2. STUDY SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Shire Regenerative Medicine, Inc.</td><td rowspan="2">Individual Study Table Referring to Part of the Dossier
Volume: <Insert volume number>

Page: <Insert page number></td><td rowspan="2">(for National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Dermagraft (Human fibroblast-derived dermal substitute)</td></tr>
<tr><td colspan="3">Protocol Number:
ABH-DERMAGRAFT-001-09</td></tr>
<tr><td colspan="3">Title of Study:
A Prospective, Multi-center, Longitudinal, Cohort Study of Dermagraft® in Subjects with Venous Leg Ulcers: A Long term Follow-up to the DEVO-Trial</td></tr>
<tr><td colspan="3">Investigators:
Multi-center, global study (Estonia, Germany, Poland, South Africa, United Kingdom, United States, and Sweden)</td></tr>
<tr><td colspan="3">Study Centers:
Multi-center study: 27 sites enrolled at least one subject: US (11 sites), South Africa (6 sites), Poland (6 sites), Germany (2 sites), Estonia (1 site), and United Kingdom (1 site).</td></tr>
<tr><td colspan="3">Publications (references):
None at the time of this report</td></tr>
<tr><td colspan="2">Study period:
Date of First Subject Enrollment: 25 May 2010
Date of Last Subject Last Visit Completed: 20 June 2012</td><td>Phase of development:
III</td></tr>
<tr><td colspan="3">Objectives:
To observe the long-term outcomes of Dermagraft, together with four-layer compression bandaging therapy, in the treatment of venous leg ulcers, compared with conventional treatment of four-layer compression bandaging therapy alone.</td></tr>
<tr><td colspan="3">Methodology:
This study was a prospective, multi-center, longitudinal, cohort study to evaluate the long term (1-year) outcomes of Dermagraft, compared with conventional therapy (four-layer compression bandaging therapy alone), in subjects who had completed ABH-DERMAGRAFT-001-08 (the “DEVO” clinical trial): a prospective, multi-center, randomized, controlled clinical investigation of Dermagraft in subjects with venous leg ulcers.

Subjects were not randomized to any treatment group in this study. Subjects were enrolled at the Study Enrollment and Initiation Visit to one of two cohorts corresponding to the treatment group they were assigned to in the DEVO clinical trial. Cross-over to Dermagraft treatment for subjects in the Control cohort from the DEVO clinical trial was available upon investigator request upon certain conditions (see Treatment Options Algorithm Flow Chart below for details). Subjects who were already assigned to the Dermagraft cohort in the DEVO clinical trial were not eligible for additional Dermagraft treatment in this 1-year observational study.

If a subject in the Control cohort from the DEVO clinical trial entered this study with an unhealed study ulcer or if he/she entered the study with a healed study ulcer that recurred during the 1-year observational period, that subject was eligible for investigational product treatment consisting of one Dermagraft application applied topically to the study ulcer, weekly, for a maximum of 8 weeks (8 applications maximum). The option to treat an eligible subject with Dermagraft was left to the investigator’s discretion, and subjects who were eligible at study enrollment (i.e. not healed at first visit) but who were not given this treatment option were to be</td></tr>
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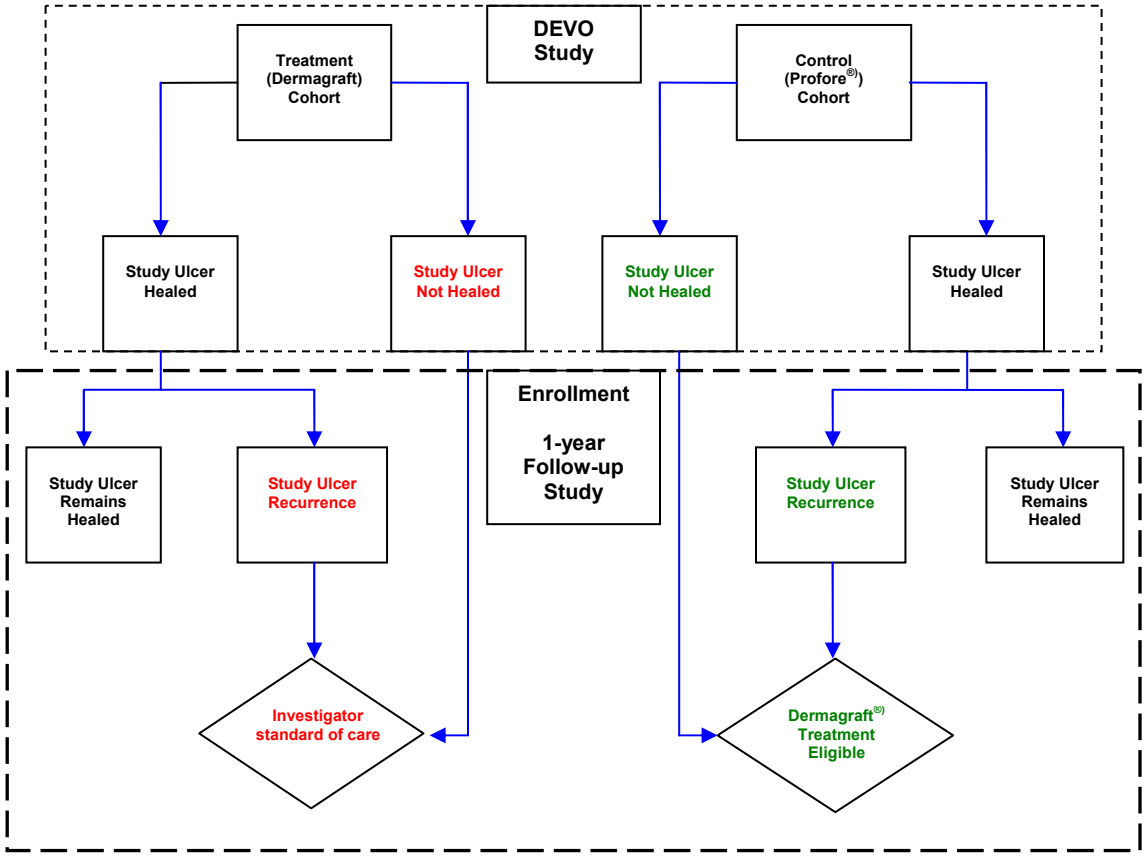
continued to be followed over the 1-year study duration. These subjects' study ulcers were then treated according to the investigator's standard of care.

Treatment Options Algorithm Flow Chart



The last month of eligibility for the Dermagraft treatment option was Month 7 (Week 42) of the 1-year observational period, to allow for sufficient observational time post-treatment. If a subject experienced a study ulcer recurrence after Month 7, he or she was no longer eligible to receive Dermagraft treatment in this study.

Subjects whose study ulcers were assigned to receive Dermagraft were followed at 8 weekly clinic visits within the 1-year observational study.

Subjects were eligible for this study if they had completed study procedures for ABH-DERMAGRAFT-001-08 Visit #23 (Week 28). Subjects in the Control cohort from the ABH-DERMAGRAFT-001-08 study with unhealed study ulcers may have been enrolled into this study as early as Visit #21 (Week #20), to allow for cross-over treatment with Dermagraft. All subjects were to sign and date an informed consent form and eligibility criteria were to be assessed before screening procedures were undertaken.

At the Study Enrollment and Initiation visit (Month 0, Week #28 or as early as Week #20 in ABH-DERMAGRAFT-001-08), subjects who had completed study procedures for ABH-DERMAGRAFT-001-08, signed and dated the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form for this study, were enrolled according to this study's Inclusion and Exclusion criteria, and their ulcer history, ulcer and leg characteristics were recorded; together with any current study ulcer and/or study leg treatments (e.g. dressings, compression bandaging, topical applications, or debridement) and concomitant medications. Observational evaluations included weekly clinic visits for Dermagraft applications (8 weeks maximum) at which time study ulcer status (healed or not healed) and study ulcer size (cm^2) were recorded. Dermagraft applications were prepared according to the Sponsor-provided directions for use (with translations provided at the country level), and study ulcer and/or study leg treatments (e.g. dressings, compression bandaging, or topical applications), concomitant medications, and any adverse events occurring

since the last correspondence were recorded on case report forms.

Follow-up Correspondence was conducted at 1, 3, 5, 7, 9, and 11 months post-enrollment, and Clinical Evaluation visits were conducted at 2, 4, 6, 8, 10, and 12 months post-enrollment. The Follow-up Correspondence procedures were based on the Observational Study Questionnaire, which was comprised of a series of questions to be read to the subject and spaces to record responses. Subjects were contacted by telephone by site personnel to gather information on their study ulcer and/or study leg characteristics and current treatments, additional clinic visits or medical services/procedures related to their study ulcer and/or study leg care, concomitant medications, and adverse events. At the Clinical Evaluation Visits (at 2, 4, 6, 8, 10, and 12 months), the study ulcer and/or study leg characteristics and current treatments, any additional clinic visits or medical services/procedures related to the study ulcer and/or study leg care, concomitant medications, and any adverse events were recorded on a case report form (CRF).

Since this was a longitudinal, cohort study and not a randomized, controlled study, no inference was made with respect to a primary outcome variable between the two cohorts. However, the primary objective of the study was to conduct an exploratory analysis on the primary outcome variable, with the primary outcome variable defined as the binary outcome "ulcer recurrence" or "no ulcer recurrence" by the end of the 1-year observational period. A secondary exploratory objective was the incidence of complete study ulcer healing by the end of the 1-year observational period for all study ulcers not healed at the time of study enrollment. Additional secondary measures were the incidence of study ulcer infection-related events, time to study ulcer recurrence, change in study ulcer size, and time to healing for the study ulcer.

Number of subjects (planned and analyzed):

Estimating that approximately 40% of the active subjects from investigational centers in the ABH-DERMAGRAFT-001-08 clinical study would be enrolled in this 1-year observational study, approximately 90 subjects per cohort were planned to enter this study, for an estimated total of 180 subjects. This number was an under-estimation as two hundred seventeen (217) subjects were enrolled and analyzed in this study.

Diagnosis and main criteria for inclusion:

Eligible subjects were subjects who had completed ABH-DERMAGRAFT-001-08, up to and including the final visit, Visit #23 (Week 28), with the following exception: if a subject was part of the Control cohort, and the study ulcer under observations in ABH-DERMAGRAFT-001-08 was not healed at Week 16 (Visit #19) visit, the subject was eligible for enrollment in the ABH-DERMAGRAFT-001-09 study as early as Week 20 (Visit #21). Eligible subjects signed and dated a separate study-specific IRB/IEC-approved informed consent to participate in the 1-year observational study, including the ability to correspond with the site for follow-up information and a willingness to attend scheduled clinic visits and unscheduled clinic visit(s) in the event of a study ulcer recurrence or other Adverse Events. All subjects had read, signed and dated the IRB/IEC- approved informed consent before screening procedures were performed.

Subjects had to fulfill the following inclusion criteria to be eligible for enrollment into this study:

1. Subject had completed the clinical trial ABH-DERMAGRAFT-001-08, up to and including the final visit, Visit #23 (Week 28), with the following exception: if subject was part of the Control cohort, and the study ulcer under observation in ABH-DERMAGRAFT-001-08 was not healed at the Week 16 (Visit # 19) visit, the subject was eligible for inclusion into this long-term study as early as Week 20 (Visit #21).
2. Subject understood study requirements and was available to participate in the 1 year long observational follow-up. This included an ability to correspond with the site for follow-up information and a willingness to attend scheduled clinic visits and unscheduled clinic visits in the event of an ulcer recurrence or other Adverse Events.
3. Subject had read, signed, and dated the IRB/IEC approved Informed Consent Form before screening procedures were undertaken. The informed consent form was adapted and used in each country and included all the required elements. Each informed consent form was translated into all local languages for countries and subjects participating in the study.

Subjects who met any one of the following exclusion criteria were not eligible for enrollment into the study:

1. Subjects who withdrew or were terminated from the clinical trial ABH-DERMAGRAFT-001-08 before Visit #23 (Week 28). Additionally, any subjects who were not available for the 1 year-long observational period in this study were excluded.

2. Subjects who were unable to understand the aims and objectives of the trial.
3. Subject who had any condition(s) which seriously compromised the subject's ability to complete this study, or had a known history of poor compliance with medical treatment.

Test product, dose and mode of administration, batch number:

Dermagraft is a human dermal replacement therapy consisting of human dermal fibroblasts cultured in vitro onto a bioresorbable mesh to provide a living, metabolically active dermal tissue. Dermagraft was supplied as a 2 inch x 3 inch (5 cm x 7.5 cm) graft, enclosed in sealed ethylene vinyl acetate (EVA) bag for transport, and shipped on dry ice. Dermagraft was applied topically by the Investigator to the study ulcer, plus standard-of-care regimen plus four-layer compression bandaging therapy following systematic debridement. Dermagraft batch numbers are listed in Appendix 16.1.6.

Duration of treatment:

Weekly applications of Dermagraft for a maximum of 8 weeks (8 applications maximum).

Reference therapy, dose and mode of administration, batch number:

The Investigator's standard-of-care therapy plus four-layer compression bandaging therapy (Profore), cohort for observation only.

Statistical Methods:

Analysis Populations:

Intention-to-Treat Population: The Intent-to-Treat population (ITT) was defined as all subjects enrolled in the study at baseline (Study Enrollment Visit – Month 0). Subjects were analyzed according to cohort assignment derived from the original treatment assignment in the ABH-DERMAGRAFT-001-08 clinical trial.

Intention-to-Treat Recurrence Population: The ITT Recurrence (ITTrec) population was defined as those subjects in the ITT population whose study ulcer were healed in the ABH-DERMAGRAFT-001-08 study when enrolled in this study. This population was used for study ulcer recurrence analysis.

Per-Protocol Population: The Per Protocol (PP) population included those ITT subjects who completed up to Clinical Evaluation Visit #5 (Month 10).

Per-Protocol Recurrence Population: The PP Recurrence (PPrec) population was defined as those subjects in the PP population whose study ulcers were healed when enrolled in the study. This population was used for the study ulcer recurrence analysis.

Primary Efficacy Endpoint and Analysis:

Unless otherwise specified, all efficacy analyses were based on the ITT population. All statistical tests were 2-sided and performed at the 5% level of significance. All confidence intervals were 2-sided 95% confidence intervals (CIs). All efficacy information was listed.

The primary efficacy endpoint was study ulcer recurrence within the 1-year observational period for all study ulcers healed at the time of study enrollment (Month 0). Subjects' study ulcer recurrence status (recurrence or no recurrence) was based on the last available data either at Study Exit visit (at 12 months or 1 year post-enrollment) or the Early Termination visit.

A Fisher's exact test was conducted to test the difference in study ulcer recurrence rates between Dermagraft and Control. Two-sided Exact 95% CIs for the difference in recurrence rates were also presented. The primary analysis was conducted in ITTrec and PPrec populations.

Key Secondary Efficacy Endpoints and Analysis:

Unless specified otherwise, the secondary efficacy endpoints described below were analyzed for both ITT and PP populations. No formal statistical hypothesis testing was performed between Dermagraft and Control

Incidence of complete study ulcer healing: The number and percent of subjects with incidence of complete study ulcer healing over the 1-year observational period for all study ulcers not healed at the time of study enrollment (Month 0), where complete ulcer healing defined as 100% epithelialization, with no evidence of drainage or scab was presented. The incidence of complete study healing was defined as the number of study ulcer status recorded as healed on a CRF.

For the Control cohort, subjects were categorized into two groups: (1) Subjects whose study ulcers were not

treated with Dermagraft; and (2) Subjects whose study ulcers were treated with Dermagraft during the 1-year observational period.

Incidence of study ulcer infection-related events: The number and percent of subjects with incidence of study ulcer infection-related events reported in the AE CRF during the 1-year observational period were summarized by study ulcer status at Month 0 and treatment. Subjects in the Control group whose study study ulcers received Dermagraft applications were summarized in a separate table.

Time to study ulcer recurrence: Time to study ulcer recurrence was defined as time (in days) from the date of last ulcer healed prior to or at study enrollment to the date the study ulcer was first recorded as recurred during the 1-year observational period. The plot of survival curve and quartile estimates (25th, 50th (median), and 75th) of survival function with corresponding 95% CIs were presented and determined by the Kaplan-Meier product-limit method. If the quartile estimates could not be estimated, the 10th and 20th percentile estimates with corresponding 95% CIs were presented. The populations for this analysis were the ITTrec and PPrec.

Change in study ulcer size: Change in study ulcer size from the date of Dermagraft application during the 1-year observational period to weekly study ulcer size measurement were summarized using descriptive statistics for subjects in control group who received Dermagraft applications during the 1-year observational period.

Time to study ulcer healing: Time to study ulcer healing (in days) is defined as the time from the date of Dermagraft application during the 1-year observational period to the date the study ulcer status was recorded as "healed" for subjects in the Control group who received Dermagraft applications during the 1-year observational period. The plot of survival curve and quartile estimates (25th, 50th (median), and 75th) of survival function with corresponding 95% CIs were presented and determined by the Kaplan-Meier product-limit method. If the quartile estimates could not be estimated, the 10th and 20th percentile estimates with corresponding 95% CIs were presented.

Exploratory Efficacy Variable(s) and Analyses

The proportion of subjects reporting study leg ulcer pain, study leg swelling and/or any new ulcers was summarized by cohort and study ulcer status at Month 0 for all visits.

Safety Analysis:

The safety analysis was performed using the ITT Analysis Set. Safety variables included adverse events (AEs), clinical laboratory variable and vital signs.

SUMMARY – RESULTS AND CONCLUSIONS:

Subject Disposition, Demographics, and Baseline Characteristics:
The majority of subjects in the Dermagraft and Control groups (ITT population) completed the study (79.4% vs 80.0%) and 20.6% vs 20.0% withdrew from the study prematurely due to an adverse event (1 subject in the Dermagraft group died due to unknown causes, not related to study ulcer; no Control subject withdrew from the study due to an AE), lost to follow-up, the Investigator's evaluation, request by the subject, and Other reasons.

The median age for the subjects in the Dermagraft and Control groups was 64.0 years for each group (range: Dermagraft 28 to 90 years and Control 24 to 97 years); 37.3% vs 48.2% of subjects were male and 62.6% vs 51.8% were female; and the majority were White (65.4% in both groups), with fewer Black and African Americans (15.9% vs 18.2%), Hispanic (8.4% vs 5.5%), Asian subjects (6.5% vs 9.1%), and subjects of Other races (2.8% vs 1.8%). The Dermagraft vs Control groups were also similar for mean height (167.23 vs 168.44 cm), weight (86.25 vs 87.23 kg), and BMI (30.76 vs 30.57 kg/m^2). Over half the subjects in the Dermagraft and Control groups were obese (57.9% vs 54.5%), and the remainder were overweight (21.5% vs 24.5%), normal (18.7% vs 20.0%), or underweight (1.9% vs 0.9%) according to the Centers for Disease Control (CDC) BMI categories for adults.

At Month 0, a greater proportion of subjects in the Dermagraft group showed healed study ulcers compared to the Control group (81.3% vs 62.7%). At the beginning of the 1-year observational study, the study ulcer of 1 subject (0.9%) in the Dermagraft group had recurred compared with 5 subjects (4.5%) in the Control group.

Efficacy Results:

Primary Efficacy Results: Study Ulcer Recurrence

The proportion of subjects with healed study ulcers at Month 0 that recurred during the 1-year observational study in the Dermagraft group was lower, but not significantly so, than that for the Control group (9.2% vs 13.0%) in the ITTrec population.

Study Ulcer Recurrence with the 1-year Observation Period for Subjects with Study Ulcers Healed at Month 0 (ITTrec population)

	Dermagraft (N=87) n (%)	**Control (N=69) n (%)**
Subjects with study ulcer healed at Month 0 [1]	87 (100.0%)	69 (100.0%)
Subjects with study ulcer recurrence [2]	8 (9.2%)	9 (13.0%)
Difference in proportions (Control – Dermagraft)	0.0385	
Exact 95% CI for difference in proportions [3]	-0.060, 0.140	
p-value [4]	0.452	

Source: Table 1.1.1.
[1] Percentage was determined based on sample size of each group in ITTrec population
[2] Percentage was determined based on the number of subject with study ulcer healed at Month 0
[3] Exact 95% CI for the difference proportion was determined based on the bootstrap method with 1,000,000 iterations.
[4] P-value was determined based on Fisher's exact test.

Key Secondary Efficacy Analyses

The proportion of subjects with complete study ulcer healing for study ulcers not healed at Month 0 was 55.0% in the Dermagraft group and 63.4% in the Control subjects who were crossed-over to receive Dermagraft treatment. The remainder of the Control group (64 subjects) had study ulcers that were healed at Month 0, and therefore did not receive Dermagraft applications, and did not show any further healing of the study ulcer during the 1-year observational period.

The incidence of study ulcer infection-related events in the Dermagraft and Control groups was relatively low (2.3% vs 1.4%) for subjects with healed study ulcers at Month 0 and somewhat higher (10.0% vs 31.7%) for subjects with study ulcers that were not healed at Month 0. In the Control subjects whose study ulcers were treated with Dermagraft, 20.0% of those who had healed study ulcers at Month 0 and 31.7% of those who had study ulcers that were not healed at Month 0 experienced at least one study ulcer infection related event.

The time to study ulcer recurrence was analyzed by Kaplan-Meier survival analysis. The time for 10% of the subject's study ulcers to recur for the Dermagraft group was 365 days and that for the Control group was 254.0 days.

In the Control subjects whose study ulcers received Dermagraft, the size of the study ulcer decreased from a mean of 5.15 cm^2 at Month 0 to 2.34 cm^2 by Week 7 in the ITT population; the median time to complete study ulcer healing was 101.0 days.

During the first 6 months of the study, the highest proportion of subjects (whose study ulcers were not healed at Month 0) reported study ulcer pain (defined as physical uneasiness that ranges from mild aches to acute discomfort that was localized to the study ulcer and scored by the subject on a scale of 0-to-10 at each visit) at Month 3 (40.0%) for the Dermagraft group and Month 1 (34.1%) for the Control group, followed by lower proportions thereafter. New (non-study) ulcers (not present at Month 0) were reported more frequently in the Control group whose study ulcers were not healed at Month 0 (4.9% (2/41 at Month 1, and 7.3% (3/41) at Months 3 and 5) than in the Control group whose study ulcers were healed at Month 0 (1.4% (1/69) at Month 1 and 3), and compared with the Dermagraft group whose study ulcers were not healed at Month 0 (5.0% (1/20) at Month 1) and the Dermagraft group whose study ulcers were healed at Month 0 (1.1% (1/87) at Months 1, 5, 9, and 11).

Safety Results:

Subjects in the Control group whose study ulcers received Dermagraft received a range from 1 to 8 applications and a median of 8 applications, in accordance with the study's protocol.

Overall, 57.9% and 65.5% of subjects in the Dermagraft and Control groups, respectively, experienced at least one treatment-emergent adverse event (TEAE) during the study. In the Control group, 80.4% of subjects whose study ulcers received Dermagraft and 54.7% of subjects whose study ulcers did not receive Dermagraft experienced at least one TEAE during the study.

The most frequently reported TEAEs (>5%) for the Dermagraft group vs the Control group whose study ulcer received Dermagraft vs the Control group whose study ulcer did not receive Dermagraft were: skin ulcer (17.8% vs 41.3% vs 12.5%), infected skin ulcer (3.7% vs 28.3% vs 0.0%), oedema peripheral (10.3% vs 13.0% vs 10.9%), pain in extremity (5.6% vs 10.9% vs 6.3%), venous ulcer pain (2.8% vs 10.9% vs 0.0%), hypertension (1.9% vs 10.9% vs 1.6%), nasopharyngitis (8.4% vs 2.2% vs 0.0%), wound infection (0.0% vs 8.7% vs 0.0%), cellulitis (2.8% vs 6.5% vs 1.6%), and excoriation (1.9% vs 2.2% vs 6.3%).

The majority of TEAEs were mild or moderate. Severe TEAEs were experienced by 9.3% of subjects in the Dermagraft group, 10.9% of Control subjects whose study ulcers received Dermagraft, and 9.4% of Control subjects whose study ulcers did not receive Dermagraft.

None of the TEAEs were considered to be related to Investigational Medicinal Product (IMP) in any of the treatment groups. Study ulcer-related AEs were experienced by 15.9% of subjects in the Dermagraft group, 63.0% of subjects in the Control group whose study ulcers received Dermagraft, and 6.3% of subjects in the Control group whose study ulcers did not receive Dermagraft. Study leg-related AEs were experienced by 39.3% of the Dermagraft group, 73.9% of Control subjects whose study ulcers received Dermagraft, and 29.7% of Control subject whose study ulcers did not received Dermagraft.

There were a total of 8 deaths during the study: 2 subjects each in the Dermagraft group and the Control subjects whose study ulcers received Dermagraft, and 4 subjects in the Control group whose study ulcers did not receive Dermagraft; none of the deaths were considered related to IMP. Other SAEs were experienced by 13.1% of subjects in the Dermagraft group, and 13.0% of Control subjects whose study ulcers received Dermagraft, and 12.5% of Control subjects whose study ulcers did not receive Dermagraft. The only SAEs that were experienced by more than 1 subject was cellulitis by 2 subjects (4.3%) in the Control group whose study ulcers received Dermagraft and non-cardiac chest pain by 2 subjects (1.9%) in the Dermagraft group.

A total of 7 subjects experienced AEs that led to dose discontinuations: 2 subjects (1.9%) in the Dermagraft group, 2 subjects (4.3%) in the Control group whose study ulcers received Dermagraft, and 3 subjects (4.7%) in the Control group whose study ulcers did not receive Dermagraft.

Out of range values for clinical chemistry and hematology were recorded for some subjects during the study, but these were not considered clinically significant and did not reflect a consistent pattern of change in any treatment group. Vital signs at Month 0 showed no evident patterns of high or low values across subjects.

OVERALL CONCLUSIONS:

The results of this study support the following overall conclusions:

- Ulcer recurrence as measured by the proportion of subjects with healed study ulcers at Month 0 that recurred during the 1-year observational study was lower in the Dermagraft group, but not significantly so, than that for the Control group (9.2% vs 13.0%) and the time to 10% of subjects having study ulcer recurrence was 365 days in the Dermagraft group compared with 254 days in the Control group.
- No serious or new safety concerns were identified in this current study, compared with the preceding DEVO study.

Date of the report: 06 February 2014