

Abstract

Background: Chronic venous leg ulcers (VLU) affect an estimated 2.5 million adults in the United States, with 600,000 new cases occurring annually. These wounds are associated with substantial morbidity, and annual treatment costs exceed \$3 billion. The current standard of care includes cleaning, debridement, low-adherent dressings that promote moist wound healing, multilayer elastic high compression bandaging, leg elevation, and lower extremity exercise. When treated with the current standard of care, approximately 50% of VLUs remain unhealed at 6 months.

Methods: This 20-week, single-center, investigator-blinded, parallel-group, controlled, pilot study randomized 82 patients with hard-to-heal VLUs to standard care (compression) plus an advanced, poly-N-acetyl glucosamine, nanofiber-derived, wound healing technology (pGlcNAc) or to standard care alone. Included were adults (aged ≥ 21 years) with partial thickness VLUs. Excluded were those with infection. The primary endpoint was percent of patients achieving complete healing at 20 weeks among all subjects randomized to treatment.

Results: Participants were 50% female, 46% non-Hispanic Caucasian, and mean age was 61.5 (SD 13.8) years. There were no significant group differences at baseline. At 20 weeks, the percent of patients achieving complete healing was 86.4% for patients receiving standard care plus every other week administration of pGlcNAc versus 45.0% of those receiving standard care alone ($p=0.005$). No significant treatment-related adverse events or reactions occurred during the study and no subjects experienced increased pain or edema.

Conclusions: This pGlcNAc advanced wound healing technology was effective in treating patients with hard-to-heal VLUs. Treatment was not associated with significant adverse effects.

Background

- There are approximately 600,000 new cases of VLUs each year in the United States.¹
- VLUs are associated with substantial morbidity, decrements in quality of life and economic burden.^{2,3}
- When treated with the current standard of care, about 50% of VLUs remain unhealed at 6 months,⁴ and up to 60% recur within 4 years.⁵
- There is a compelling need for new therapies that offer improved efficacy for the management of VLUs.
- Talymed® is a bioactive, tissue paper-thin membrane material approved by the U.S. Food and Drug Administration (FDA) for the management of various wounds, including diabetic ulcers, venous ulcers, pressure ulcers, and ulcers of mixed vascular etiologies.

pGlcNAc Advanced Wound Healing Technology

- Talymed® (Marine Polymer Technologies, Inc., Danvers, MA) is a bioactive scaffold-like membrane derived from the polysaccharide polymer, poly-N-acetyl glucosamine (pGlcNAc).
- pGlcNAc nanofibers were developed from a proprietary microalgae fermentation process, and have a unique 3-D structure.
- In diabetic mouse models, application of pGlcNAc to full thickness wounds significantly increased the rate of wound healing compared to control materials.⁶
- Increased wound healing rates may occur in response to enhanced angiogenesis and granulation tissue formation, in concert with rapid epithelialization.⁶



Methods

Patients from 3 wound centers in the Southeastern U.S. (St. Francis Hospital, Charleston, SC; The Regional Medical Center of Orangeburg, Orangeburg, SC; and ESU, Inc., Pooler, GA) were recruited from October 2008 through December 2009 for this randomized, investigator-blinded, parallel-group, controlled trial (ClinicalTrials.gov Identifier: NCT00720239; study registration date: February 7, 2008).

Inclusion Criteria: Included were adults age ≥ 21 years; with partial thickness VLUs diagnosed within the past 4 weeks without recent skin grafts or use of growth factors; viable and clean wound bed with granulation tissue and $\geq 90\%$ free of necrosis; wound size between 2 and 20 cm²; and duration of wound <6 months.

Exclusion Criteria: Excluded were those with thickness ulcers extending beyond the epidermis; current wound, skin or systemic infection; insufficient blood supply to wound (ankle-brachial index <0.8 or >1.3); history of collagen vascular disease, severe arterial disease, organ transplant, Charcot, sickle cell disease; previous radiation therapy to the wound site; current hemodialysis; treatment with another investigational drug or device within 30 days of study initiation; and those who were pregnant.

Eligible patients were randomly assigned to 1 of 4 study arms using computer-generated, stratified, permuted block randomization.

All patients received VLU standard of care, which included cleaning and drying the wound, applying a moisture-barrier product, a nonadherent absorptive primary dressing and multi-layer compression bandaging. Standard care also included providing patients with instructions for daily, at-home self-care (elevating the affected leg for at least 30 minutes and performing 3 to 4 lower-extremity exercise sets daily). Surgical, autolytic, or chemical debridement was not performed for any wounds during the course of the study.

In addition to standard care, patients assigned to active treatment had pGlcNAc applied directly to the wound immediately before administration of the primary nonadherent absorptive dressing.

- Group A** received a single application of pGlcNAc (at week 1) plus standard care;
- Group B** received pGlcNAc once every second week (biweekly) plus standard care;
- Group C** received pGlcNAc once every third week plus standard care;
- Group D** (the control group) received standard care alone.

The investigator was blinded to group assignment. Patients and certified wound care nurses, who provided wound treatment and applied the wound healing product, were not blinded to subject group assignment.

Assessment and Statistical Analysis

- Patients were seen twice weekly for the first 3 weeks and then weekly until wound closure. Study nurses measured wound length and width at each visit and recorded adverse events, including deterioration of the wound bed (color, debris, pain, exudate, or inflammation) or changes in the peri-wound skin.
- All statistical calculations were performed using SAS software (version 6.10 for Windows, SAS Inc., Cary, NC).
- Comparisons between treatment groups for baseline demographic, illness, and ulcer characteristics were performed using chi-square tests or t-tests.
- The primary efficacy endpoint was the proportion of patients with complete wound healing (defined as complete wound epithelialization and closure) at week 20 in the intent-to-treat population (all randomized subjects).
- Patients lost to follow-up or withdrawn by investigators due to adverse events prior to week 20 were assumed not to have achieved complete wound healing, and data from the last observation were carried forward (LOCF).

Results

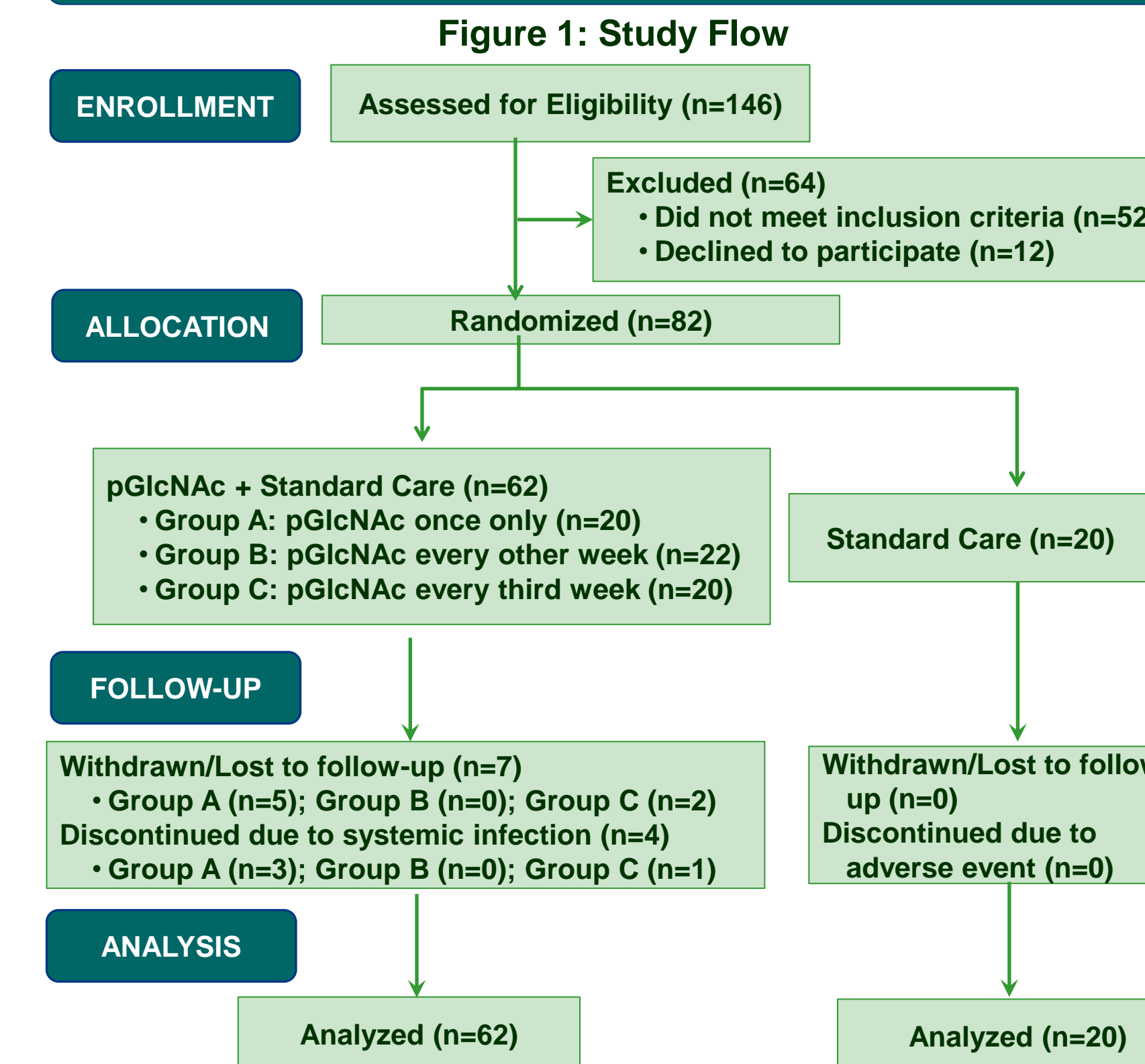


Figure 3: Wound Healing with pGlcNAc Every 3rd Week



Table 1: Baseline Sample Characteristics

Characteristics	Group A (n=20)	Group B (n=22)	Group C (n=20)	Group D (n=20)	P-Value
Race, N (%)					
Non-Hispanic White	10 (50%)	13 (59%)	6 (30%)	9 (45%)	0.29
Black	10 (50%)	9 (41%)	14 (70%)	11 (55%)	
Female, N (%)	15 (75%)	9 (41%)	7 (35%)	10 (50%)	0.06
Age, years, mean (SD)	59 (13.5)	63.2 (14.8)	60.8 (12.2)	63.0 (15.3)	0.74
Ulcer age, months, mean (SD)	3.4 (1.5)	3.6 (1.8)	2.7 (2.1)	2.7 (1.6)	0.25
Ulcer size, cm², mean (SD)	12.1 (11.3)	9.8 (7.3)	10.5 (10.3)	12.8 (12.0)	0.78
Hypertension, N (%)	14 (70%)	16 (73%)	15 (75%)	16 (80%)	0.90
Diabetes, N (%)	12 (60%)	12 (55%)	14 (70%)	12 (60%)	0.78
BMI ≥ 40 kg/m², N (%)	8 (40%)	12 (55%)	10 (50%)	7 (35%)	0.57
Arthritis, N (%)	6 (30%)	12 (55%)	10 (50%)	10 (50%)	0.40
Blood clotting disorders, N (%)	4 (20%)	9 (41%)	2 (10%)	4 (20%)	0.14

Table 2: Percentage of Patients Completely Healed at Week 20

Group A: pGlcNAc Once Only (n=20)	Group B: pGlcNAc Every Other Week (n=22)	Group C: pGlcNAc Every 3rd Week (n=20)	Group D: Standard Care (n=20)
45.0% (9)	86.4% (19)*	65.0% (13)	45.0% (9)

* $p=0.005$ versus Control Group

- As shown in Table 2, only Group B (pGlcNAc applied every other week) had a significantly greater proportion of patients with completely healed wounds compared with standard care ($p=0.005$).
- Four patients developed systemic infections that were determined to be unrelated to their wounds or study treatment. No significant treatment-related adverse events or reactions occurred during the study and no subjects experienced increased pain or edema.

Conclusions

- Although standard compression therapy can be effective in many cases, patients with chronic VLUs pose serious challenges for clinicians.
- This randomized, controlled, investigator-blinded, intent-to-treat pilot study demonstrated that pGlcNAc advanced wound healing technology was effective in the treatment of patients with VLUs with a mean VLU duration of 3 months, and that its application was not associated with significant adverse effects.

References

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