.<sup>13</sup> Overall, these healing rates for full-thickness diabetic foot ulcers leave room for exploration of alternative treatment methods.

One such alternative is an acellular biomaterial derived from pig small intestine submucosa (SIS; OASIS Wound Matrix; HEALTHPOINT, Ltd, Fort Worth, TX), which is described in this manuscript. It has been extensively evaluated in preclinical models and in clinical use since its properties were first reported in 1989.<sup>14</sup> This material, a thin, translucent layer of the intestine, is approximately 0.15 mm thick and consists primarily of a collagen-based extracellular matrix (ECM). Unlike previously developed purified collagen wound care products, other components of the ECM are retained in intact, active forms.<sup>15,16</sup> These include glycosaminoglycans (ie, hyaluronic acid),<sup>17</sup> proteoglycans, fibronectin,<sup>18</sup> and other matrix-associated factors, such as basic fibroblast growth factor<sup>15</sup> and transforming growth factor- $\beta$ .<sup>15</sup>

A clinical trial was designed to test the hypothesis that treatment of full-thickness diabetic ulcers with OASIS Wound Matrix would result in 12-week healing rates similar to those seen when Regranex Gel is applied on a daily basis. Regranex Gel was chosen as the control because at the time the study was initiated, it was one of the few wound care products on the market that had an indication for increasing the incidence of complete healing of diabetic ulcers. Furthermore, it was the only growth factor product approved by the Food and Drug Administration for the treatment of diabetic foot ulcers.

## METHODS

A total of 98 patients with chronic, full-thickness diabetic ulcers were enrolled in the prospective, randomized, multicenter clinical trial. Enrollment was limited to 40 patients per site. Eligible patients were randomly assigned to receive either OASIS Wound Matrix ( $n = 50$ ) in combination with standard care or Regranex Gel ( $n = 48$ ) in combination with standard care. Patients were followed for up to 12 weeks, and were given the option of cross-over treatment if healing did not occur. Recurrence at 6 months was also evaluated. Ulcer size was measured at baseline and weekly until healing occurred, defined as full epithelialization of the wound with the absence of drainage. Data were analyzed for frequency of 100% wound closure and time to 100% wound closure. All patients were treated on an outpatient basis.

The “per protocol” patient population, defined as all patients who completed the trial through the 12-week study period, was used for the data analyses. The intent-to-treat population was used to assess safety through the reporting of complications and adverse events.

## Study population

The clinical trial was conducted at 9 outpatient institutions across the United States and Canada in consideration of International Conference on Harmonisation E6 GCP (Good Clinical Practice) guidelines. The study protocol and informed consent forms were reviewed and approved by either an independent institutional review board (IRB) or each study location’s own IRB. Informed consent was obtained from each patient before enrollment.

Eligible patients were age 18 or older, met all entry criteria (Table 1), and had been diagnosed with a nonhealing diabetic ulcer present for longer than 30 days. Exclusion criteria are summarized in Table 2. Assessment of inclusion and exclusion criteria was based on available data at the time of enrollment. Monitoring of the study was performed by MED Institute, West Lafayette, IN, an independent contract research organization (CRO).

Patients were assigned to a treatment group using a centralized computer system that randomly assigned patients to 1 of the 2 treatment arms. The system was designed to balance the treatment arms by assigning patients from each study site in a block randomization scheme, with a block size equal to 4. Individual investigators were blinded to the size of the block, eliminating the possibility that a prospective patient’s assignment could be determined before randomization.

## Treatment protocol and follow-up

Patients were evaluated in the clinic at weekly intervals. Study supplies, including the primary treatment products (OASIS Wound Matrix or Regranex Gel), gauze, normal saline, nonadherent dressings, paper tape, and pressure relief shoes, were

**Table 1.**

### SUMMARY OF INCLUSION CRITERIA

Characteristic	Inclusion Requirement
Patient age	$\geq 18$
Diagnosis	Type 1 or type 2 diabetes
Ulcer size	1 to 49 cm <sup>2</sup>
Ulcer depth	Extends through both the epidermis and dermis
Ulcer classification	Grade I, Stage A (University of Texas classification) <sup>28</sup>
Ulcer duration	>1 month and nonhealing
Wound bed characteristics	Viable wound bed with granulation tissue

**Table 2.****SUMMARY OF EXCLUSION CRITERIA**

- Exposed bone, tendon, or fascia
- Clinically defined and documented severe arterial disease
- History of radiation therapy to the ulcer site
- Ulcer of nondiabetic pathophysiology
- Receiving corticosteroids or immune suppressives
- History of collagen vascular disease
- Malnutrition (albumin <2.5 g/dL)
- Known allergy to porcine-derived products
- Known hypersensitivity to any component of Regranex Gel (eg, parabens)
- Religious or cultural objection to the use of porcine products
- Uncontrolled diabetes (A1C >12%)
- Previous organ transplant
- Ulcer clinically infected
- Signs of cellulitis, osteomyelitis, necrotic or avascular ulcer bed
- Undergoing hemodialysis
- Insufficient blood supply to the ulcer (TcPO<sub>2</sub> <30 mm Hg or toe-brachial index <0.70)
- Active Charcot or sickle cell disease
- Received treatment with any other investigational drug or device within the last 30 days
- Unable to comply with the procedures described in the protocol
- Enrolled in a clinical evaluation for another investigational wound care device or drug

provided by the study sponsor (Cook Biotech Incorporated, West Lafayette, IN). Supply usage was recorded for later cost analysis.

At each visit, wounds were cleansed and debrided based on the investigator's clinical assessment before treatment. If the patient was randomized to receive OASIS, the product was cut slightly larger than the ulcer, placed on the wound bed, and moistened with sterile normal saline. A secondary dressing was then applied to protect the healing environment and to maintain direct contact of OASIS with the wound bed. The clinician determined at each weekly visit whether OASIS should be reapplied. The amount of OASIS applied was based on the amount of matrix observed on the surface of the wound and the extent of epithelialization at each change of the secondary dressing. The amount was recorded on the case report forms.

For patients randomized to receive Regranex Gel, wounds were similarly cleansed and debrided based on the investigator's clinical assessment on a weekly basis. The gel was applied daily by the patient according to the product's package insert. Specifically, patients were instructed to apply the appropriate amount of Regranex Gel to the full area of the wound bed, cover the site with a saline-moistened gauze dressing, and leave the dressing in place for 12 hours. They were instructed to remove the dressing after 12 hours, rinse the ulcer with saline to remove the residual gel, and then recover the wound site with a new piece of gauze.

Pressure-relief shoes (DH Pressure Relief Shoe; Royce Medical Co, Camarillo, CA) were provided to each study site.

However the off-loading technique used at the site was left to the judgment of the individual clinician based on what was thought to provide optimal off-loading and adherence to therapy. Familiarity with the technique was believed to be more important than the use of the same technique across all sites. Patients within both treatment groups at an individual site were instructed similarly. Strict ambulation restrictions were advised, consistent with the standard of care for patients with diabetic foot ulcers. However, the level of adherence to these recommendations was not strictly controlled or documented.

Patients whose wounds were not healing by the 12th week were given the option to cross over to the other treatment arm; in other words, OASIS-treated patients could receive Regranex Gel and vice versa. If the surface area of the wound reduced by 50% or more after 4 weeks of cross-over treatment, participation in the cross-over arm was continued until healing, up to a maximum of 8 more weeks.

No standardized regimen was recommended after the study treatment period. However, efforts were made to see all patients at a final 6-month follow-up visit to determine the durability of ulcer closure.

**Study evaluations**

Demographic and baseline data collected and statistically analyzed included patient gender, race, age, baseline weight, baseline glycosylated hemoglobin (A1C), baseline albumin, baseline transcutaneous oxygen pressure (TcPO<sub>2</sub>), and toe-brachial index. Baseline ulcer information included ulcer location, duration, status, and surface area. Baseline medical history information included patient's status regarding diabetes type, hypertension, endocrine disease, immunosuppression, Alzheimer's disease, connective tissue disease, musculoskeletal disease, peripheral vascular disease, and dementia. In addition, baseline levels of granulation and avascular tissue, baseline debridement status, and the amount of drainage were recorded. These baseline characteristics were used as covariates in the final statistical analysis to judge their influence on treatment success.

Following initiation of treatment, patients were evaluated weekly for up to 12 weeks for healing and complications. At baseline and at each follow-up visit, ulcer healing was evaluated and recorded by photo planimetry or by measuring the length and width of the ulcer (length was the longest edge-to-edge measurement of the ulcer and width was taken from the longest ulcer dimension perpendicular to the length).

The primary outcome measure of the trial was prospectively specified as the incidence of complete wound healing by 12 weeks. The time to healing was computed as the day during the weekly visit at which the surface area of the wound was noted as zero and completely healed.

### Statistical analysis

Study data were collected and entered into a study database by the CRO using quality control procedures. A 100% quality assurance check of the database data sets versus the case report forms was performed. The database was transferred to a statistical services company (StatKing Consulting Ltd, Fairfield, OH) for analysis. All statistical analyses were performed using SAS software, version 8.2 for Windows (SAS Inc, Cary, NC).

Frequency of wound healing at 12 weeks in the OASIS Wound Matrix and Regranex Gel treatment groups was analyzed using Fisher's exact test at the 1-sided  $\alpha = .05$  level of significance. A test of noninferiority of the OASIS product to the Regranex Gel product was conducted using a 5% noninferiority bound. Because ulcers located on the planter surface of the foot are often more difficult to heal, a subgroup analysis was performed on the patients with plantar ulcers. This subgroup analysis was evaluated using Fisher's exact test at the 2-sided  $\alpha = .05$  level of significance.

Healing data were reexamined using baseline demographics and wound characteristics as covariates, and their effects were assessed. All tests (eg, demographics, correlations) were conducted at the 2-sided  $\alpha = .05$  level of significance.

The difference in success proportions adjusting for each of a set of potential covariates was tested using the Cochran-Mantel-Haenszel (CMH) Test and the Breslow-Day test of the homogeneity of odds ratios across strata. Time to healing was examined using a Cox proportional hazards regression model.

Continuous demographic and baseline variable treatment group means were compared using an analysis of variance (ANOVA) with a linear model containing treatment effects. Response profiles of categorical demographic and baseline variables were compared using a chi-square test. Subgroup analysis was performed when differences in demographic and baseline variables between treatment groups were identified. This was done to further examine the effect of these differences on incidence of healing. The subgroups were analyzed using Fisher's exact test at the 2-sided  $\alpha = .05$  level of significance.

Correlations among response-continuous variables were calculated using Pearson correlation coefficients, except in the case of the correlation between a continuous response and a binary response, in which point biserial correlation coefficients were computed. Tests for significant correlations were computed using *t* tests.

Differences between the proportion of patients with specified types of adverse events in each treatment group were compared using a chi-square test.

## RESULTS

### Patients

Blind, prospective randomization of study participants was used to eliminate bias in the assignment of treatment groups. Of the

98 patients enrolled in the trial, 73 patients (OASIS group,  $n = 37$ ; Regranex Gel group,  $n = 36$ ) completed their assigned treatment. The primary adherence issue leading to exclusion from the per protocol patient population was missing 2 or more consecutive weekly office visits or 3 or more total visits (11 patients). Other protocol adherence issues that led to patients not completing treatment during the study period included the wound worsening (6 patients), a desire to change wound treatment (1 patient), withdrawal of consent by the patient or family (2 patients), hospitalization and/or deteriorating health (2 patients), death (1 patient), and use of another wound therapy not specified in the protocol (2 patients). There were no significant differences between the 2 treatment groups. Table 3 lists the types of protocol nonadherence for each group.

Patient demographics and baseline values were similar for both groups on all values measured, with the exception of the diabetes diagnosis; significantly more patients in the OASIS group (49%) had type 1 diabetes than in the Regranex Gel group (22%) ( $P = .018$ ). The average baseline ulcer area for the OASIS group was 5 cm<sup>2</sup>, compared with 3.2 cm<sup>2</sup> for the Regranex Gel group ( $P = .234$ ). The median baseline ulcer areas for both groups were the same at 2.1 cm<sup>2</sup>. Selected baseline and demographic data are presented in Table 4.

### Incidence of healing

At the end of the 12-week treatment period, 49% (18/37) of patients receiving OASIS Wound Matrix were considered healed versus 28% (10/36) of patients receiving daily treatment with Regranex Gel ( $P = .055$ ) (Table 5). A test of noninferiority was conducted on the healing proportions using a margin of 0.05 (no more difference than 5% less). The results of this test indicated noninferiority of the healing proportion for the OASIS group when compared with the Regranex Gel group ( $P = .01$ ).

**Table 3.**

### PATIENTS NOT COMPLETING 12-WEEK FOLLOW-UP

Reason	OASIS	Regranex
Missed visits (2 consecutive and/or >3 total)	11	9
Reasons for missed visits:		
Nonadherence to follow-up visits	4	7
Hospitalization unrelated to study or target wound	3	0
Target wound infection	3	2
Tendon/bone exposure	1	0
Withdrew consent	0	2
Received other wound care therapy	1	1
Death	1	0
Total	13	12

**Table 4.****SELECTED BASELINE DEMOGRAPHICS**

	Treatment Group		P Value
	OASIS	Regranex	
Gender			.738
Male (%)	23 (62%)	21 (58%)	
Female (%)	14 (38%)	15 (42%)	
BMI ± SD	31.7 ± 7.6 (range: 18.9–51.2)	33.4 ± 7.4 (range: 21.6–48.7)	.347
Age, years, mean ± SE	58 ± 2.3 (range: 34–91)	57 ± 1.9 (range: 24–77)	.893
A1C, %, mean ± SE	7.9 ± 1.8 (range: 5.4–11.6)	8.8 ± 2.4 (range: 2.6–13.7)	.161
TcPO <sub>2</sub> , mm Hg, mean ± SE	63.2 ± 3.4 (range: 50–70)	62.7 ± 13.7 (range: 38–139)	.977
Albumin, g/dL, mean ± SE	3.9 ± 0.9 (range: 2.8–6.6)	3.8 ± 0.5 (range: 3.3–4.6)	.698
Toe-brachial index, mean ± SE	1.06 ± 0.07 (range: 0.78–1.6)	0.94 ± 0.07 (range: 0.71–1.2)	.287
Type 1 diabetes	18 (49%)	8 (22%)	.018
Type 2 diabetes	19 (51%)	28 (78%)	
Baseline ulcer location			.323
Plantar surface	27 (72%)	21 (58%)	
Other	10 (28%)	15 (42%)	
Baseline ulcer duration			.677
1-3 months	17 (46%)	19 (53%)	
4-6 months	8 (22%)	4 (11%)	
7-12 months	5 (13%)	6 (17%)	
>12 months	7 (19%)	7 (19%)	
Baseline ulcer size (cm <sup>2</sup> ), mean ± SE	5.0 ± 1.4 (range: 1.0–40.0)	3.2 ± 0.5 (range: 1.0–20.0)	.234

**Subgroup analysis**

Subgroup analyses were performed when differences were identified between groups on demographic and baseline variables. Because diabetes type was the only demographic or baseline variable in which the groups did not evenly match, patients were stratified according to their diabetes diagnosis; the incidence of healing was then reexamined. Of the patients with type 1 diabetes, 33% (6/18) of OASIS-treated patients healed versus

25% (2/8) of Regranex Gel-treated patients ( $P = 1$ ). Of the patients with type 2 diabetes, 63% (12/19) of patients treated with OASIS healed versus 29% (8/28) of patients treated with Regranex Gel ( $P = .034$ ) (Table 5).

The subset of patients having wounds on the plantar surface of the foot was also analyzed. Of the patients with plantar ulcers, 52% (14/27) of OASIS-treated patients healed versus 14% (3/21) of Regranex Gel-treated patients ( $P = .014$ ) (Table 5).

**Table 5.****INCIDENCE OF HEALING AT 12 WEEKS**

		Healed (%)		Not Healed (%)	
		OASIS	Regranex	OASIS	Regranex
All patients ( $P = .055$ )	OASIS	18 (49%)	19 (51%)	19 (51%)	19 (51%)
	Regranex	10 (28%)	26 (72%)	26 (72%)	26 (72%)
Plantar ulcers ( $P = .014$ )	OASIS	14 (52%)	13 (48%)	13 (48%)	13 (48%)
	Regranex	3 (14%)	18 (86%)	18 (86%)	18 (86%)
Type 1 diabetes ( $P = 1.000$ )	OASIS	6 (33%)	12 (67%)	12 (67%)	12 (67%)
	Regranex	2 (25%)	6 (75%)	6 (75%)	6 (75%)
Type 2 diabetes ( $P = .034$ )	OASIS	12 (63%)	7 (37%)	7 (37%)	7 (37%)
	Regranex	8 (29%)	20 (71%)	20 (71%)	20 (71%)

### Time to healing

No significant difference was found in the mean time to healing between treatment groups (67 days for the OASIS group and 73 days for the Regranex Gel group,  $P = .245$ ). A Cox proportional hazards regression model was run on the time-to-healing data. Although no significant difference between the survival curves for the 2 groups was indicated ( $P = .087$ ), the model predicted an improved trend of healing for the OASIS group. At 7, 9, and 12 weeks, the predicted healing proportions in the OASIS group were 25%, 35%, and 47%, respectively, compared with 13%, 20%, and 28%, respectively, for the Regranex Gel group. This model indicates that at 7 weeks, patients in the OASIS group were approximately twice as likely to heal as those in the Regranex group. Survival curves for each group are presented in Figure 1. At no point in the survival curve analysis did the Regranex Gel curve cross over the OASIS curve, indicating a greater likelihood of healing at all points along the curve of the OASIS arm.

### Covariate analysis

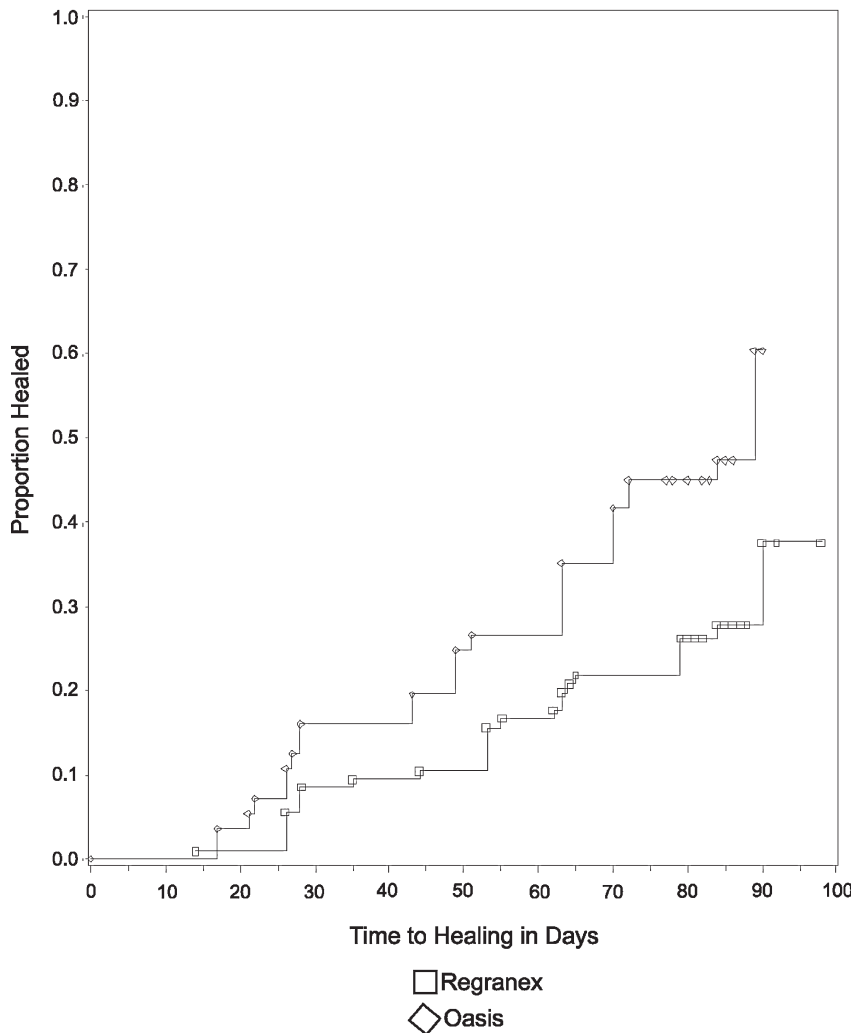
Wound healing was also assessed after adjusting for baseline measures treated as covariates. Results showed that the proportion of patients completely healed in the OASIS group was not significantly different from the proportion of patients healed in the Regranex Gel group after adjusting for the following covariates: baseline debridement ( $P = .089$ ), vascular disease status ( $P = .071$ ), ulcer duration ( $P = .098$ ), percentage of granulation tissue ( $P = .653$ ), hypertension ( $P = .127$ ), endocrine disease status ( $P = .074$ ), musculoskeletal disease status ( $P = .074$ ), percentage of avascular tissue ( $P = .892$ ), gender ( $P = .068$ ), baseline albumin level ( $P = .706$ ), baseline surface area  $<2 \text{ cm}^2$  ( $P = .076$ ), race ( $P = .109$ ), drainage ( $P = .715$ ), age ( $P = .072$ ), toe-brachial index ( $P = .719$ ), and wound duration ( $P = .075$ ).

Covariate analyses of interest revealed significant differences in healing proportions between treatment group after adjusting for type 1 and type 2 diabetes ( $P = .030$ ) and ulcer location ( $P = .026$ ). The covariate analyses indicated that patients with type 2 diabetes were less likely to heal in the Regranex Gel arm than in the OASIS arm ( $P = .030$ ). After adjusting for diabetes type, the odds ratio was 3.06,

**Figure 1.**

#### SURVIVAL PLOT ANALYSIS

A Cox proportional hazards regression showed no significant difference ( $P = .0872$ ) between the survival curves for the 2 groups, but the model predicted an improved trend of healing for the OASIS group at all time points.



indicating that patients in the OASIS group were 3 times more likely to achieve healing than those in the Regranex Gel group.

The covariate analyses also indicated that patients having ulcers in the plantar area were more likely to heal in the OASIS arm ( $P = .026$ ), supporting the subgroup analysis in this regard. After adjusting for ulcer location, odds ratio calculations indicate that patients in the OASIS group were 3 times more likely to achieve healing than those in the Regranex Gel group (odds ratio = 3.02). Of the 73 "per protocol" patients, 48 (66%) had ulcers in the plantar area; healing occurred in 52% of patients in the OASIS and 14% of patients in the Regranex group.

### Crossover patients and 6-month follow-up

Of the 73 patients, 12 in the Regranex Gel group crossed over to receive OASIS; 1 patient healed. Nine patients in the OASIS arm crossed over to receive Regranex Gel; 2 healed. No statistical analyses were performed with these data due to the limited number of patients evaluated.

Approximately half (37) of the 73 patients were seen at a 6-month or later follow-up visit. Ulcers from 14 of these 37 patients had healed within the 12-week study period; 10 remained healed at the follow-up visit. Data are summarized in Table 6.

### Safety

The complications/adverse events reported in the trial (Table 7) were typical for a patient population with hard-to-heal diabetic foot ulcers and in line with previous reports.<sup>13,19</sup> A total of 27 study-relevant events were reported for all patients, 17 for the OASIS group and 10 for the Regranex Gel group. Between the 2 treatment groups, no significant differences were found in the proportion of patients experiencing complications/adverse events.

### DISCUSSION

The standard of care for diabetic ulcers requires extensive medical attention and resources from health care providers, yet most wounds treated with standard care fail to heal within 12 weeks.<sup>7</sup> Because of inadequate healing rates, the development of novel therapeutic approaches is necessary. Recent advances in the care of diabetic ulcers have included active growth factor therapy and application of tissue-engineered skin substitutes. Healing rates with these products are generally higher than with standard care alone, in the 34% to 37% range.<sup>10,11,13</sup> Opportunities exist for alternatives that would reduce morbidity, improve quality of life, and ease the economic burden associated with these chronic nonhealing wounds.

In a prospective, randomized, multicenter clinical trial, OASIS Wound Matrix applied on a weekly basis led to complete healing in 49% of ulcers treated, versus 28% of ulcers treated with a recombinant growth factor therapy for 12 hours daily. Although these results are not statistically significant,

**Table 7.**

### COMPLICATIONS/ADVERSE EVENTS

Complication/Adverse Event	OASIS (n = 17)	Regranex (n = 10)
Depression/mood disorder	1	0
Pain/discomfort	2	1
Limb injury	0	2
Skin injury	0	1
Gastrointestinal disorder	1	0
Septic arthritis	0	1
Respiratory tract infection	0	1
Wound infection in nonstudy ulcer	3	1
Wound infection in study ulcer	9	3
Death	1	0

they are clinically significant, in that OASIS appeared to have nearly twice the healing rate as Regranex Gel.

The ease of application and the uncomplicated treatment protocol associated with OASIS may have several advantages. Unlike Regranex Gel, OASIS can be stored at room temperature. There are no complicated calculations to perform to decide proper dose of OASIS, and there is no need for daily reapplication and dressing changes. This may result in better patient adherence to therapy and improved ease of use by the clinician.

Although overall healing rates between groups did not reach statistical significance, subgroup analysis revealed that OASIS may be superior to Regranex Gel in treating ulcers located on the plantar surface of the foot. In addition, plantar ulcers treated with OASIS were more likely to heal than ulcers located elsewhere. This finding was unexpected because plantar ulcers are generally more difficult to heal than ulcers in other locations. Although further study is warranted, the improved rate of healing of plantar ulcers following treatment with OASIS is encouraging.

The OASIS treatment group had a fairly even distribution of patients with type 1 and type 2 diabetes (49% and 51%, respectively), whereas 78% of patients in the Regranex Gel group had type 2 diabetes and 22% had type 1 diabetes. Therefore, a subgroup analysis was performed to determine if patients with type 2 diabetes were less likely to heal when treated with Regranex Gel. This analysis revealed that ulcers in patients with type 1 and type 2 diabetes were equally responsive to Regranex Gel (25% vs 29% healing, respectively). However, ulcers in patients with type 2 diabetes were more responsive to treatment with OASIS than ulcers in patients with type 1 diabetes (63% vs 33% healing, respectively). Because of the limited size of this data set, additional study is warranted to verify these findings.

The trial endpoint was incidence of complete healing at 12 weeks, with an assessment of recurrence made after an additional 6 months. Previous data on the use of Regranex Gel

**Table 6.**

### RESULTS AT 6-MONTH FOLLOW-UP (n = 37)

	OASIS	Regranex
Total patients seen at follow-up	19	18
Patients healed at 12 weeks	8	6
Patients remaining healed at 6 months	6	4
% Recurrence	25%	33%

show that healing rates approach 50% by week 20, but that during a 90-day follow-up period, 30% of healed patients will have ulcer recurrence.<sup>10</sup> In the present study, OASIS treatment led to complete healing in 49% of patients within 12 weeks, with 25% recurrence after 6 months. Treatment with Regranex Gel resulted in complete closure in 28% of patients, with 33% recurrence after 6 months. These results are consistent with the reported incidence of ulcer recurrence in the diabetic population.<sup>10,20,21</sup> However, the limited number of patients analyzed after 6 months necessitates further investigation into recurrence rates following treatment with OASIS as well.

Although no statistical differences were noted in the type or frequency of complications between groups, more cases of infection were reported in the OASIS-treated ulcers (9) than in the Regranex Gel-treated ulcers (3). In addition, 1 patient in the OASIS group died during the study. This death was due to complications of diabetes and was not related to the OASIS application or study participation.

Of the 12 patients with infection of the target wound, 5 did not complete the study (3 in the OASIS arm and 2 in the Regranex Gel arm). However, wound infection itself was not the reason the patients did not complete the trial. These patients were removed from the study due to missed visits related to scheduled surgery and/or acute hospitalization or due to deterioration manifested as bone or tendon exposure.

The other 6 patients with infections in the OASIS arm and the 1 patient with an infection in the Regranex Gel arm completed the 12-week study protocol. One of the patients in the OASIS arm healed within the 12-week study period.

The infection rates in the present study are consistent with prior reports,<sup>13,19</sup> but are still concerning given that in both groups some patients failed to complete the 12-week protocol because of interrupted treatment due to wound infection. Although prospective patients with clinical signs of infection were excluded from the trial, many chronic ulcers are persistently colonized subclinically. Subclinical colonization was not assessed as a condition of inclusion. It may be that the infections observed reflect the severity of colonization present at baseline and that the various wound cleansing methods used across centers did not adequately control the bacterial load. Furthermore, infections in the Regranex Gel arm may be related to self-care associated with daily reapplication of the product and dressing changes. It should be noted that the majority of patients were able to overcome their infection and complete the study protocol. This suggests that the infections noted were minor and were controlled with either the wound cleansing protocol, antibiotics, or the treatment itself.

The average amounts of OASIS Wound Matrix and Regranex Gel used during the study were tracked and their costs com-

pared. The average amount of OASIS used per patient was 10 sheets measuring  $3 \times 3.5$  cm<sup>2</sup>, with a total cost of approximately \$250. The average amount of Regranex Gel used per patient was slightly less than 2 15-gram tubes of gel, costing approximately \$1070. Considering the degree of efficacy achieved, cost is an important factor in deciding which wound care therapy to use.

The present study has limitations similar to those reported in other controlled, randomized investigations of wound management when a large number of sites are participating.<sup>12,13</sup> The off-loading technique was not strictly controlled across centers, the extent and frequency of debridement was not standardized, and the frequency of dressing changes between weekly visits was left to the clinical judgment of the individual clinicians. The differences in the OASIS and Regranex Gel treatment protocols precluded the ability to blind the study. The 50% adherence with follow-up visits at 6 months does not allow for adequate assessment of long-term effectiveness of either treatment. Although the study design may contribute to some of the differences in healing and complications, including the infection rates observed, this design was chosen to reflect differences in current clinical practice. It may, therefore, be more applicable to the general patient population than a clinical efficacy trial.

Clinician feedback revealed that OASIS wound matrix was easy to apply, was nontoxic, and did not induce adverse immunologic or sensitization reactions. These observations and clinical findings are consistent with the known properties of the biomaterial, support preclinical findings of efficacy and safety in animal models,<sup>22,23</sup> and support the initial observations of effectiveness in the human population.<sup>24,25</sup> Results indicate that OASIS can be used to manage full-thickness diabetic ulcers due to its protective properties and ability to act as a natural template for tissue regrowth.<sup>26</sup>

Wound care products such as SIS, which are derived from acellular ECM tissues and minimally processed to retain the 3-dimensional architecture and composition of the ECM, offer an ideal environment for healing wounds. The complex composition of collagens, proteoglycans, glycosaminoglycans, and other ECM-associated factors found in the OASIS Wound Matrix<sup>15-18</sup> appear to provide the needed native tissue architecture for the propagation of new and healthy tissue. It further serves as a stable structure for cell attachment, proliferation, and differentiation.<sup>27</sup> The data from the present clinical trial show that this biomaterial is as effective as Regranex in healing chronic diabetic ulcers and effectively led to complete wound closure in 49% of patients by 12 weeks.

## CONCLUSION

Despite the limitations inherent to a controlled, randomized, multicenter wound management trial—specifically, imperfect

standardization of off-loading, debridement, and dressing change regimens—the data from the present trial offer a valid and direct comparison of treatment modalities and more accurately reflect actual clinical practice than if these variables were strictly controlled. In this study, OASIS was as effective as Regranex Gel in treating full-thickness diabetic foot ulcers and appears to be a viable treatment option for these patients. ●

## REFERENCES

- Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 1999;22:382-7.
- Holzer SE, Camerota A, Martens L, Cuerdon T, Crystal-Peters J, Zagari M. Costs and duration of care for lower extremity ulcers in patients with diabetes. *Clin Ther* 1998;20:169-81.
- Glover JL, Weingarten MS, Buchbinder DS, Poucher RL, Deitrick GA, Fylling CP. A 4-year outcome-based retrospective study of wound healing and limb salvage in patients with chronic wounds. *Adv Wound Care* 1997;10:33-8.
- Apelqvist J, Ragnarson-Tennvall G, Persson U, Larsson J. Diabetic foot ulcers in a multidisciplinary setting: an economic analysis of primary healing and healing with amputation. *J Intern Med* 1994;235:463-71.
- Ragnarson-Tennvall G, Apelqvist J. Cost-effective management of diabetic foot ulcers: a review. *Pharmacoeconomics* 1997;12:42-53.
- Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower-extremity ulcers among patients with diabetes. *Diabetes Care* 2004;27:2129-34.
- Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. *Diabetes Care* 1999;22:692-5.
- Leipzig LS, Glushko V, DiBernardo B, et al. Dermal wound repair: role of collagen matrix implants and synthetic polymer dressings. *J Am Acad Dermatol* 1985;12:409-19.
- Gao ZR, Hao ZQ, Li Y, Im MJ, Spence RJ. Porcine dermal collagen as a wound dressing for skin donor sites and deep partial skin thickness burns. *Burns* 1992;18:492-6.
- OrthoMcNeill Prescribing information for REGRANEX, becaplermin gel.
- Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998;21:822-7.
- Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Arch Surg* 2002;137:822-7.
- Marston WA, Hanft J, Norwood P, Pollak R; Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003;26:1701-5.
- Badylak SF, Lantz GC, Coffey AC, Geddes LA. Small intestinal submucosa as a large diameter vascular graft in the dog. *J Surg Res* 1989;47:74-80.
- Hodde JP, Hiles MC. Bioactive FGF-2 in sterilized extracellular matrix. *Wounds* 2001;13:195-201.
- McDevitt CA, Wildey GM, Cutrone RM. Transforming growth factor  $\beta$ 1 in a sterilized tissue derived from the pig small intestine submucosa. *J Biomed Mater Res* 2003;67A:637-40.
- Hodde JP, Badylak SF, Brightman AO, Voytik-Harbin SL. Glycosaminoglycan content of small intestinal submucosa: a bioscaffold for tissue replacement. *Tissue Eng* 1996;2:209-17.
- McPherson TB, Badylak SF. Characterization of fibronectin derived from porcine small intestinal submucosa. *Tissue Eng* 1998;4:75-83.
- Smiell JM. Clinical safety of becaplermin (rhPDGF-BB) gel. *Am J Surg* 1998;176:68S-73S.
- Smiell JM, Wieman TJ, Steed DL, Perry BH, Sampson AR, Schwab BH. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair Regen* 1999;7:335-46.
- Embil JM, Papp K, Sibbald G, et al. Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. *Wound Repair Regen* 2000;8:162-8.
- Prevel CD, Eppley BL, Summerlin DJ, et al. Small intestinal submucosa: utilization as a wound dressing in full-thickness rodent wounds. *Ann Plast Surg* 1995;35:381-8.
- Allman AJ, McPherson TB, Badylak SF, et al. Xenogeneic extracellular matrix grafts elicit a Th2-restricted immune response. *Transplantation* 2001;71:1631-40.
- Brown-Etris M, Cutshall WD, Hiles MC. A new biomaterial derived from small intestine submucosa and developed into a wound matrix device. *Wounds* 2002;14:150-66.
- Demling RH, Niezgodka JA, Haraway GD, Mostow EN. Small intestinal submucosa wound matrix and full-thickness venous ulcers: preliminary results. *Wounds* 2004;16:18-22.
- Badylak S. The extracellular matrix as a scaffold for tissue reconstruction. *Semin Cell Dev Biol* 2002;13:377-83.
- Lindberg K, Badylak SF. Porcine small intestinal submucosa (SIS): a bioscaffold supporting in vitro primary human epidermal cell differentiation and synthesis of basement membrane proteins. *Burns* 2001;27:254-66.
- Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. *J Foot Ankle Surg* 1996;35:528-31.